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RESEARCH ARTICLE

CRYSTAL ENGINEERING OF NABUMETONE BY COCRYSTALLIZATION

Sonawane Aravind R,[1] Rawat Swati S[1], Bhagyshree Khadse[1], Marathe Rajendra [2]

[1] Shri Bhagwan College of Pharmacy, Dr. Y. S. Khedkar Marg, N-6, CIDCO, Aurangabad, 431005, (M.S.), India [2]Government College of Pharmacy, Opp. Govt. Polytechnic college, Vedant Road, Osmanpura, Aurangabad,431005,(M.S.), India.

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ABSTRACT

Pharmaceutical cocrystals are multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions. The objective of this study was to investigate the use and validate the success rate of Hansen solubility parameters (HSPs) for the indicating cocrystal formation and guide for cocrystal screening. Nabumetone as a model drug selected which carries dosage form design challenges. Present work emphasizes prediction of miscibility of nabumetone and cocrystal former (CCF) for cocrystal formation. Prediction was based on differences in the HSPs between drug and CCF; calculated by combined Hoftyzer-Van Krevelen and Fedors group contribution. Cocrystallization was carried out using the equimolar 1:1, 0.1 mMol stoichiometric ratios of nabumetone and CCFs *via* solvent evaporation technique followed by vaccum drying. The obtained systems/samples were characterized by FT-IR, DSC and PXRD for identification of cocrystal formation.

Results showed formation of new phases designated as a cocrystal. The investigated approach was effective in predicting miscibility of the drug and selected conformer's. Proposed HSPs-based approach would be useful for short listing potential coformers prior to complex laboratory screening experiments.

Key words: Cocrystals, Nabumetone, Cocrystal formers, Hansen solubility parameter.

1. INTRODUCTION:

Over the past number of years, fraction of new chemical entities (NCE) approaching the marketplace are very infrequent and steadily decreasing. For the successful development and commercialization of NCEs (also called as API) it required that API should possess adequate processability, stability, and bioavailability. Once the complete understanding of the physicochemical and biopharmaceutical properties of the drug substance is known then formulator can design dosage of clinical relevance. Crystal engineering is an emerging area which relates to molecular solids possesses crystalline state. There are few challenges associated with the nature of API in the development and manufacturing of solid dosage forms such as tablet is poor tabletting performance. In particular, usually the industry demands for crystals with stable and better processing characteristics such as flow properties and compressibility. Currently pharmaceutical co-crystals have become an important part of a landscape that was previously occupied only by polymorphs, salts, and solvates/hydrates as it offers opportunity to diversify the number of crystal forms known for an API and to improve their physical properties of clinical relevance with patent protection as a business driven strategy. Regulatory road map for polymorphs approval is quite clear and for cocrystals draft guidance is on scientific advisory from public. From Intellectual property perspectives polymorphs and cocrystal patents are approved in different countries.

Pharmaceutical cocrystals are the crystalline materials comprised of two or more compound both of which are solids at room temperature, bond together in a crystal lattice through non-covalent intermolecular interactions, often including hydrogen bonding. Cocrystals are miscible systems at a molecular level, hence the proposition was brought in that miscibility could be a good indication tool of cocrystal formation between two molecules in the solid state, which would help researchers to avoid going through exhausting cocrystal screening studies. Hence in the present study, the selection of cocrystal system is based on Hansen solubility parameter (HSP) calculated by combined Hoftyzer-Van Krevelen and Fedors group contribution method for drug and all CCFs. The concept of a solubility parameter (δ) was introduced by Hildebrand and Scott, who proposed that materials with

*Corresponding author: Sonawane Aravind R | Email: aravindsonawane@gmail.com

similar δ values would be miscible. The HSP model, which was developed later, is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding). HSP have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces. In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. It has been suggested that HSP could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets. Further, Velaga et al investigated HSP as a tool for predicting the miscibility of indomethacin with different coformers and investigated predicted for formation of cocrystals[Error! Bookmark not defined.],

Nabumetone a novel non steroidal anti-inflammatory drug (NSAID) which is distributed pharmaceutical for treatment of arthritis with lower incidence of gastrointestinal irritancy compared to ibuprofen and diclofenac. However, it posse's low aqueous solubility (less than 1 mg/ml), poor compressibility and flow properties.

The prime focus of present study was to validate the HSP for the indicating cocrystal formation by predicting miscibility between drug and coformer and thus guide cocrystal screening in a less time consuming and an efficient way. Irrespective of prediction by HSP, all forms of Nabumetone-CCF were investigated and compared with predicated data. The prepared cocrystals were characterized by Melting point, Microscopy, Fourier transform infrared spectroscopy (FT-IR), Differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD).

2. MATERIALS AND METHODS:

2.1. Materials: Nabumetone was received from GlaxoSmithKline (Nasik, India) as a gift sample for research purpose. All the other chemicals and solvents were of analytical grade and procured from Research Lab Fine chemicals (Mumbai, India). All chemicals were used as received without further purification.

2.2. Prediction of cocrystallization

Till the date, the area of cocrystal research is devoid of a model prediction tool for CCFs selection in cocrystal formation. The selection of appropriate cocrystals formers (CCFs) for cocrystallization is generally done on the basis of general approaches such as based on supramolecular synthons approach and use of GRAS (Generally regarded as safe) listed CCFs, etc. Hansen solubility parameter (HSPs) is calculated by combined Hoftyzer-Van Krevelen and Fedors group contribution method for drug and all CCFs as below:

Equation 1: Total solubility parameter

$$\delta t = \sqrt{(\delta^2 d + \delta^2 p + \delta^2 h)}$$

Where, δt: Total solubility parameter

δd, $\delta p, \delta h$ are dispersion, polar, hydrogen forces respectively

Equation 2: Dispersion forces $\delta d = \frac{\sum Fdi}{\sum Vm}$

Equation 3: Polar forces $\delta p = \frac{\sqrt{\sum Fpi}}{\sum Vm}$

Equation 4: Hydrogen bonding forces $\delta h = \sqrt{\frac{\sum Fhi}{\sum Vm}}$

Where **Fdi, Fpi, Fhi** are the group contribution to dispersion forces, group contribution to polar forces, Fhi group contribution to hydrogen bonding energy respectively.

i is the structural group within the molecule.

Vm is the group contribution to molar volume.

Equation 5: Volume-dependent solubility parameter

$$\delta v = \sqrt{(\delta^2 d + \delta^2 p)}$$

Equation 6: Miscibility difference & prediction:

$$\Delta\delta t = |\delta t2 - \delta t1|$$

Where, $\Delta\delta t$ is difference in total solubility parameter between the drug and the carriers.

δt1, δt2 are total solubility parameters of carrier and drug

Additionally GRAS status of the CCFs is crucial parameter with respect of regulatory prerequisite[Error! Bookmark not defined.]

2.3. Cocrystal preparation and characterization

2.3.1. Preparation of cocrystals:

Cocrystallization was carried out using the solvent evaporation technique followed by vaccum drying. Nabumetone and CCF dissolved in ethanol (0.1:0.1 mM) with slight warming until dissolution was practically complete and then allowed slowly to evaporate in vacuum for 1 hr at 50^{0}C. The obtained systems/samples were characterized by FT-IR, DSC and PXRD for identification of cocrystal formation.

2.3.2 Fourier Transform (FT-IR) spectroscopy: Shimadzu FT-IR spectrometer Prestige 21 with DRS assembly was used in Attenuated total reflectance (ATR) mode for collecting IR spectra of samples. The spectra's were collected over the range of 4000-400 cm^{-1} in 45 scans, with a resolution of 5 cm^{-1} for each sample.

2.3.3. Differential scanning calorimetry (DSC): Thermal analysis by differential scanning calorimetry of the cocrystals was performed using a differential scanning

calorimeter DSC-60A Shimadzu calorimeter. The sample powders (3-7mg) were placed in aluminum pans, sealed hermetically and then these hermetically sealed aluminum pans were heated at a scanning rate of 20 °C/min from 50 °C to 350 °C under constant purging dry nitrogen flow (20 mL/min). Empty aluminum pan was used as a reference.

2.3.4. Powder X-ray diffraction (PXRD): PXRD patterns of pure drug and the optimized cocrystals formulation were recorded on a Bruker-axs D8 advance X-ray diffractometer (Bruker systems Inc., Germany) using Cu Kα x-radiation (λ=1.5406Å) at 40kV and 40 mA power. The diffraction pattern was recorded for each sample over the 2θ range of 5-50º, with a scan rate of 0.1º/min. The obtained data was processed using Diffract plus V1.01 software available with instrument. The instrument was previously calibrated using a silicon standard.

3. RESULTS:

3.1. Hansen solubility parameter for cocrystal prediction:

The selection of appropriate cocrystals formers for pharmaceutical cocrystallization of NAB was accomplished *via* the miscibility of a drug and CCFs (as calculated by HSP). The representative example of HSP calculation for NAB and CCF Malonic acid is shown in **Table 1 and 2**. Similarly HSP was calculated for all the selected CCFs as summarized in **Table 3.**

Table 1: Hansen solubility parameter calculation of Nabumetone by Hoftyzer-Van Krevelen and Fedors group contribution method

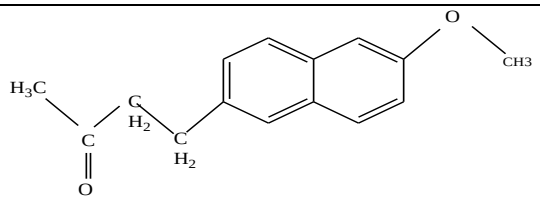
Nabumetone					
Group	**Frequency**	**Fdi**	**Fpi**	**Fhi**	**Vm**
-CH_2	2	540	0	0	32.2
-CH_3	2	840	0	0	67
-O	1	100	160000	3000	3.8
-CO	1	290	592900	2000	10.8
>C=	4	280	0	0	-22
CH=	6	1200	0	0	81
Ring closure	2	380	0	0	32
Conjugation in ring	5	0	0	0	-11
Σ		3630	752900	5000	193.8
Determination of Partial solubity paratmeters δd ,δv ,δh and total solubility parameters (dt)			δd = 18.73, δ^2d = 350.81 δp = 4.48, δ^2p = 20.07 δh= 5.08, δ^2h = 25.8 δv = 19.29 δt = 19.92		

Table 2: Hansen solubility parameter calculation of Malonic acid by Hoftyzer-Van Krevelen and Fedors group contribution method

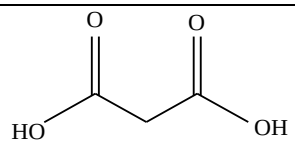
Malonic acid					
Group	**Frequency**	**Fdi**	**Fpi**	**Fhi**	**Vm**
-COOH	2	1060	352800	20000	57
-CH_2	1	270	0	0	16.1
Σ		1330	352800	20000	73.1
Determination of Partial solubity paratmeters δd, δp, δh and total solubility parameters (dt)		δd = 18.19, δ^2d = 330.88 δp = 8.13, δ^2p = 66.10 δh = 16.54, δ^2h = 237.57 δv = 19.92 δt = 25.89			

Table 3: Prediction of miscibility between Nabumetone and CCF

Sr. No.	Drug/CCFs	δ_d	δ_p	δ_h	δ_t	$\Delta\delta_d$	Prediction of Miscibility
1	Nabumetone	18.73	4.48	5.08	19.92	-	-
2	Saccharin	23.74	9.17	10.17	27.41	7.49	-
3	Nicotinamide	17.76	11.95	12.88	24.98	5.06	Miscible
4	Hippuric acid	17.67	6.87	10.72	21.78	1.86	Miscible
5	m-Hydroxy benzoic acid	22.11	7.28	18.17	29.53	9.61	-
6	Adipic acid	17.63	4.89	12.83	22.34	2.42	Miscible
7	Fumaric acid	17.38	7.07	15.43	24.29	4.37	Miscible
8	Tartaric acid	20.25	11.4	27.22	35.79	15.87	-
9	Citric acid	20.92	8.14	21.47	31.06	11.14	-
10	Glutaric acid	17.76	5.64	13.78	23.17	3.25	Miscible
11	Maleic acid	17.38	7.07	15.43	24.29	4.37	Miscible
12	Malonic acid	18.19	8.13	16.54	25.89	5.97	Miscible
13	Oxalic acid	18.6	10.42	18.73	28.38	8.46	-
14	P-Amino benzamide	20.87	7.66	13.6	26.02	6.1	Miscible
15	Mandelic acid	20.66	6.08	16.6	27.19	7.27	-
16	Ferulic acid	18.37	4.92	14.56	23.95	4.03	Miscible
17	Cinnamic acid	18.6	3.42	8.88	20.89	0.97	Miscible
18	P-Amino benzoic acid	20.77	4.34	13.56	25.19	5.27	Miscible
19	Palmitic acid	16.46	1.46	5.9	17.55	2.37	Miscible
20	Vanillic acid	19.15	6.61	16.88	22.49	6.72	Miscible
21	Salicylic acid	20.1	6.22	15.4	26.07	6.15	Miscible
22	Piperazine	17.78	3.32	8.33	19.91	0.01	Miscible
23	Ascorbic acid	27	17.96	33.96	46.95	27.03	-
24	Benzoic acid	19.62	4.35	10	22.45	2.53	Miscible

3.2 Characterization and cocrystals detection by DSC, FTIR and PXRD:

The predicted cocrystals were verified experimentally using DSC for miscibility and cocrystal detection. The signs of melting point depression were the signs of miscibility and cocrystal formation as the new phase with a new melting point was observed. A single endothermic sharp peak was observed for each cocrystal confirming about the new crystalline phase. Representative DSC spectra's for nabumetone-malonic acid as shown in figure with characteristic DSC endotherm at about 71° C as shown in **Figure 1**. However melting endotherm can be higher or lower than endotherm of API. The melting endotherms obtained form DSC of all the investigated cocrystals is summarized in **Table 4**.

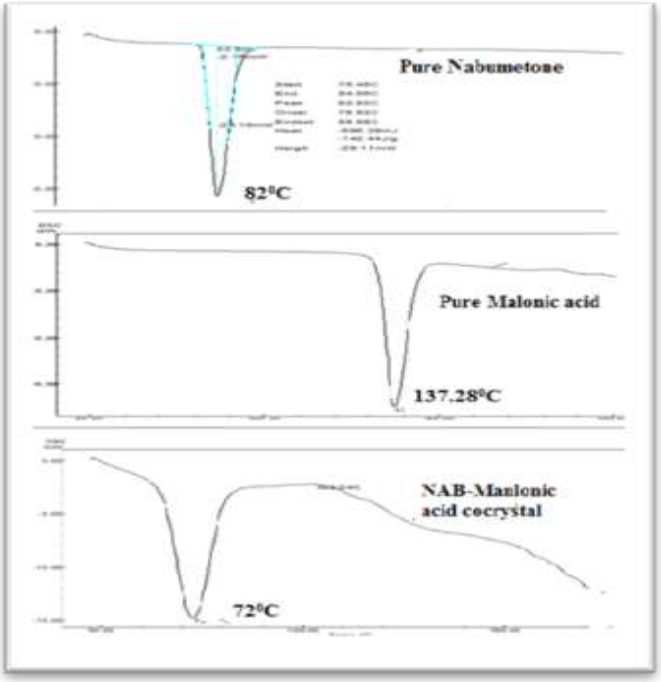


Figure 1: DSC thermogram of Pure Nabumetone, Malonic acid and NAB-Malonic acid cocrystal

Hydrogen bonding in cocrystals by FTIR spectroscopy is detected by decrease in intensity of O-H peak and appearance of low frequency broad O-H band.**Error! Bookmark not defined.** As seen from Nabumetone-malonic acid cocrystal, characteristic peaks at 3396, 2949, 2910, 2848, 2351 ±5 cm^{-1} indicative of hydrogen bond formation with retention of parent drug peak. The representative FTIR spectra of Nabumetone-Malonic acid cocrystal as shown in **Figure 2.**

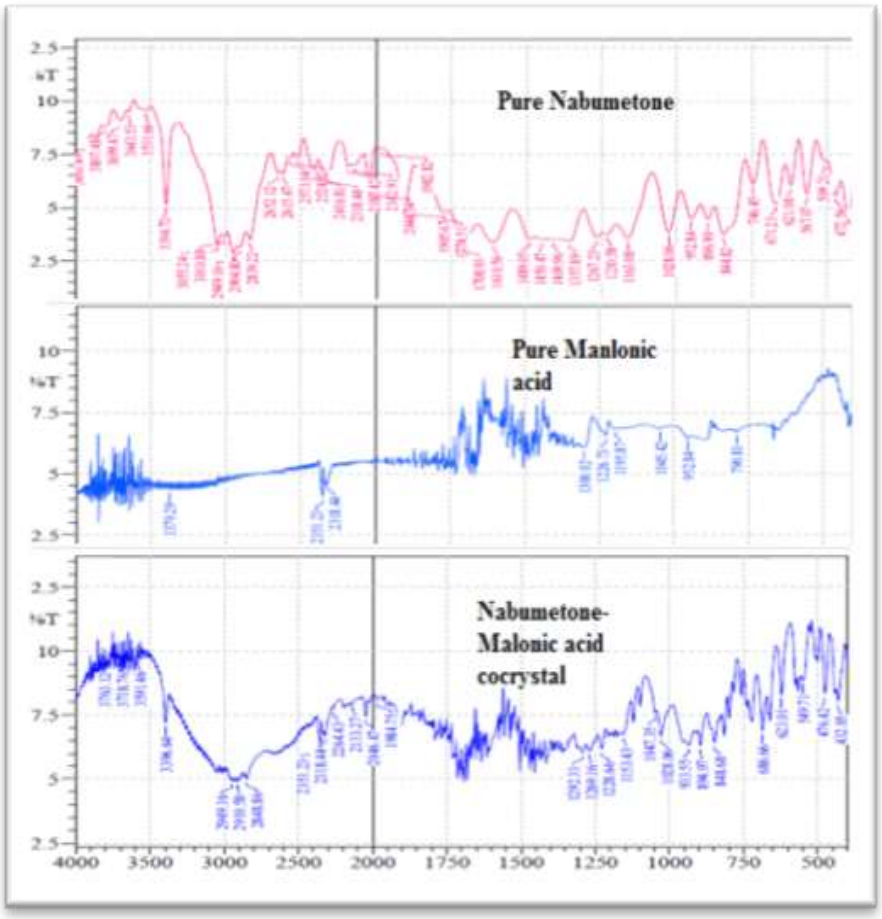


Figure 2: FTIR spectra of Pure Nabumetone, Malonic acid and NAB-Malonic acid cocrystal

Table 4: Summary of Cocrystal prediction and Correlation of HSP with experimental findings

Sr.no.	Formulations	Miscibility by HSP	DSC Melting Endotherm (^{0}C)	DSC and IR	Prediction and success
1	Nabumetone	--	82	--	--
2	Nabumetone-m-hydroxy B.A F	No	76	--	Yes
3	Nabumetone-adipic acid F	Yes	78	No	--
4	Nabumetone-benzoic acid F	Yes	66	Yes	Yes
5	Nabumetone-cinnamic acid F	Yes	73	Yes	Yes
6	Nabumetone-citric acid F	No	80	No	Yes
7	Nabumetone-mandelic acid F	No	79	No	Yes
8	Nabumetone-tartaric acid F	No	82	No	Yes
9	Nabumetone-ferulic acid F	Yes	79-89	No	--
10	Nabumetone-malonic acid F	Yes	72	Yes	Yes
11	Nabumetone-saccharin F	No	78	No	Yes
12	Nabumetone-nicotinamide F	Yes	80	No	--
13	Nabumetone-fumaric acid F	Yes	83.83	No	--
14	Nabumetone-ascorbic acid F	No	83	No	Yes
15	Nabumetone-maleic acid F	Yes	344	Yes	Yes
16	Nabumetone-p-amino benzoic acid F	Yes	83	No	--
17	Nabumetone-palmitic acid F	Yes	78	No	--
18	Nabumetone-salicylic acid F	Yes	71	Yes	Yes
19	Nabumetone-oxalic acid F	No	77	No	Yes
20	Nabumetone-vanillic acid F	Yes	82	No	--
21	Nabumetone-hippuric acid F	Yes	82	No	--
22	Nabumetone-p-amino benzamide F	Yes	77	No	--
23	Nabumetone-Piperazine F	Yes	84	No	--
24	Nabumetone-glutaric acid F	Yes	76	Yes	Yes

After successful detection of cocrystal by DCS and FTIR, detected cocrystals were subjected to powdered XRD study. Representative co-crystal of NAB and Benzoic acid PXRD pattern as shown in **Figure 3.**

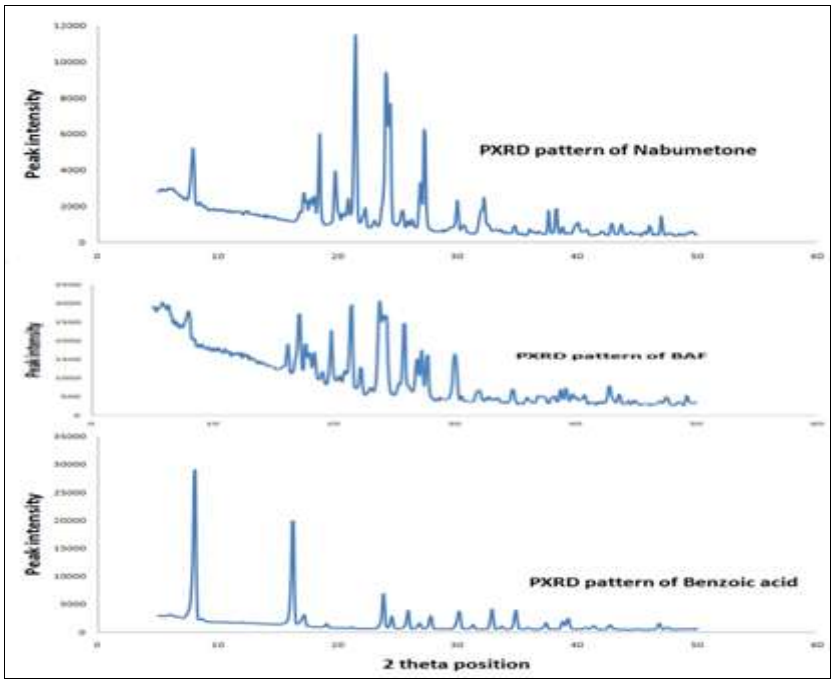


Figure 3: Powdered X-ray diffraction pattern of Pure Nabumetone, benzoic acid and NAB-benzoic acid cocrystal

Nabumetone and Benzoic acid cocrystal shows distinct PXRPD pattern having significant 2θ peaks at about 7.9, 18.5, 19.8, 21.5, 24, 24.4, 27.2, 30, 32.2, 37.6, 38.1 and 47 ±0.2 degrees. The pattern is also characterized by the additional 2θ peaks at about 16.1, 17.1, 25.8, and 27.7 ±0.2 degrees.

4. DISCUSSION:

Present research follows HSP as a tool to predict miscibility between NAB and selected CCFs. Theoretically miscibility between dug and CCF is primitive step which ultimately lead to cocrystal formation.**Error! Bookmark not defined.** Out of twenty three selected CCFs sixteen shows miscibility with NAB as predicted by HSP determined by combined Hoftyzer-Van Krevelen and Fedors group contribution method. Miscibility criteria used as indicated by Greenhalgh et al. materials with $\Delta\delta t < 7\ MP^{0.5}{}_a$ are miscible, while systems with $\Delta\delta t > 7\ MP^{0.5}{}_a$ **Error! Bookmark not defined.** are immiscible. Hence, prediction approach concluded that almost 70% CCFs were miscible with NAB. After successful prediction, experimental screening for cocrystals (*prepared by solvent evaporation technique followed by vaccum drying)* was conducted by DCS, FTIR and PXRD.

Cocrystal detection by DSC and FTIR methodology shows promising findings, out of 23 CCFs screened, 13 formed the cocrystals with NAB namely Benzoic acid, m-hydroxy benzoic acid, Cinnamic acid, Citric acid, Mandelic acid, Tartaric acid, Malonic acid, Saccharin, Ascorbic acid, Maleic acid, Salicylic acid, Oxalic acid, and Glutaric acid. FTIR detection of cocrystals shows a decrease in O-H stretching frequency indicates that hydroxyl group is participating in hydrogen bonding. The extent of hydrogen bonding (ultimately Cocrystals) can be determined by extent of decrease in frequency and relative band broadening. The lowering of frequency is the function of degree and strength of hydrogen bonding. Because of hydrogen bonding, the Carbonyl stretching shifted towards lower frequency indicates presence of unionized carboxylic acid group (often 10- 20 cm^{-1} decrease in frequency was seen. Formation of cocrystals can be well predicted by FT-IR data but it's not the alone tool for detecting cocrystals, further characterization by DSC. Thermal behavior shows distinct endothermic peaks of cocrystal phase which was higher or lower than the pure NAB.

AS discussed above present study investigates prediction and experimental approaches independently to know the potential of miscibility prediction by HSP between NAB and selected CCFs. In scientific, domain remarkable path was investigated by Velaga et al for prediction of miscibility between Indomethacin and 33 selected CCFs. The conclusive part indicates, in order to generalize miscibility observations for prediction of miscibility for cocrystals formation, drugs with different physicochemical profiles and diverse cofomers need to be tested.

HSP approach was effective predicting miscibility between drug and CCF but all the predictive miscible systems were not resulted in cocrystals when tested experimentally. Out of 23 selected systems/CCFs 16 miscible systems were predicted by HSP; from which 13 were detected as cocrystals when screened experimentally; indicates miscibility is prime step to form cocrystal. This observation is in support with Velaga et al **Error! Bookmark not defined.** concluding. Furthermore not all miscible systems formed cocrystals; discrepancy for the same can be due to method of cocrystallization, stoichiometric ratio of CCFs used type of solvent used, type and amount of solvent used for prepration of cocrystals.

5. CONCLUSION:

In conclusion, the present study was aimed to investigate the use of Hansen solubility parameter in prediction of cocrystal formation between Nabumetone and CCFs. The investigated approach was effective in predicting miscibility of the drug and coformers. Furthermore not all miscible systems formed cocrystals *(this observation is in support with Velaga et al concluding***Error! Bookmark not defined.***)*; discrepancy for the same can be due to method of cocrystallization, stoichiometric ratio of CCFs used type of solvent used, type and amount of solvent used for prepration of cocrystals. Thus, the proposed HSPs-based approach would be useful for short listing potential coformers prior to complex laboratory screening experiments, leading to greater efficiency in cocrystal screening program. The detected cocrystals can be further transformed to develop bioequivalent dosage as like parent form or even improved one. Future prospects of work reveal detailed evaluation of detected cocrystals for formulation, development and equivalency with marketed formulation.

6. ACKNOWLEDGEMENTS:

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