High pressure effect on internal structure and atomic dynamics of pharmaceutical compounds

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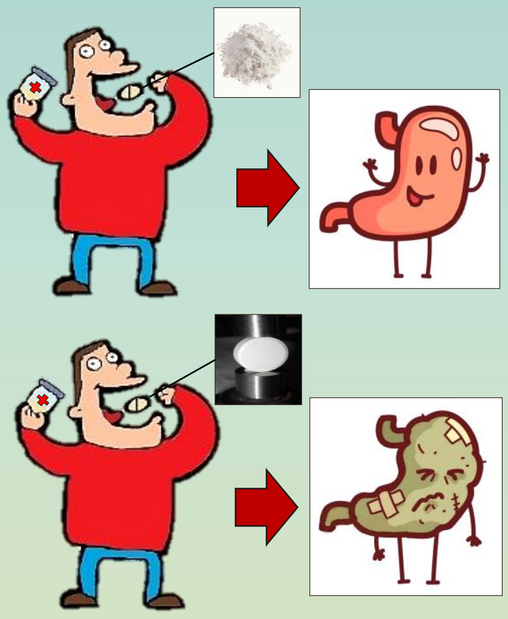
Study of the properties of pharmaceutical compounds

The study of pressure-induced changes in the crystal structure and atomic dynamics **in complex molecular crystals** is **an urgent task** of condensed matter physics and organic chemistry.

This is due to many **unique physical phenomena** realized in **organic crystals at high pressure:** polymorphic phase transitions, reorientation phenomena in molecular crystals, amorphization. All these phenomena are closely related to the complex geometry of the hydrogen bond, its anisotropic nature of compression at high pressure.

It should be noted that **structural studies of molecular crystals are extremely important for optimizing the process of pharmacological production**, where complex molecular components under additional mechanical influences (grinding or tableting) in the initial substance may develop **irreversible polymorphic phase transitions** or **amorphization**, which may lead to **significant changes** in the physical, chemical and pharmaceutical properties of **the pharmacological material.**

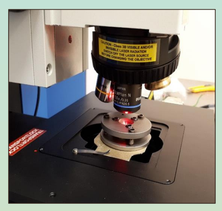


The harm of irreversible phase transition of pharmaceutical compound developed under high pressure

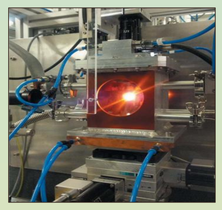
Experimental techniques

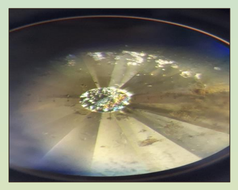
The effect of high pressure simulates the processes of mechanical and chemical effects on pharmacological compounds, and is also a controlled method of changing the balance of interatomic interactions of a molecular crystal, the mutual orientation of molecules, and the geometry of hydrogen bonds. Structural studies at high pressure allows us to determine the prerequisites and mechanisms for the development of polymorphic phase transitions, a unique phenomenon of amorphization of complex molecular crystals of pharmacological purpose at the atomic or microstructural level.

To perform these tasks, detailed structural studies of a wide class of organic crystals were performed under the influence of high pressures and temperatures using X-ray diffraction and Raman spectroscopy.



Researches at LabRAM spectrometer Horiba, FLNP JINR (Dubna, Russia)

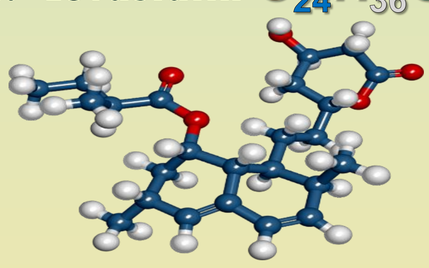


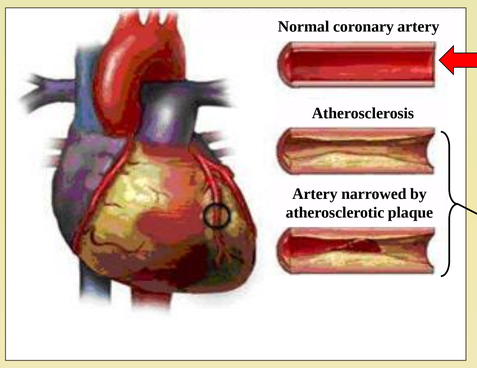


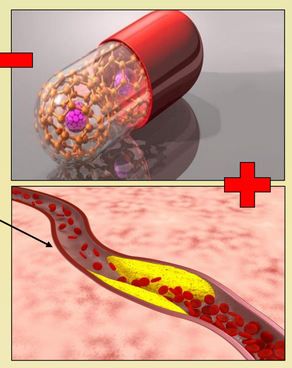
Researches at the Extreme Conditions Beamline (ECB) P02.2, PETRA-III DESY (Hamburg, Germany)

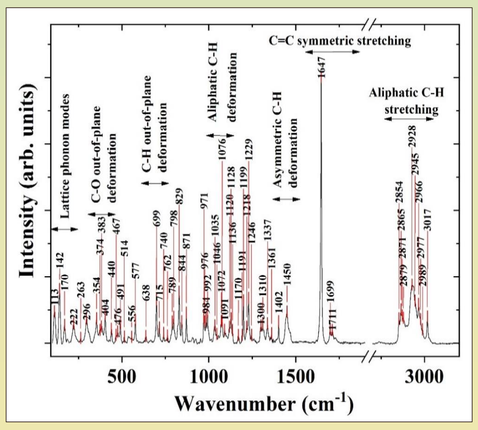
Experimental results

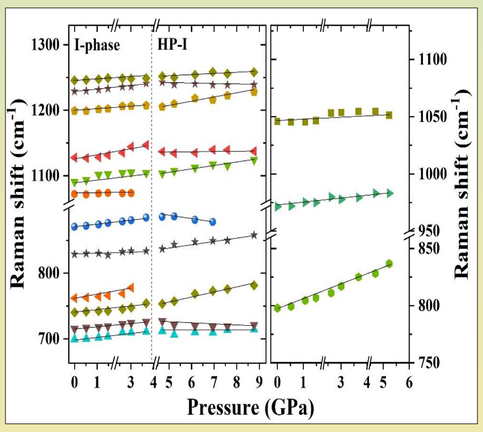
I. Lovastatin $C_{24}H_{36}O_5$







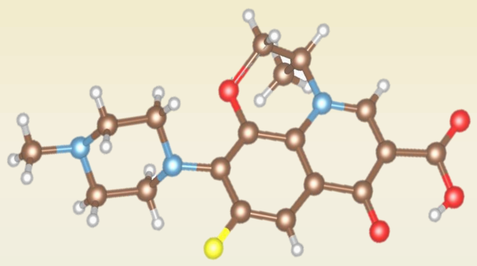




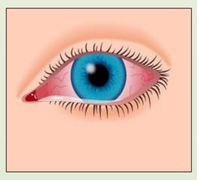
Pressure-induced polymorphic phase transitions and the process of amorphization in a hypolipidemic agent-**lovastatin $C_{24}H_{36}O_5$** were studied. The vibrational spectra of the lovastatin have been studied by means of Raman spectroscopy at pressures up to 11 GPa. Changes in the behavior of Raman lines under high pressure were observed at pressure of 3 and 5.2 GPa. These changes may indicate polymorphic phase transitions of lovastatin under high pressure. At pressures above 10 GPa, a gradual transformation to the amorphous phase was revealed. Around this phase transformation, noticeable anomalies were found in the pressure behavior of various lovastatin vibration modes.

Raman, cm^{-1}	Vibrational modes assignment
113, 142, 170	Lattice phonon modes
222, 263 (vw), 296	CH_3 torsional vibration
354, 374(sh), 383, 404	C-O out-of-plane deformation
404, 440, 467(sh), 476, 491	Aliphatic C-CH_3 stretches/ring deformation/ C-O in-plane deformation
638(w)	O-H out-of-plane deformation
829, 844, 871	Aliphatic C-CH_3 stretches
971, 976(sh), 984, 992	Out-of-plane C-H deformation in *cis*-vinylenes
1035, 1072, 1076	Aliphatic C-H deformation
1120, 1128, 1136, 1170	Coupled C-O stretches
1402, 1450	Asymmetric C-H deformation
1647(s), 1699, 1711	C=C sym stretching in dienes, C=O in esters
2865, 2928(br), 2945(sh), 2966	Aliphatic C-H stretching (sym and asym in CH_2 and CH_3)

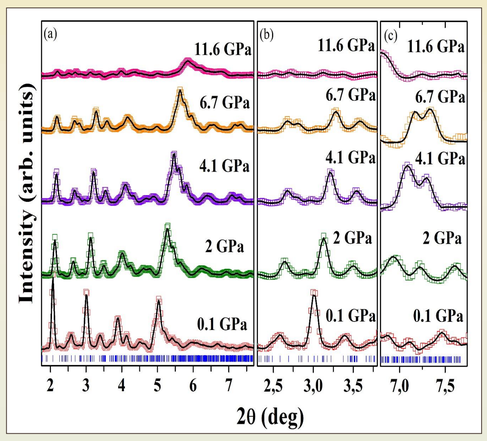
II. Ofloxacin $C_{18}H_{20}FN_3O_4$

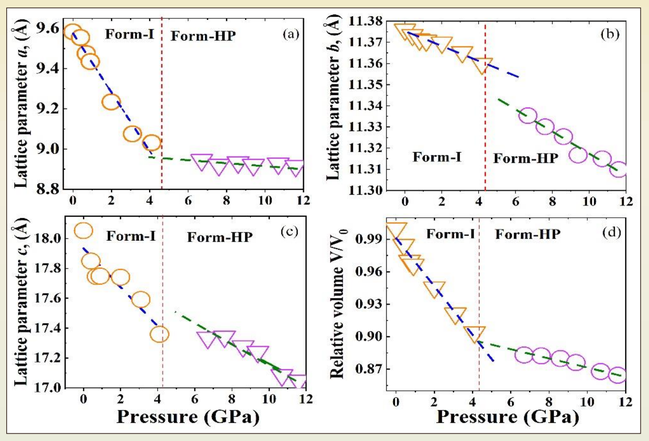


fighting bacterial infections



X-Ray diffraction



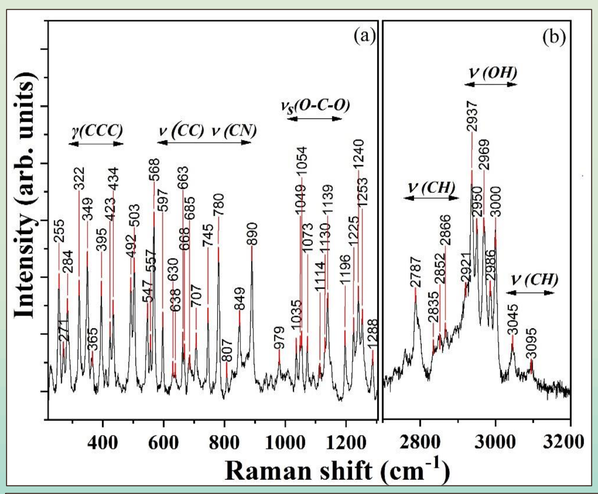


Compressibility coefficients		
Form	Initial form	HP-form
k_a, Å	0.0153(2)	0.0415(1)
k_b, Å	0.0038(4)	0.0047(3)
k_c, Å	0.0073(2)	0.0037(4)
B_0, GPa	32(2)	57(3)

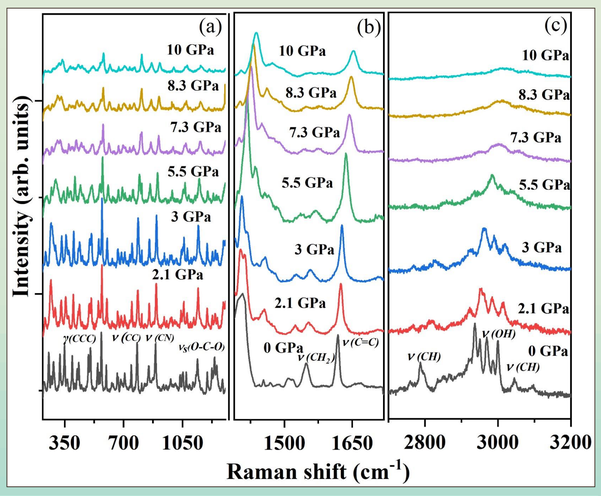
Pressure-induced polymorphic phase transitions in the pharmacological component an effective antibiotic for the treatment of infections - **ofloxacin $C_{18}H_{20}FN_3O_4$** have been studied.

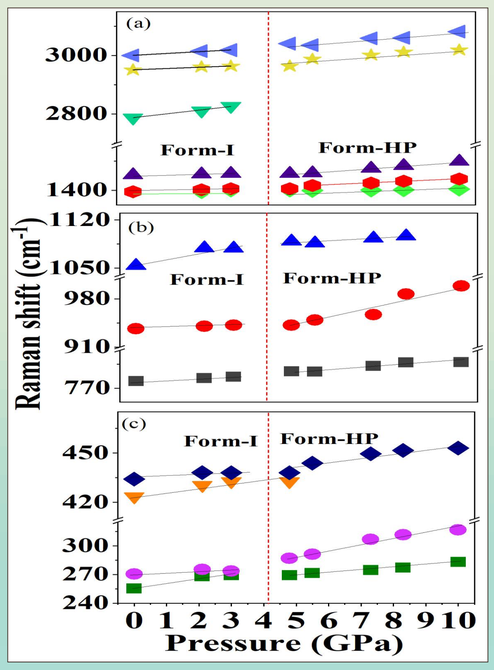
The crystal structure of the ofloxacin have been studied using the **X-ray diffraction** at pressures up to 11.6 GPa. The pressure-driven polymorphic phase transition above 4.1 GPa from the initial monoclinic C2/c form of ofloxacin to monoclinic form-HP with the P2/c symmetry was observed. The phase transition was accompanied by anomalies in pressure dependencies of the lattice parameters, unit cell volume, interatomic angles and distances.

Raman Spectroscopy



Raman, cm^{-1}	Vibrational modes assignment
434, 452	γ(CCC) out-of-plane deformations
550, 785, 1051, 1401	CC, CN stretching vibrations from A and B rings
1250	υ_s O-C-O
1387, 1400	the bending vibration of OH group
1453, 1469, 1486	υ CH bending vibrations
2786	υ (CH) stretching vibration of N–CH_3
2968, 2985	and antisymmetric stretching vibrations
3043	υ(CH) stretching vibration





The vibrational spectra of the **ofloxacin** have been studied by means of **Raman spectroscopy** at pressures up to 10.1 GPa. The pressure-driven polymorphic phase transition above 4.1 GPa from the initial form of ofloxacin to form-HP found in **X-ray diffraction results was proved by Raman spectroscopy**. The phase transition was accompanied by anomalies in vibration modes. Changes in the behavior of Raman lines under high pressure were observed at pressure of 4.1 GPa. These changes may indicate polymorphic phase transitions of ofloxacin under high pressure.

At pressures above 8.8 GPa, a gradual transformation to the amorphous phase was revealed. Around this transformation, noticeable anomalies were found in the pressure behavior of various ofloxacine vibration modes.

Kichanov, S.E., Belozerova, N.M., Dyussembekova, et al., "The pressure-induced changes of crystal structure and vibrational spectra of ofloxacin", Journal of Molecular Structure (2021). [under revision]