SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA 18112 Mechanichemistry for Sustainable Industry
STSM title: The application of Mechanochemical treatments for thermomechanical activation of surfaces on the crystalline heterogenous solids
STSM start and end date: 13/04/2022 to 21/04/2022
Grantee name: Aleksandar Cvetkovski
Grantee date of birth: 13.05.1971
Grantee affiliation: University professor
Host name: Prof. Dr. Jasmin Suljagic
Host institution: Department of Chemical Engineering, University of Tuzla

PURPOSE OF THE STSM:

Study on the correlation of mechanochemical treatment of solid powdered mixtures of two different classes of drugs on the propensity to cocrystallize their components into multicomponent crystalline single phases (drug-drug cocrystal), or amorphous or liquid crystalline phases that are of life science relevance (pharmaceutical, food, agrochemical, environmental protection and etc.).
The project's concept encompasses investigation the relationship between the process parameters (performance of powder mixing, temperature, time for treatment) and formulation parameters (molecular structure, degree of crystallinity or/amorphous, polymorphic forms, molar ratio of the components, type of wetting agents). The screening approach relates to how the performing of the mixing powder mixtures, both within the different type of equipments (ball and chopper mixer) and manual grinding (mortar with pestle) influence the conversion of the different component into the new unique solid phases toward the process of cocrystallization. Furthermore, the thermodynamic and kinetic study on the new multicomponent systems reveals the phase stability during the processing and different ambient conditions.
The crystal structure of the selected model, molecular salt metformin diclofenac for optimizing the mechanochemical method of its preparation, was previously determined by single-crystal XRD techniques and the results are in process of publication (A.Cvetkovski & P.Gilli, V. Bertolasi)

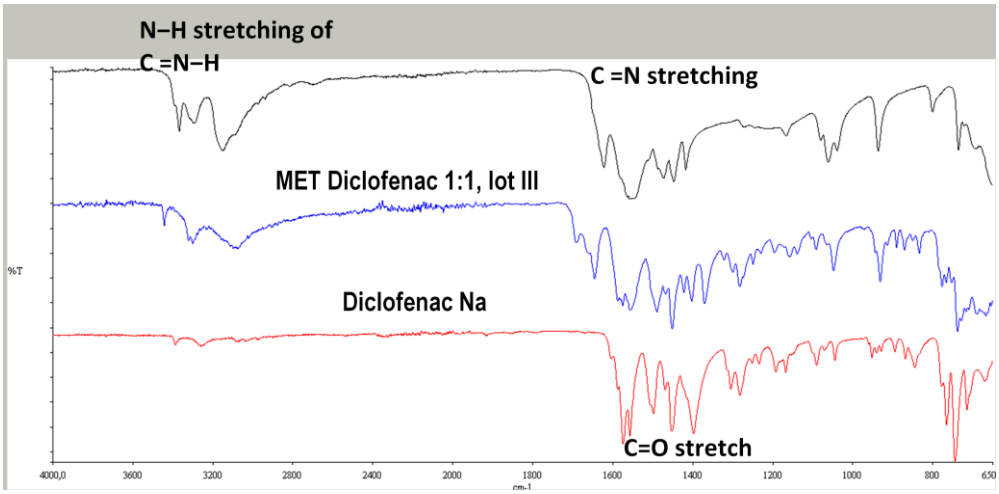
DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

Drug models from the group of oral antidiabetic drugs for treatment of diabetes type II with biguanide molecular structures were utilized for cocrystallization screening performed by mechanochemical treatment of the solid powdered mixtures. The biguanide drugs belong to superbase, the strongest in nature organic bases with two protonation constants: pKa1 ≈12.5 and pKa2 ≈ 2.7 and neutral form. Survey across the Cambridge Crystallography Database (CCD) was supporting tool for providing insight into the currently deposited crystal structures with biguanide drug metformin. Hence, the CCD was supportive in selection of conformer for cocrystalluzation. The conformer for molecular salts was selected to be painkiller drug diclofenac which by its molecular structure is mono carboxylic acid.
We started the screening experiments in three (3) lines.

1 set. Powder mixture of metformine neutral (free base) form and diclofenac neutral form (free acid) was processed by two procedures: Firstly, manually grinding and subsequently kneading by adding droplets of ethanol in mortar and pestle for 30 minutes. Drying the kneaded wet paste 24h, and sieving it to powder with uniform particle size.
2 set. Powder mixture of metformine hydrochloride and diclofenac sodium was processed by kneading manually in mortar and pestle by adding droplets of ethanol-water mixture during the 60 min. For comparison, the reaction of neutralization of metformin hydrochloride and diclofenac sodium was performed by dissolving both components in methanol, evaporating the solvent on roto-evaporator on 40 ^{o}C, and dissolving the sediment in isopropanol as a selective solvent within the formed sodium chloride is not dissolved and remain as sediment, but formed compound of molecular salt metformin diclofenac is soluble. Additionally, isoporpanol solution was evaporated, and the powder sediment was collected.
3rd set. Simulation the ball mill. Filling mixture of powders (diclofenac acid form and metformin free base) into the metal tube with one porcelain ball (device for powder particle size uniformity for spectroscopy, fixed on the rotational agitator).
Prepared samples was put in chambers on two different conditions (25 ^{o}C 60% RH, and 40 ^{o}C 70% RH) in order to test the stability of the formed phase of molecular salt in the timeframe of one year.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

The characterization relates to confirmation of the formed pure solid phase of molecular salts that is product of neutralization reaction between metformin monocation and diclofenac anion.
The FT-IR Spectroscopy was applied for determination of the formed new phase based on the shifting of vibration bands in the spectra of the formed molecular salt metformin diclofenac from the band that relate to wave number characteristic form the pure compounds.
The FT-IR results reveal that treating the pure phase of compounds, both in neutral forms, metformin free base and diclofenac acidic forms by kneading in mortar with pestel lead to the formation of molecular salt metformin diclofenac toward the reaction of neutralization (Spectra depicted below).
Additional spectra assignation is currently underway for revealing complete vibration profile of the molecular salt.



FUTURE COLLABORATIONS (if applicable)

The further collaboration continues in terms of performing solid-state characterize the samples prepared in during the STSM mission at the University in Tuzla by applying DSC-TG and Raman Spectroscopy that would be carry out at the institutions in N. Macedonia. In addition the kinetic study on solubility and dissolution profile testing would be of interest to be carried out.

CONFERENCE PARTICIPATION (if applicable)

Submitted Abstract for Poster Presentation of determined crystal structures for which during the STSM CA

18112 held on the University in Tuzla, join team have set up methods for screening protocols for optimizing the large scale preparation of the solid compounds by applying Mechanochemical principles.
On the Poster Presentation will be designated Acknowledgment to CA18112 Mechanochemistry for Sustainable Industry on the 25th International Conference on the Chemistry of the Organic Solid State July 3 – 8, 2022 in Ohrid, N.Macedonia
Conference link: https://wp.nyu.edu/abudhabi-iccoss2021/

POSSIBLE PUBLICATION
Additional DSC-TG analyses are expected to be completed, complementary characterization by Raman Spectroscopy to confirm phase transition phenomena and interactions, before the manuscripts would be prepared.