# Advanced ssNMR techniques to study of specific pharmaceutical materials based on solid solutions and dispersions of active ingredients in polymer matrix

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## Introduction

In many clinical studies it has already been demonstrated that higher efficiency of APIs (active pharmaceutical ingredients) significantly reduces menace of many diseases. API has higher efficiency when has good bioavailability and that is good solubility in human fluids and good permeability in gastrointestinal tract (GIT). Based on this pharmacokinetical properties of API Food and Drug Administration (FDA) created The Biopharmaceutical Classification System (BCS). BCS is based on aqueous solubility and intestinal permeability of the drug substance in human. It classifies API into one of four classes.

### The Biopharmaceutical Classification System (BCS)

| PERMEABILITY \ SOLUBILITY | LOW | HIGH |
|---|---|---|
| HIGH | **Class 2** lipophilic: simvastatin, atorvastatin | **Class 1** amfifilic: pravastatin, losartan |
| LOW | **Class 4** problematic: acyklovir, furosemid | **Class 3** hydrophilic: gabapentin, valcyklovir |

**The highly soluble API** – when the highest oral dose is soluble in ≤ 250 ml of aqueous media over the pH range of 1.2 to 6.8. **The highly permeable API** – when the highest oral dose is absorb of > 90% in GIT.

Unfortunately a lot of pharmaceutical substances (especially classes 2. and 4., 40 – 60% of world production of drugs) exhibit low bioavailability and solubility in water. That is why current **pharmaceutical research focuses on increasing solubility and thus also bioavailability** of these substances.

### API-polymer systems

In our work we focussed our attention on the study of structural properties of APIs in the prepared **solid polymer dispersions, solutions and co-crystals** exhibiting increased solubility. Nowadays we are testing properties of acetylsalicylic acid (AcSalAc) as an API system with relatively low solubility. One of several procedures of creating bioavailable system – lyofilization (lyo), was used to combine this API with polymeric nontoxic water soluble matrix – polyvinylpyrrolidon(PVP), poly[N-(2-hydroxypropyl)metacrylamide] (HPMA), poly(2-ethyl-2-oxazoline) (PEO) and polyethylene glycol (PEG). The polymers were used with different molecular weight. As a solvents of this API-polymer system were used nontoxic and biodegradable compounds, which solubilize API and polymer matrix as water, ethanol and tert-butanol (T-but).

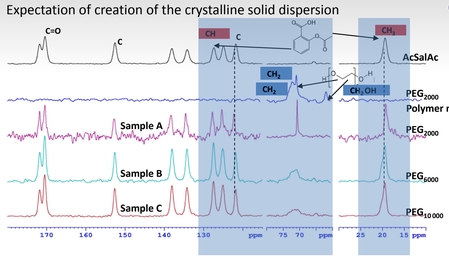
**Samples of API-polymer system:**

**Sample A**: AcSalAc/ T-but, 30 % + $PEG_{2000}$/ T-but, 70 %
**Sample B**: AcSalAc/ T-but, 30 % + $PEG_{6000}$/ T-but, 70 %
**Sample C**: AcSalAc/ T-but, 30 % + $PEG_{10\,000}$/ T-but, 70 %
**Sample D**: AcSalAc/ T-but, 30 % + $PVP_{7600}$/ T-but, 70 %
**Sample E**: AcSalAc/ T-but, 30 % + $PVP_{40\,000}$/ T-but, 70 %
**Sample F**: AcSalAc/ T-but, 30 % + $PVP_{930\,000}$/ T-but, 70%
**Sample G**: AcSalAc/ T-but, 30 % + $PEO_{50000}$/ water, 70 %
**Sample H**: AcSalAc/ T-but, 30 % + $HPMA_{18500}$/ water, 70 %
**Sample I**: AcSalAc/ T-but, 30 % + $HPMA_{54000}$/water, 70 %
**Sample J**: AcSalAc/ T-but, 30 % + $HPMA_{81000}$/ water, 70 %

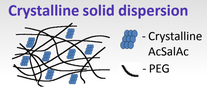
## Results

### $^{13}$C CP/MAS NMR

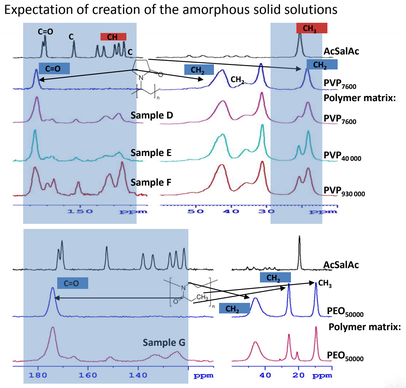
Expectation of creation of the crystalline solid dispersion



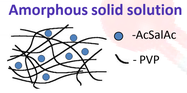

Crystalline solid dispersion



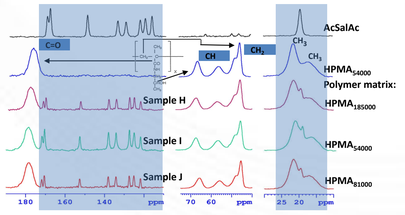

Expectation of creation of the amorphous solid solutions



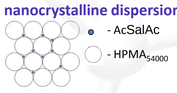

Amorphous solid solution



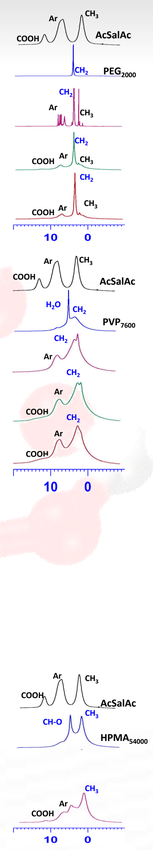

Expectation of creation of the interstitial nanocrystalline dispersion



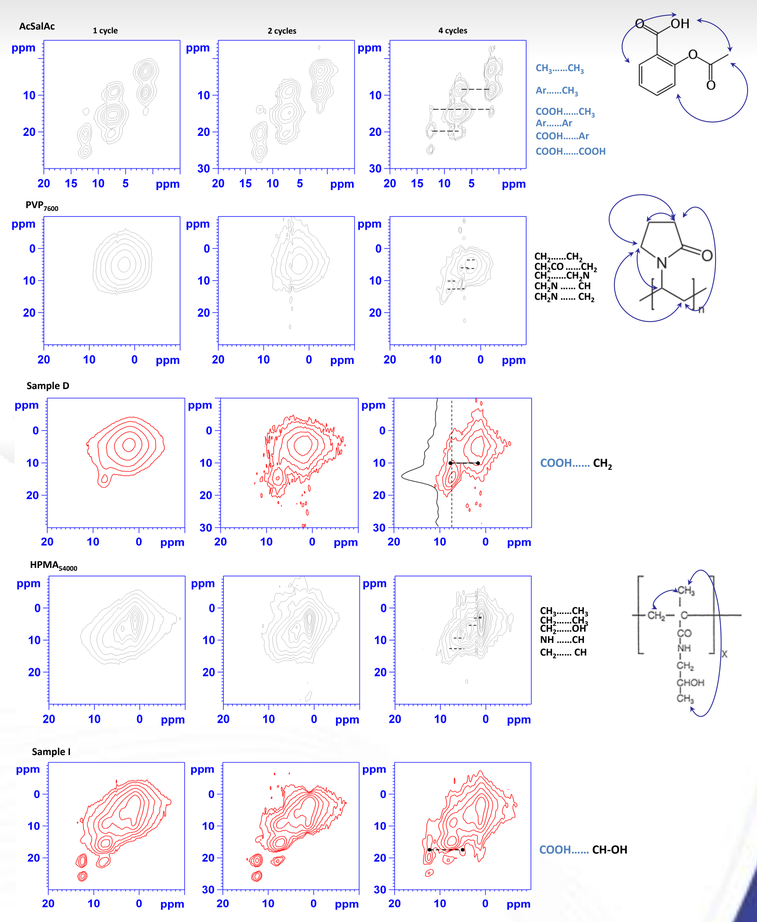

Interstitial nanocrystalline dispersion




### $^{1}$H MAS NMR




### $^{1}$H-$^{1}$H BABA DQ/MAS NMR




### Relaxation experiments of samples and particular components

**Expectation of creation of the crystalline solid dispersion**

| | CH | $CH_3$ | $CH_2$ | $CH_2$ |
|---|---|---|---|---|
| **Sample A** $T_{1\rho}$ ($^1$H) [ms] | 670 | 270 | 0.400 | 0.550 |
| $T_1$ ($^1$H) [s] | 28.4 | 29.9 | 2.5 | 3 |
| **Sample B** $T_{1\rho}$ ($^1$H) [ms] | 667 | 272 | 0.351 | 0.570 |
| $T_1$ ($^1$H) [s] | 24.6 | 26 | 2.7 | 3.4 |
| **Sample C** $T_{1\rho}$ ($^1$H) [ms] | 662 | 660 | 0.262 | 0.723 |
| $T_1$ ($^1$H) [s] | 20.9 | 22.9 | 4.5 | 3.7 |

the domain size of systems is ≈ 100nm

**Expectation of creation of the amorphous solid solutions**

| | CH | $CH_3$ | C=O | $CH_2$ | $CH_2$ |
|---|---|---|---|---|---|
| **Sample D** $T_{1\rho}$ ($^1$H) [ms] | 6 | 7 | 7 | 7 | 7 |
| $T_1$ ($^1$H) [s] | 3.5 | 2.9 | 2.9 | 3 | 3 |
| **Sample E** $T_{1\rho}$ ($^1$H) [ms] | 8 | 8 | 8 | 8.8 | 8.7 |
| $T_1$ ($^1$H) [s] | 3.7 | 3.7 | 3.6 | 3.6 | 3.7 |
| **Sample F** $T_{1\rho}$ ($^1$H) [ms] | 9 | 8.6 | 5 | 9 | 9.5 |
| $T_1$ ($^1$H) [s] | 5.9 | 4 | 4 | 4.5 | 4 |

the domain size of systems is < 10nm

| | CH | $CH_3$ | C=O | $CH_2$ | $CH_2$ | $CH_3$ |
|---|---|---|---|---|---|---|
| **Sample G** $T_1$ ($^1$H) [s] | 3.3 | 2.6 | 2.9 | 3.4 | 3.3 | 3.9 |

**Polymeric matrix systems**

| $PEG_{2000}$ | $CH_2$ | $CH_2$ |
|---|---|---|
| $T_{1\rho}$ ($^1$H) [ms] | 0.300 | 0.450 |
| $T_1$ ($^1$H) [s] | 2.2 | 2.3 |

| $PVP_{7600}$ | C=O | $CH_2$ | $CH_2$ |
|---|---|---|---|
| $T_{1\rho}$ ($^1$H) [ms] | 9.3 | 9.5 | 10.4 |
| $T_1$ ($^1$H) [s] | 2.8 | 2.8 | 3.4 |

| $PEO_{50000}$ | C=O | $CH_2$ | $CH_2$ | $CH_3$ |
|---|---|---|---|---|
| $T_1$ ($^1$H) [s] | 2. 8 | 2.7 | 2.6 | 2.7 |

**Expectation of creation of the interstitial nanocrystalline dispersion**

| | CH | $CH_3$ | C=O | $CH_2$ | $CH_2$ |
|---|---|---|---|---|---|
| **Sample H** $T_1$ ($^1$H) [s] | 38 | 1.9 | 0.9 | 0.9 | 1 |
| **Sample I** $T_{1\rho}$ ($^1$H) [ms] | 500 | 480 | 3.8 | 4 | 4 |
| $T_1$ ($^1$H) [s] | 13 | 14 | 1 | 1 | 1 |
| **Sample J** $T_1$ ($^1$H) [s] | 28 | 1.9 | 1 | 1 | 1 |

the domain size of system is 10-100nm

| $HPMA_{54\,000}$ | C=O | CH | $CH_2$ |
|---|---|---|---|
| $T_{1\rho}$ ($^1$H) [ms] | 5.6 | 5.6 | 5.5 |
| $T_1$ ($^1$H) [s] | 1 | 1 | 1 |

**Crystalline API system**

| AcSalAc | CH | $CH_3$ |
|---|---|---|
| $T_{1\rho}$ ($^1$H) [ms] | 377 | 236 |
| $T_1$ ($^1$H) [s] | 59 | 57 |

The creation of homogeneous solid dispersions, consisting of AcSalAc dispersed in various polymer matrixes, is confirmed by the identical value of $T_{1\rho}$ ($^1$H) relaxation. The AcSalAc molecule adopted high frequency motion of polymer in measured samples of the solid dispersions (short $T_1$ ($^1$H)).

## Conclusion

The API-polymeric systems of acetylsalicylic acid (API) in combination with PEG, PVP, PEO or HPMA (polymeric matrix) were prepared by lyofilization. The polymers were used with different molecular weight. The structural reason observed in polymer–drug interaction were probed by a wide range of $^{13}$C CP/MAS NMR, $^{1}$H MAS NMR, $^{1}$H DQ-BABA and relaxation experiments. It was confirmed that lyophilization of the solutions consisting of AcSalAc (30%)/ T-but with PVP (70%)/ T-but or PEO (70%)/water leads to the formation of the required amorphous solid solutions, the solution consisting of AcSalAc (30%)/ T-but with HPMA (70%)/ water leads to the formation of the interstitial nanocrystalline dispersion and the solution consisting of AcSalAc (30%)/ T-but with PEG (70%)/ T-but leads to the formation of the crystalline solid dispersion. This statement follows from dramatic broadening of NMR signals of AcSalAc in $^{13}$C CP/MAS NMR spectrum and changes in $^{1}$H $T_1$ relaxation times. In dispersions with PEG the new signal of the $CH_3$ group is observed. The decrease in value of the $T_1$ ($^1$H) relaxation times of the AcSalAc in samples confirms molecular mixing API with polymer. The correlation between API and polymer matrix in samples D, I is shown in the $^{1}$H DQ-BABA experiments. We managed to prepare API-polymeric systems with expectation of creation of the amorphous solid solutions and solid dispersions. This and other systems will be subject of the incoming studies by advanced ssNMR experiments, Raman spectroscopy, dissolution profile…

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