# Experimental Report



**Proposal:** **7-04-117** **Council:** 4/2012

**Title:** QENS study of methyl group dynamics in temazepam and inclusion complex of beta-cyclodextrin with temazepam

**This proposal is resubmission of: 7-04-107**

**Researh Area:** Physics

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**Samples:** beta-cyclodextrin/(C7H10O5)x7
temazepam + beta-cyklodextrin - complex
temazepam/C16H13ClN2O2

| Instrument | Req. Days | All. Days | From | To |
|---|---|---|---|---|
| IN6 | 0 | 4 | 21/11/2012 | 27/11/2012 |

**Abstract:**

The aim of this project is to investigate in a wide temperature range the dynamics of the methyl group of temazepam (a pharmacological drug) in its inclusion complex with beta-cyclodextrin (beta-CD), as well as in pure temazepam. In the later our 1H NMR experiments reveal the existence of three dynamically inequivalent methyl groups. One could expect that the inequivalence will disappear when temazepam is located in beta-CD cavity, but 1H NMR experiments indicate that the situation is not that simple. A QENS experiment will help in understanding better the ambiguous NMR data. Comparing the methyl groups dynamics in temazepam and in its inclusion complex with beta-CD we will establish the importance of “host-guest” interactions in this complex.

Experiment 7-04-117

The subject of our study are complexes of pharmaceutical active compounds in a bulk form and their inclusion complex with βCD.

QENS spectra were taken for temazepam, felodipine, β-cyclodextrin (b-CD), physical mixture of β-CD and felodipine and for the complex β-CD with felodipine. For temazepam QENS spectra were measured at 150 K, 300 K, felodipine: 150 K, 200K, 250K and 300K; β-CD: 150K and 300K, physical mixture 300K and complex: 150K, 200K, 250K and 300K. The measurements were performed on the time-of-flight IN6 spectrometer using an incident wavelength of 5.12 Å and with an energy resolution of 70 μeV (FWHM). The Q-range covered 0.2 – 1.96 $Å^{-1}$. The samples were placed in an aluminium flat slab holder of size 4 x 3 $cm^2$ and having thicknesses chosen to ensure that the transmission coefficient is between 0.85 and 0.9 (m = 0.53 g, m = 0.76g, m=0.90 g, m=0.82g, m=0.60 g for temazepam, felodipine, bCD, physical mixture and complex respectively). The data were treated in a standard way with the program LAMP (normalisation to vanadium, correction for detector efficiency, subtraction of empty cell, absorption correction). The individual S(Q,ω) spectra were fitted assuming a simple model consisting of a δ function of intensity $A_0$ (which accounts for the elastic part of the scattering) and a lorentzian function of intensity 1-$A_0$ and a width $\tau^{-1}$ (proportional to the correlation time) convoluted with the experimental resolution function (the Gaussian function).

The different crystallographic environments of each of the three temazepam molecules in the asymmetric unit induce the dynamic inequivalence of their methyl groups. Analysis of EISF for temazepam shows that at 150K we observe the reorientation of one methyl group with an activation energy of about 5 kJ/mol. Two other groups enter in the time-window of IN6 window at 300K. As molecule of felodipine contains four methyl groups we compared experimental EISF with models assuming 1,2,3 or 4 methyl groups can reorient. The experimental points are best described by the model of reorientations of two methyl groups. Above results for temazepam and felodipine are in a good agreement with our NMR data.

We are currently trying to develop an adequate model able to correctly describe the reorientation in βCD and in inclusion complex drug – βCD.