Analysis of Raman Spectra Signals Based on Molecular Fingerprints from DFT data

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**Abstract**

In cocrystalization-based processing of pharmaceuticals, Raman spectra is utilized as a standard tool for quality control. However, such analysis suffers from the lack of relevant tools for realtime analysis of spectra. Here we report an automation method to facilitate such analysis. For this purpose, we coupled the nonlinear multivariable functional series approximation with molecular fingerprints as derived from density functional theory calculations. As the case study, we considered the cocrystalization process of ibuprofen and nicotinamide. We showed that for any mixture, it is possible to identify the contribution (probability) of different molecular fingerprints by just reading the offline and/or online Raman spectra, with significant level of confidence. Therefore, a realtime monitoring of continuous cocrystalization-based pharmaceuticals processing is achieved. Using the model, it is possible to identify and adopt the operating conditions of system on realtime toward fingerprint (molecular structure) of interest i.e., cocrystals.

**Keywords**: pharmaceutical; molecular interactions; molecular engineering; Raman spectra

# Problem definition

Raman spectroscopy has found wide applications as a quality control tool, especially in continuous processes such as cocrystalization via twin-screw granulator [[1-3](#_ENREF_1)]. Using Raman spectroscopy, it is possible to get insight on the possibility of generation of new phases in processing of formulations [[4-6](#_ENREF_4)]. The Raman spectra can show that the interactions between compounds are either of chemical or physical nature [[7](#_ENREF_7)]. This is because of the unique spectrum for each molecule, reproducibility, applicability to wide range of physical states, and minimal sample preparation, which made Raman spectra as a common tool in analytical studies.

However, the analysis of Raman spectra requires some previous training and hands-on experiences [[8](#_ENREF_8)]. Sometimes, it is challenging to identify new phases or substances from Raman spectrometers, and expertise of user matters the most. This can be more difficult when dealing with the mixtures. Furthermore, the dependency of analysis on an trained user limits researches and also is time-consuming and slows detection time [[9](#_ENREF_9)].

It is found to be a great idea to develop method for analysis of Raman spectra so that the need for manual effort could be eliminated [[10](#_ENREF_10), [11](#_ENREF_11)]. Literature witnessed a large number of reports dealing with the application of deep learning algorithms for analysis of Raman spectra data [[9](#_ENREF_9), [11-13](#_ENREF_11)] as reviewed elsewhere [[9](#_ENREF_9)]. However, these methods are well-known to be *data-hungry* because of their need for large datasets [[14](#_ENREF_14), [15](#_ENREF_15)]. The necessity of providing experimentally collected data for training of such models makes it impossible to generate predictive models without prior experimentations [[16](#_ENREF_16), [17](#_ENREF_17)]. In addition, these models are *empirical* in nature due to fitting (training) step where collected data are used for back calculation of models weights/coefficients [[18](#_ENREF_18), [19](#_ENREF_19)]. Therefore, these models always are susceptive to fail at extrapolations i.e. when data attempted for prediction has not been present in the training dataset [[20](#_ENREF_20), [21](#_ENREF_21)], especially when a proper optimization/regression method has not been used [[22](#_ENREF_22)].

Nowadays, by using *ab initio* methods, it is possible to predict properties of materials from scratch as such methods are mature enough to tackle problems in materials engineering [[23](#_ENREF_23), [24](#_ENREF_24)]. In fact, it is possible to predict and get an insight on the interaction between molecules and their mixture behaviour through modeling on molecular scales [[25](#_ENREF_25), [26](#_ENREF_26)]. Therefore, here we implemented a bottom-up approach to develop a completely predictive method for analysis of Raman spectra. An overview of developed approach and its application is shown in Fig. 1 and details can be found in next sections.

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| Fig. . The workflow of computations in model development and its application |

# Methodology and computational details

The contacts between molecules in any mixture are most likely at prominent sites on each molecule where a donor/acceptor interactions can be realized [[25](#_ENREF_25)]. Any mixture of the molecules involves random and dynamic contacts between them. So, we can expect that all mixture associated Raman spectra measurements are contaminated due to such interactions. We refer to molecular interactions as fingerprints hereinafter. We therefore assume that a nonlinear (weak) correlation should exist among measured Raman spectra as read by spectrometer and Raman spectra of those fingerprints [[11](#_ENREF_11)], no matter identification of which fingerprint is target of measurements.

We show Raman spectra of target of measurement by  and the Raman spectra of molecule *A,* molecule *B*, and all fingerprints by , considering a total of *N* fingerprints (different donor/acceptor interactions). The nonlinear correlation, , of measured Raman intensity  to fingerprint Raman intensities,  can be given as in Eq. 1 [[27](#_ENREF_27), [28](#_ENREF_28)].

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Here, the exact form of nonlinear correlation, , is not accessible and of no concern. But it is possible to approximate, by a new function to represent the relationship between the Raman intensity  and Raman intensity of fingerprints,  as given in Eq. 2 [[27](#_ENREF_27), [28](#_ENREF_28)].

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The volterra functional series [[27](#_ENREF_27)] are a class of such function , which can express and capture such nonlinearity as given in Eq. 3, where ,  ,  ,  ,  are all unknow constant coefficients.

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This second term in Eq. 3 captures the direct contribution of each fingerprint on , the third term captures the contribution of binaries (implying two-body interactions) of fingerprints, fourth term captures the contribution of triple (implying three-body interactions) of fingerprints and so on. However, from physical implications, it is clear that interactions beyond three-body is rare, therefore we can ignore fifth terms and so on in Eq. 3. Therefore, the model equation is as given in Eq. 4.

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The coefficients  can be translated as intuitive linear weights of each fingerprint in signal once we remove the contributions due to Spectra of *A* and *B*. This can be done using Eq. 5.

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In order to calculate coefficients ,  ,  ,  , and , Eq. 4. can be rewritten in matrix form as given in Eq. 6, which can be solved as given in Eq. 7 [[28](#_ENREF_28)] where superscripts *T* and -1 refers to transpose and inverse of matrix. Here  is the vector of Raman intensity of target, is a vector of all coefficients ,  ,  ,  , and . is the matrix containing all the fingerprints .

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The matrix of fingerprints, needs Raman intensities as determined from density functional theory calculations. To do so, we identified the unique inter/intra molecular interactions that can occur between the two molecules once they contact each other as a result of donor/acceptor interactions [[25](#_ENREF_25)]. The surface donor/acceptor sites were identified based on the surface site charge densities [[29](#_ENREF_29)] by employing Hirshfeld partitioning scheme [[30](#_ENREF_30)] as implemented in DMol3 package. Then, upon structure relaxation, the Raman spectra can be calculated for any incident light and system temperature using the data from density functional theory following the method of Porezag and Pederson [[31](#_ENREF_31)]. We performed relaxations using the DMol3 package. We employed the Generalized Gradient Approximations with Perdew-Becke-Ernzerhof functional [[32](#_ENREF_32)] including implicit solvent [[33](#_ENREF_33)] as described by COnductor-like Screening MOdel (COSMO) [[34](#_ENREF_34)]. The choice of Perdew-Becke-Ernzerhof functional in current calculations is based on previous recommendations for proper treatment of possible charge transfer and long range interactions [[25](#_ENREF_25), [35](#_ENREF_35)]. To control the convergence behaviour for an enhanced self-consistent field calculations [[36](#_ENREF_36), [37](#_ENREF_37)], thermal smearing [[38](#_ENREF_38)] was also applied including double numerical basis including d-polarization function [[39](#_ENREF_39)] level of theory. The convergence tolerances are energy: 2.0×10-5 kcal/mol, force: 10-3 kcal/mol/Å, max iterations: 104, displacement: 10-5 Å [[40](#_ENREF_40)]. Once matrix is constructed from density functional theory calculations, equation 7 can be used to analysis any input Raman signal  and evaluate coefficient vector . From coefficient vector , we are interested in which are translated to intuitive linear weights of each fingerprint in signal using Eq. 5. The matrix can be singular due to nature of Raman intensities, so we compute its Moore-Penrose pseudo-inverse using a least-squares solver (*numpy.linalg.pinv*) [[41](#_ENREF_41)]. Related scripts and data can be found under “data availability” section.

# Case study

We considered the cocrystalization process of ibuprofen and nicotinamide [[25](#_ENREF_25)]. We collected Raman spectra for cocrystalization process of ibuprofen and nicotinamide from literature [[42](#_ENREF_42)]. In Ref. [[42](#_ENREF_42)], they carried out Raman spectroscopy with 532 nm excitation at a laser power of 150mW. They collected Spectra from 200 to 1800 cm-1. The collected data from Ref. [[42](#_ENREF_42)] represents the offline source. Experimental Raman spectroscopy can be either inline or offline [[1](#_ENREF_1), [2](#_ENREF_2)]. An offline data corresponds to the stored Raman spectra which are measured for product at the end of processing and inline data corresponds to the real-time Raman spectra as read by instrument installed on top of twin-screw granulation, where the probe can be installed on different locations. The molecular structure of ibuprofen and nicotinamide were retrieved from a previous work [[25](#_ENREF_25)]. All possible contacts between ibuprofen and nicotinamide were considered by following a molecular docking approach [[25](#_ENREF_25)]. The same structure optimization approach is applied to all docked molecular structures. We evaluated Raman spectra for the incident light has intensities as used in corresponding experimental measurements at four temperatures spanning actual operating conditions, i.e., 298, 343, 353 and 363 K using method of Porezag and Pederson [[31](#_ENREF_31)].

# Results and discussion

The identified fingerprints in cocrystalization process of ibuprofen (IBF), nicotinamide (NCTA) and their corresponding structure is provided as supplementary file. The normalized Raman spectra calculated using Eq. 8 from density functional theory calculations following method of Porezag and Pederson [[31](#_ENREF_31)] are shown in Fig. 4. Fig. 5 shows the weak correlation between Raman spectra of each two fingerprint.

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The error of model in prediction of Raman intensity of fingerprints is shown in Fig. 2. Prior to the application of model in prediction of real/experimental Raman intensity data as collected from literature [[42](#_ENREF_42)], we performed a sensitivity analysis by generating 104 random dummy mixtures () as  where is random number acting as the weight/probability. The difference between calculated linear weights of fingerprints, from model and  is shown as the model error in Fig. 2.

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| Fig. . Error of model in prediction of fingerprints probability (left) and summation of errors in prediction of fingerprints probability in dummy mixtures (right) | |

For the data reported in Ref. [[42](#_ENREF_42)], the model prediction of fingerprints probability is shown in Fig. 3. The presence of excess ibuprofen and nicotinamide has been confirmed in Ref. [[42](#_ENREF_42)] based on their differential scanning calorimetry measurements and the powder X-ray diffraction spectra. This can be seen with higher probability of fingerprints associated to ibuprofen and nicotinamide dimers in Fig. 3. The experimentally observed incomplete cocrystalization of ibuprofen and nicotinamide [[6](#_ENREF_6), [7](#_ENREF_7)] is evidence in the smaller probability as well as verity of fingerprints associated to cocrystals of ibuprofen and nicotinamide. Increasing temperature exposes the mixture to more ibuprofen dimer formation as the temperature get closer to ibuprofen melting temperature [[25](#_ENREF_25)]. This can be easily observed in increasing trend of fingerprints probability associated to the ibuprofen dimer. It can be seen that the cocrystal structure CO3 (fingerprint 3) is the most prominent cocrystal would be obtained at the end of holt melt extrusion.

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| Fig. . Prediction performance of model in estimating probability of fingerprints in Raman data as collected from Ref. [[42](#_ENREF_42)]. ***Left***: for mixture extruded at temperatures 70, 75, 80, 85, and 90 ℃ screwed at 40 rpm as labelled by Fig2c70, Fig2c75, Fig2c80, Fig2c85, and Fig2c90 respectively. ***Right***: for mixture extruded at screw speeds 40, 60, 80, 100, and 120 rpm at 90℃ as labelled by Fig3c40, Fig3c60, Fig3c80, Fig3c100, and Fig3c120 respectively. | |

The application of developed model brings the opportunity to monitor realtime effect of the operating condition of holt melt extrusion via twin screw granulator on the change and evolution of fingerprints (molecular structures) such as temperature, screw speed, number of compartment and so on. Therefore, we are able to identify and adopt the operational parameters on the fly toward the target formulation.

It is possible to explore full operational design space by performing molecular dynamic simulations on mixture of the two molecule and then extracting Raman intensities. Applying the model to these Raman intensities of trajectories from molecular dynamic, the computational interplay of operating condition (temperature, residency time or screw speed) on fingerprints can be determined and therefore it can be used for high throughput screening of process parameters.

# Conclusion

In this work, we report a model to analysis the probability of different phases/structures based on the Raman spectroscopy. The model does not require experimental data and is developed on top of density functional theory calculations. The model can be simply adopted to any system of interested by carrying out the density functional theory calculations and building the fingerprint matrix, , which is transferable. We showed that for any mixture, it is possible to identify the contribution (probability) of different molecular fingerprints by just reading the offline and/or online Raman spectra with significant level of confidence. The model brings the opportunity of realtime monitoring particle formation in continuous cocrystalization-based pharmaceuticals processing.

# Data availability

The associated data of this paper can be found under ***Downloads*** page at: <https://sites.google.com/view/makhansary>, using tag ID = ***CoCryM.ExSysR***.

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# Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

# CRediT author statement

**Milad Asgarpour Khansary**: Conceptualization, Methodology, Programming, Computations, Validation, Writing- Reviewing and Editing. **Gavin Walker**: Supervision. **Saeed Shirazian**: Reviewing and Editing.

# Appendix

## Normalized computed Raman spectra

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| Fig. . DFT-based calculated Raman spectra of fingerprints | | | |

## Weak correlation between fingerprints

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| Fig. . Weak correlation among pairs | | |

**References**

1. Andrews, G.P., et al., *The development of an inline Raman spectroscopic analysis method as a quality control tool for hot melt extruded ramipril fixed-dose combination products.* Int J Pharm, 2019. **566**: p. 476-487.

2. Soares, F.L.F. and R.L. Carneiro, *Green Synthesis of Ibuprofen–Nicotinamide Cocrystals and In-Line Evaluation by Raman Spectroscopy.* Crystal Growth & Design, 2013. **13**(4): p. 1510-1517.

3. Omar, J., A. Boix, and F. Ulberth, *Raman spectroscopy for quality control and detection of substandard painkillers.* Vibrational Spectroscopy, 2020. **111**: p. 103147.

4. Tang, C., T.-C. Ling, and K.H. Mo, *Raman spectroscopy as a tool to understand the mechanism of concrete durability—A review.* Construction and Building Materials, 2020: p. 121079.

5. Doumeng, M., et al., *A comparative study of the crystallinity of Polyetheretherketone by using density, DSC, XRD, and Raman spectroscopy techniques.* Polymer Testing, 2020: p. 106878.

6. Mendes, T.d.O., et al., *Raman Spectroscopy as a fast tool for whey quantification in raw milk.* Vibrational Spectroscopy, 2020: p. 103150.

7. Asgarpour Khansary, M., et al., *Correlation of sorption-induced swelling in polymeric films with reference to attenuated total reflectance Fourier-transform infrared spectroscopy data.* European Polymer Journal, 2017. **91**: p. 429-435.

8. He, H., et al., *Applications of Raman spectroscopic techniques for quality and safety evaluation of milk: A review of recent developments.* Critical Reviews in Food Science and Nutrition, 2019. **59**(5): p. 770-793.

9. Mozaffari, M.H. and L.-L. Tay, *A Review of 1D Convolutional Neural Networks toward Unknown Substance Identification in Portable Raman Spectrometer.* arXiv preprint arXiv:2006.10575, 2020.

10. Xie, Y., et al., *How to achieve auto-identification in Raman analysis by spectral feature extraction & Adaptive Hypergraph.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2019. **222**: p. 117086.

11. Khansary, M.A., G.M. Walker, and S. Shirazian. *Correlating Raman Spectra of Ibuprofen, Nicotinamide and their Dimers*. in *Material Science and Engineering Congress*. 2020. Darmstadt, Germany: Deutsche Gesellschaft für Materialkunde e.V.

12. Berghian-Grosan, C. and D.A. Magdas, *Raman spectroscopy and machine-learning for edible oils evaluation.* Talanta, 2020. **218**: p. 121176.

13. LeCun, Y., Y. Bengio, and G. Hinton, *Deep learning.* Nature, 2015. **521**(7553): p. 436-444.

14. Lussier, F., et al., *Deep learning and artificial intelligence methods for Raman and surface-enhanced Raman scattering.* TrAC Trends in Analytical Chemistry, 2020. **124**: p. 115796.

15. Kauwe, S.K., et al., *Can machine learning find extraordinary materials?* Computational Materials Science, 2020. **174**: p. 109498.

16. Sevetlidis, V. and G. Pavlidis, *Effective Raman spectra identification with tree-based methods.* Journal of Cultural Heritage, 2019. **37**: p. 121-128.

17. Farajnezhad, A., et al., *Correlation of interaction parameters in Wilson, NRTL and UNIQUAC models using theoretical methods.* Fluid Phase Equilibria, 2016. **417**: p. 181-186.

18. Ejraei, A., et al., *Lower and upper critical solution temperatures of binary polymeric solutions.* Fluid Phase Equilibria, 2016. **425**: p. 465-484.

19. Asgarpour Khansary, M., et al., *Representing solute solubility in supercritical carbon dioxide: A novel empirical model.* Chemical Engineering Research and Design, 2015. **93**: p. 355-365.

20. Asgarpour Khansary, M. and M.A. Aroon, *On the consistency and correctness of thermodynamics phase equilibria modeling and correlation reports published in Fuel journal.* Fuel, 2015. **140**: p. 810-811.

21. Khansary, M.A. and M.A. Aroon, *Reply to the comments “On the consistency and correctness of thermodynamics phase equilibria modeling and correlation reports published in Fuel journal”.* Fuel, 2015. **142**: p. 306-307.

22. Asgarpour Khansary, M. and A. Hallaji Sani, *Using genetic algorithm (GA) and particle swarm optimization (PSO) methods for determination of interaction parameters in multicomponent systems of liquid–liquid equilibria.* Fluid Phase Equilibria, 2014. **365**: p. 141-145.

23. Asgarpour Khansary, M., et al., *A molecular scale analysis of TEMPO-oxidation of native cellulose molecules.* Heliyon, 2020. **6**(12).

24. Asgarpour Khansary, M., M.A. Aroon, and S. Shirazian, *Physical adsorption of CO2 in biomass at atmospheric pressure and ambient temperature.* Environmental Chemistry Letters, 2020. **18**(4): p. 1423-1431.

25. Asgarpour Khansary, M., G. Walker, and S. Shirazian, *Incomplete cocrystalization of ibuprofen and nicotinamide and its interplay with formation of ibuprofen dimer and/or nicotinamide dimer: A thermodynamic analysis based on DFT data.* Int J Pharm, 2020. **591**: p. 119992.

26. Khansary, M.A., A. Marjani, and S. Shirazian, *On the search of rigorous thermo-kinetic model for wet phase inversion technique.* Journal of Membrane Science, 2017. **538**: p. 18-33.

27. Ivakhnenko, A.G., *Polynomial Theory of Complex Systems.* IEEE Transactions on Systems, Man, and Cybernetics, 1971. **1**(4): p. 364-378.

28. Khansary, M.A., A.H. Sani, and S. Shirazian, *Mathematical-thermodynamic solubility model developed by the application of discrete Volterra functional series theory.* Fluid Phase Equilibria, 2015. **385**: p. 205-211.

29. Brinck, T. and J.H. Stenlid, *The Molecular Surface Property Approach: A Guide to Chemical Interactions in Chemistry, Medicine, and Material Science.* Advanced Theory and Simulations, 2019. **2**(1).

30. Hirshfeld, F.L., *Bonded-atom fragments for describing molecular charge densities.* Theoretica chimica acta, 1977. **44**(2): p. 129-138.

31. Porezag, D. and M.R. Pederson, *Infrared intensities and Raman-scattering activities within density-functional theory.* Physical Review B, 1996. **54**(11): p. 7830-7836.

32. Perdew, J.P., K. Burke, and M. Ernzerhof, *Generalized Gradient Approximation Made Simple.* Physical Review Letters, 1996. **77**(18): p. 3865-3868.

33. Zhou, Y., et al., *Effect of a Hydrogen Bond on Molecular Probing Properties in the Solvent.* J Phys Chem A, 2020. **124**(3): p. 520-528.

34. Klamt, A., *COSMO-RS From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design*. 2005: Elsevier

35. Ghasemi, A., et al., *Using quantum chemical modeling and calculations for evaluation of cellulose potential for estrogen micropollutants removal from water effluents.* Chemosphere, 2017. **178**: p. 411-423.

36. Rabuck, A.D. and G.E. Scuseria, *Improving self-consistent field convergence by varying occupation numbers.* The Journal of Chemical Physics, 1999. **110**(2): p. 695-700.

37. Pulay, P., *Improved SCF convergence acceleration.* Journal of Computational Chemistry, 1982. **3**(4): p. 556-560.

38. Leavens, C.R., *Effect of thermal smearing on the electron-phonon spectral function obtained by inversion of normal metal tunneling data.* Solid State Communications, 1985. **54**(7): p. 625-628.

39. Delley, B., *An all‐electron numerical method for solving the local density functional for polyatomic molecules.* The Journal of Chemical Physics, 1990. **92**(1): p. 508-517.

40. Karezani, E., A. Hallajisani, and M. Asgarpour Khansary, *A quantum mechanics/molecular mechanics (QM/MM) investigation on the mechanism of adsorptive removal of heavy metal ions by lignin: single and competitive ion adsorption.* Cellulose, 2017. **24**(8): p. 3131-3143.

41. Strang, G., *Linear Algebra and Its Applications*. 2006: Thomson, Brooks/Cole.

42. Karimi-Jafari, M., et al., *Impact of polymeric excipient on cocrystal formation via hot-melt extrusion and subsequent downstream processing.* Int J Pharm, 2019. **566**: p. 745-755.

43. Lazarević, J.J., et al., *Intermolecular and low-frequency intramolecular Raman scattering study of racemic ibuprofen.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2014. **126**: p. 301-305.

44. Vueba, M.L., M.E. Pina, and L.A. Batista de Carvalho, *Conformational stability of ibuprofen: assessed by DFT calculations and optical vibrational spectroscopy.* J Pharm Sci, 2008. **97**(2): p. 845-59.

45. Jubert, A., et al., *Vibrational and theoretical studies of non-steroidal anti-inflammatory drugs Ibuprofen [2-(4-isobutylphenyl)propionic acid]; Naproxen [6-methoxy-α-methyl-2-naphthalene acetic acid] and Tolmetin acids [1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid].* Journal of Molecular Structure, 2006. **783**(1-3): p. 34-51.

46. Rossi, B., et al., *Vibrational properties of ibuprofen–cyclodextrin inclusion complexes investigated by Raman scattering and numerical simulation.* Journal of Raman Spectroscopy, 2009. **40**(4): p. 453-458.

47. Soares, F.L. and R.L. Carneiro, *Evaluation of analytical tools and multivariate methods for quantification of co-former crystals in ibuprofen-nicotinamide co-crystals.* J Pharm Biomed Anal, 2014. **89**: p. 166-75.

48. Oberoi, L.M., K.S. Alexander, and A.T. Riga, *Study of interaction between ibuprofen and nicotinamide using differential scanning calorimetry, spectroscopy, and microscopy and formulation of a fast-acting and possibly better ibuprofen suspension for osteoarthritis patients.* J Pharm Sci, 2005. **94**(1): p. 93-101.

49. Hédoux, A., et al., *Raman spectroscopy of racemic ibuprofen: Evidence of molecular disorder in phase II.* International Journal of Pharmaceutics, 2011. **421**(1): p. 45-52.

50. Ramalingam, S., et al., *FT-IR and FT-Raman vibrational spectra and molecular structure investigation of nicotinamide: A combined experimental and theoretical study.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2010. **75**(5): p. 1552-1558.

51. Jaworska, A., et al., *Nicotinamide and trigonelline studied with surface-enhanced FT-Raman spectroscopy.* Vibrational Spectroscopy, 2012. **63**: p. 469-476.

52. Sallum, L.F., et al., *Optimization of SERS scattering by Ag-NPs-coated filter paper for quantification of nicotinamide in a cosmetic formulation.* Talanta, 2014. **118**: p. 353-8.

53. Chernyshov, I.Y., I.V. Ananyev, and E.A. Pidko, *Revisiting van der Waals Radii: From Comprehensive Structural Analysis to Knowledge-Based Classification of Interatomic Contacts.* Chemphyschem, 2020. **21**(5): p. 370-376.

54. Mantina, M., et al., *Consistent van der Waals radii for the whole main group.* J Phys Chem A, 2009. **113**(19): p. 5806-12.