Sevukarajan et al /J. Pharm. Sci. & Res. Vol.3(6), 2011,1288-1293

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and Characterization of a Pharmaceutical Co-Crystal: (Aceclofenac: Nicotinamide)

Sevukarajan M*, Thanuja B, Riyaz Sodanapalli, and Rahul Nair
Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy,Tirupati-517501, India

Abstract:
Several methods can be approached to modify the physico-chemical properties of the Active Pharmaceutical ingredients. Here in this research work the designated supramolecular synthon approach, with a strategy to exploit acid-amide and acid-chloride heterosynthons has been used to prepare Aceclofenac-Nicotinamide molecular complexes. The molecular complexes were prepared by neat grinding (ACF-NI NG) and solution crystallization methods with DMSO as solvent (ACF-NI). FTIR, DSC, Mass analysis and SEM has been used to study the prepared molecular complexes. The results conclude the successful formation of the ACF-NI and ACF-NI NG molecular complexes. Appearance of single DSC endothermic peak and in the FT-IR results, changes observed in the vibrational frequencies associated with amide, acid and chloride groups of the reactants prove to be effective diagnostic features to confirm the formation of molecular complexes.

Keywords: Aceclofenac, Molecular Complexes, Neat Grinding, Nicotinamide, Solution Crystallization.

INTRODUCTION:

Pharmaceutical industry focuses either on the development of the new solid dosage forms or the new drug delivery systems for the drugs. This will be based on the problems faced by drugs during their development (1). There are important intellectual property, regulatory and efficacy implications if one is able to discover new compositions of matter for active pharmaceutical ingredients (API's) (2).

In general, pharmaceutical crystal forms are preferred by developers and regulatory authorities, because crystallization tends to afford highly pure products that are superior with respect to reproducibility and scalability (3). Moreover, a unique crystalline form may exhibit distinctive physicochemical properties and could in turn affect the dissolution, manufacturing, physical stability, permeability, and oral bioavailability of an API (4). Thus, it is apparent that selection of an appropriate crystal form for downstream development and processing is of primary importance in pharmaceutical development.

Atypical crystal form selection process comprises two stages of development after a target API molecule has been selected: discover as many pharmaceutical crystal forms as possible; then examine the physicochemical properties of the newly discovered crystal forms (5). At the stage of crystal form discovery, two primary approaches are used. The more straightforward approach is largely based on trial-and-error. The alternative approach for crystal form discovery is the supramolecular architecture which recognizes supramolecular synthons (6) as a design tool and can be more selective, time-efficient, and cost-effective. The supramolecular synthon approach uses crystal engineering (7) to carefully analyze the relevant supramolecular arrangements that an API might exhibit by utilizing the Cambridge Structural Database (CSD) (8) and effectively prioritizes all possible guest molecules for crystal form screening of drugs. This approach will lead to discover crystal forms including, but not limited to, salts, hydrates, solvates, and, more recently, co-crystals (9).

Pharmaceutical co-crystals are defined as multiple component crystals in which at least one component is molecular and a solid at room temperature (the co-former) and forms a supramolecular synthon with a molecular or ionic API (10) Numerous APIs that exhibit undesirable solubility or stability and possess multiple hydrogen-bonding sites have been (or potentially can be) studied in the context of co-crystallization. One of such potential APIs was identified to be Aceclofenac and is of interest for co-crystallization. Aceclofenac is a BCS class II drug with a pKa of 4.7. It has the capability of forming both the salt and co-crystal and it is a novel NSAID (11).

Chemically Aceclofenac has a carboxylic acid functional group and two chlorine atoms. The design strategy I of this molecule is to exploit the robust carboxylic-acid-amide heterosynthon and amide-chlorine atom heterosynthon when primary amide containing Nicotinamide is used as co-former while II strategy is to exploit the carboxylic acid dimer with exofunctional which acts as either a hydrogen bond donor or acceptor. So this chosen API renders itself to be amenable for the synthesis of co-crystals.

Nicotinamide is a GRAS status co-crystallizing compound. It is a primary amide with two hydrogen bond donors (NH_2) and an acceptor (C=O), demonstrate a remarkable ability to form hydrogen bonds for the formation of an intermolecular drug molecule: co-crystal former synthon. A second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring (12). This makes the molecule very versatile for a variety of hydrogen bonded interactions which makes Nicotinamide to be excipient of choice.

MATERIALS

Aceclofenac (ACF) was procured from Yarrow chemicals, Mumbai. Nicotinamide (Ni) was purchased from Otto chemicals. All the other chemicals used were of analytical grade.

METHODS

Preparation of co-crystals:

Neat Grinding method:

The accurately weighed drug and co-former, 354 mg of ACF and 122 mg of Ni (1:1 molar ratio) were ground in mortar-pestle for 30 min. the powder obtained was collected and stored in desiccator till further use. (ACF-NI NG)

Solvent Evaporation Method:

The accurately weighed drug and co-former, 354 mg of ACF and 122 mg of Ni (1:1 molar ratio) were dissolved in 1 ml of Dimethyl Sulphoxide (DMSO) and left for slow evaporation. The fine crystals were obtained after 5 days, which were collected into a tight container and stored in desiccators till further use (ACF-NI).

Characterization of co-crystals:

The pure drug, excipient and the co-crystals obtained from neat grinding and solvent evaporation methods were subjected to FT-IR, DSC and SEM studies.

Fourier Transform Infrared (FT-IR) Studies:

For the pure drug, co-former and co-crystals Fourier Transform Infrared (FT-IR) spectra were obtained. The spectra were recorded in a Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 cm^{-1} at the spectral resolution of 2 cm^{-1}.

Differential Scanning Calorimetry (DSC) Studies:

Thermal analysis of drug, co-former and prepared co-crystal were recorded on a DSC (NETZSCH DSC 204). All the samples are scanned at 10^0C/min. The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 10^0/min was employed over a temperature range of 0^0 - 350^0C with nitrogen purging. Powder sample was weighed into an aluminium pan was used as reference.

Mass analysis:

Solid samples are introduced in a sample cup and are loaded into solid probe in mass spectrometer instrument JEOL GCMATE II. Then sample is heated to form vapor and is subjected into electron beam to produce ions and then ions are separated by analyzer and detected by SEM detector and recorded finally.

Scanning electron microscopy (SEM):

The surface characteristic of prepared crystal was studied by SEM (ZEISS Electron Microscope, EVO MA 15). Powder samples was mounted onto aluminum stub using double sided adhesive tape and sputter coated with a thin layer of gold at 10 Torr vacuum before examination. The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode.

RESULTS AND DISCUSSION:

FT-IR studies:

FT-IR studies have been performed for the pure drug, co-formers and the prepared co-crystals. From the FT-IR results [Figure 1] it can be confirmed that there is interaction between the pure drug and excipient. In the FT-IR spectrum of the pure drug the peak at 850.51 can be assigned to C-Cl stretch, whereas the peaks at 1718.59 and 3319.49 can be assigned to C=O acid and O-H stretch of the carboxylic acid functional group.

In the FT-IR spectrum of the ACF-NI the peak attributed to the C-Cl stretch has been shifted to 862.18 whereas the peak attributed to the C=O acid and O-H stretch of the carboxylic acid functional group has been shifted to 1712.79 and 3290.79 respectively when compared with the pure drug. In the FT-IR spectrum of the ACF-NI NG the peak corresponding to the C-Cl has been shifted from 850.51(in pure drug FT-IR spectrum) to 862.18, whereas the peaks of the C=O and O-H of the acid has been shifted from 1718.59and 3319.49 (in pure drug FT-IR spectrum) to 1712.79 and 3290.79 [Figure 1, 2 and Table 1].

Table 1: Comparison of interpretation of IR spectrum of ACF, Ni and co-crystals

Functional group assigned to	NI	ACF	ACF-NI	ACF-NI NG
C-Cl stretch	--	850.51	862.18	850.61
C=O of acid functional group	--	1718.59	1712.79	1716.65
O-H stretch of acid	--	3319.49	3290.79	3317.56
C=O stretch of amide	1681.93	--	1747.92	1680.0
N-H stretch	3367.71	--	3446.79	3365.78

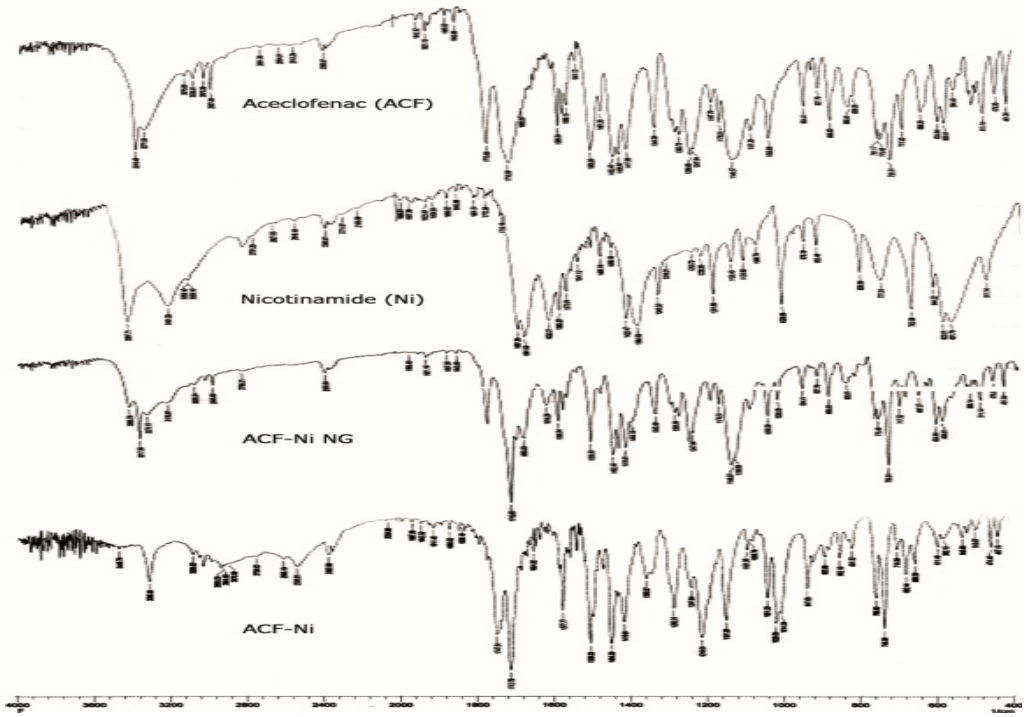

Figure 1: FT-IR spectrum for ACF, Ni and co-crystals.

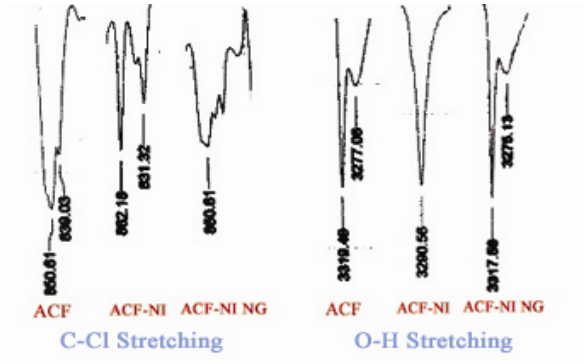

Figure 2: FT-IR spectrum showing C-Cl stretching and O-H stretching

The peak at 1681.93 can be assigned to C=O stretching, in ACF-NI this peak has been shifted to 1747.92, whereas in ACF-NI NG this peak has been shifted to 1680.0.

In ACF-NI NG the decrease in frequency implies that the functional groups participate in strong hydrogen bond. As, there is significant shift of wavelength only to lower numbers in both ACF-NI and ACF-NI NG, it can be confirmed that a proton transfer did not occur. So, the formation of the co-crystal can be confirmed.

In ACF-NI the increase in frequency corresponding for the C-Cl stretching of the ACF, C=O stretch of amide and N-H stretching corresponding to the Ni indicate the functional groups participate in weak hydrogen bond and the decrease in frequency corresponding to the C=O of carboxylic acid functional group of ACF and C=O stretch of Ni implies that the functional groups participate in strong hydrogen bond.

Possible Hydrogen Bond Motifs:

Five expected Possible Hydrogen bond motifs that are possible between ACF and Ni were predicted and given in Figure 3.

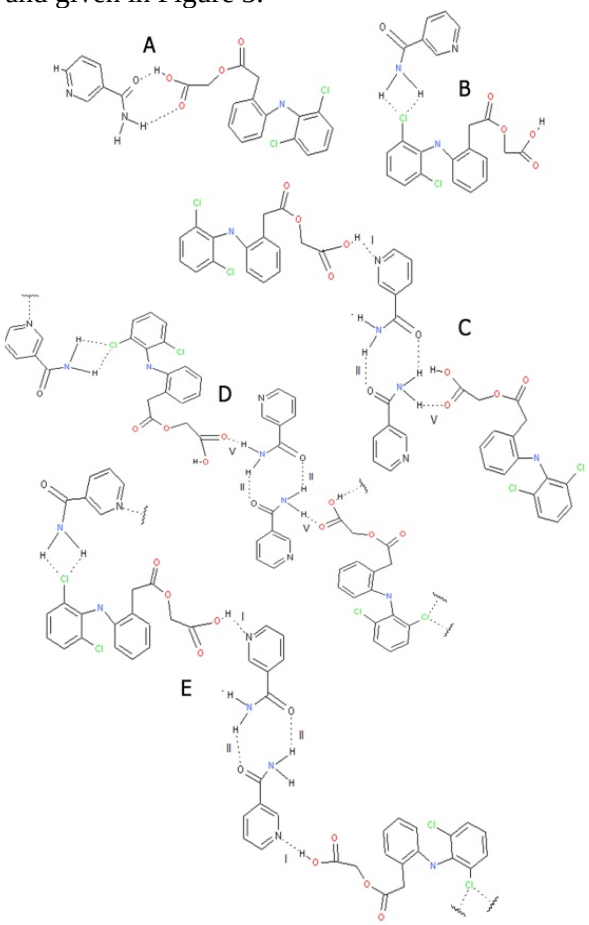

Figure 3: Possible Hydrogen bond motifs between ACF and Ni.

1. First expected hydrogen bond motif is the acid-amide heterosynthon formation between the primary amide group of Ni and acid group of ACF [Figure 3 A].
2. The second expected motif between the ACF and Ni occurs by the formation of chloride-amide heterosynthon [Figure 3 B].
3. There is a possible chance of Ni forming amide-amide dimer and ACF may be linked to Ni either by acid-pyridine heterosynthon (synthon I) or acid-amide heterosynthon (synthon V) which was given by third expected hydrogen motif [Figure 3 C].
4. The fourth expected motif is the formation of an amide-amide dimer by Ni amide group and ACF linking to the amide by acid-amide heterosynthon (Synthon V) and amide-chloride heterosynthon [Figure 3 D].
5. This fifth expected hydrogen bond motif is formation of an amide-amide dimer with ACF linking to the amide by acid-pyridine heterosynthon (Synthon I) and amide-chloride heterosynthon [Figure 3 E].

Differential Scanning Calorimetry (DSC) Studies:

The thermal profile of the drug, co-former and co-crystals has been studied. The DSC curve of the pure drug showed a sharp endothermic peak at 156.4^{0}C. From the DSC curves of the ACF-NI NG, the neat grinding product the melting point was observed to be 86.3^{0}C where as for the thermal profile of ACF-NI reveals a sharp melting point at 90.2^{0}C [Figure 4].

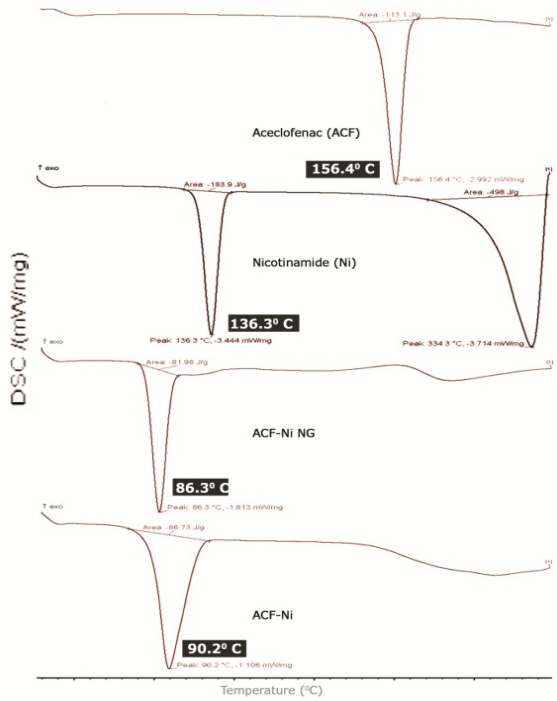

Figure 4: Comparative DSC thermograph spectrum for ACF, Ni and co-crystals.

The increased melting point of the ACF-NI (90.2^{0}C) when compared to the melting point of the ASP-NI might be due the crystal packing nature in ACF-NI. The melting points of the products were different from those observed in ACF (156.4^{0}C) and Ni (136.3^{0}C) and the appearance of the single peak in the ACF-NI co-crystals DSC curve confirms the formation of a new solid phase. The results were given in Figure 4.

Mass spectroscopy:

Mass spectroscopy has been performed for the pure drug, excipient, ACF–NI and ACF-NI NG [Figure 5].

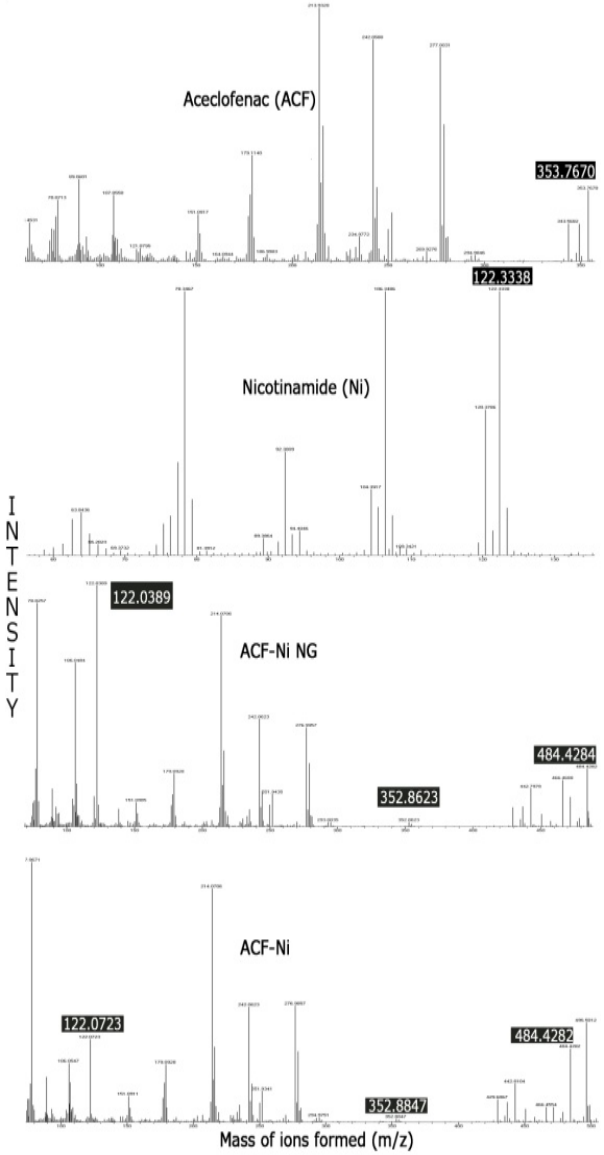

Figure 5: Comparative Mass spectrum for ACF, Ni and co-crystals

For the pure drug the theoretical formula weight is 354.18 and the exact mass is 353.022 and in the mass spectrum of the pure drug the peak at 353.76 indicates the ‘n’ peak, similarly the peak at 122.33 indicates the n peak for the excipient, Nicotinamide (for which the molecular weight is 122.23).

Theoretically if the complex has been formed between the ACF and Ni in the 1:1 stoichiometric ratio, then the mass of the complex will be 476.36. As the electron impact ionization of the solid samples has been performed, ionization of the molecular complex might have possible, if the same ionization has been performed by liquid sampling method (by dissolving the sample in suitable solvent later subjected to ionization) the two components might have separated and the detection of the complex might not have been possible.

For the co-crystals, ACF-NI NG the presence of m/z peak at 484.82 indicates the formation of the molecular complex and for the ACF-NI the m/z peak at 477 also represents the same. The appearance of separate m/z peaks at 353 and 122 in both ACF-NI and ACF-NI NG ensures that no covalent bonds have been formed and the bonds between the Aceclofenac and Nicotinamide were weak hydrogen bonds and so separated during ionization.

Scanning electron microscopy (SEM):

SEM analysis has been performed for the pure drug, excipients and co-crystals. The pure drug exhibited irregular shape with smooth surface.

The co-crystals also exhibited irregular shape but the shape was different with those of the pure drug and excipient. From the SEM analysis, the ACF-NI NG showed reduced particle size. [Figure 6]

CONCLUSION:

In these days, the use of co-crystals is an emerging trend to improve the physico-chemical properties of the API's. The knowledge of complementary functional groups to create a new co-crystal has been successfully implemented in this research work. The Aceclofenac-Nicotinamide molecular complexes were prepared by neat grinding (ACF-NI NG) and solution crystallization methods with DMSO as solvent (ACF-NI). These were characterized by FTIR, DSC, Mass studies and SEM. The results from FTIR, DSC, Mass studies and SEM confirm the formation of the new crystal phases. From the FT-IR results, possible hydrogen bond motifs were generated. From this research work it can be established that Aceclofenac and Nicotinamide can form a co-crystal by both neat grinding method and solution crystallization method by using DMSO as solvent. Also, it can be concluded that FT-IR, DSC and Mass were effective tools for co-crystal screening and also. The analysis of the crystal forms to study their pharmaceutically significant nature is necessary, which is the subject of further study.

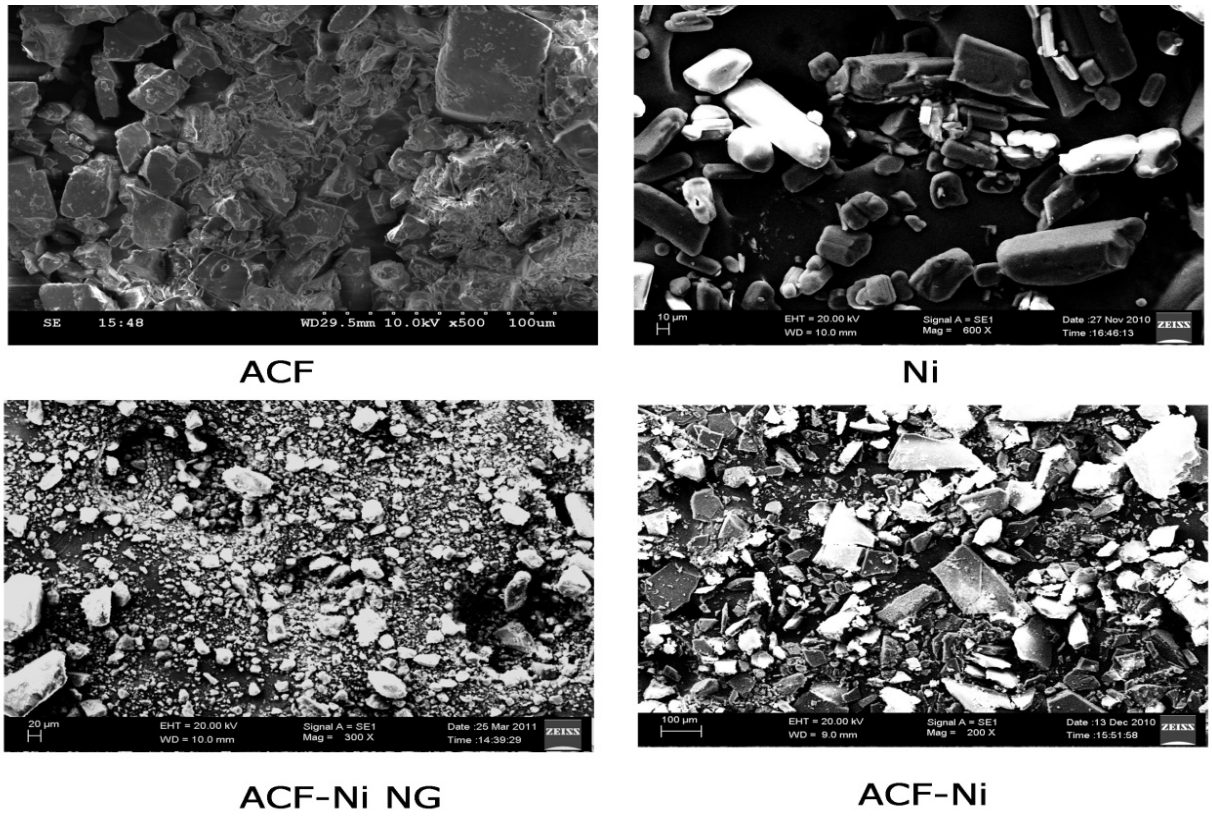

Figure 6: SEM Photographs for ACF, Ni and co-crystals

ACKNOWLEDGEMENTS:

The authors wish to thank the management of Sree Vidyanikethan College of pharmacy for providing the necessary facilities for carrying out the research work.

REFERENCES:

1. Sheth AR. and Grant DJW. *Kona 2005,* 23: 36-48.
2. Scott. Childs L, Patrick Stahly G and Aeri Park. *State Mol. Pharm.* 2007, 4(3): 323-338.
3. Byrn S.R., Pfeiffer RR. and Stowell JG. "Solid-State Chemistry of Drugs" 2nd ed. SSCI, West Lafayette, IN, 1999.
4. Jones W., Motherwell WD. and Trask A.V. *MRS Bull.,2006,* 341, 875–879.
5. Miranda L. Cheney, David R.Weyna, Ning Shan, Mazen Hanna, Lukasz Wojtas and Michael J. Zaworotko. 2010, 10,4401-4413.
6. Aakeroy CB. and Salmon DJ. *Cryst.Eng.Comm.* 2005, 7(72), 439–448.
7. Desiraju G R. *Angew. Chem*. Int. Ed. Engl. 1995, 34, 2311–2327.
8. Ashwini Nangia. *Current Trends in science*, Platinum Jublee Special. 2010;35-51.
9. Nate Schultheiss, and Ann Newman. *Cryst. Growth Des*. 2009, 9 (6), 2950–2967.
10. Bond A. B. *Cryst.Eng.Comm. 2007,* 9(9), 833–834.
11. Mutalik S., Prambil A., Krishnan M., Achuta NU. *Int J Pharm*. 2008, 350, 279-290.
12. Andreas Lemmerer, Catharine Esterhuysen and Joel Bernstein. *J. Pharm. Sci*. 2010, 9(9), 4054-4071.