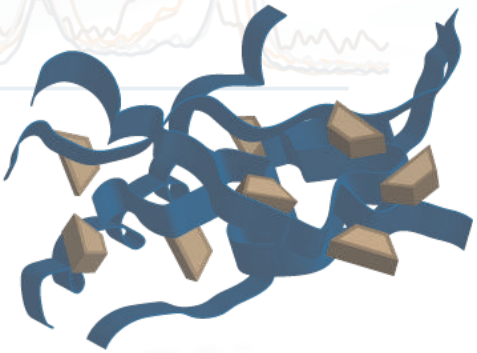
Joint Laboratory of Solid-State NMR
IMC AS CR and JHIPC AS CR

5.
Workshop on Solid-State NMR and Computational Methods



5. prosince 2011, Praha

Ústav makromolekulární chemie AV ČR, v.v.i.
Heyrovského nám. 2
162 06 Praha 6

Společná laboratoř NMR spektroskopie pevného stavu
ÚMCH AV ČR, v.v.i. a ÚJH AV ČR, v.v.i.

pořádají

dne 5.12.2011

v

klubu B
Ústavu Makromolekulární chemie AV ČR, v.v.i.
Heyrovského nám. 2, Praha 6

5.workshop NMR pevného stavu a souvisejících výpočtových metod

v rámci projektu

NMR krystalografie aktivních farmaceutických substancí pro průmyslové aplikace
(NPV II – ZDRAVÝ A KVALITNÍ ŽIVOT, č.p. 2B08021)

řešitelských pracovišť

ÚMCH AV ČR, VŠCHT Praha

pod patronací vedoucích řešitelských týmů

Ing. Jiřího Bruse PhD a prof. RNDr. Bohumila Kratochvíla, Dsc

Bližší informace o projektu naleznete
http://www.imc.cas.cz/nmr/projekt/projekt.htm

Výsledky prezentované na tomto workshopu a celý tento workshop se mohl uskutečnit díky podpoře Ministerstva školství, mládeže a tělovýchovy České republiky - výzkumný program 2B08021

Program

9:15	*zahájení*
9:30 - 10:15	**Brus Jiří** *ÚMCH AV ČR* NMR krystalografie komplexu: Na[3-cobalt(**III**) bis(1,2-dicarbollide)]-poly(ethylen oxid)
10:15 - 10:45	**Urbanová Martina** *ÚMCH AV ČR* Polymorfismus aktivních farmaceutických ingrediencí, 13C CP/MAS NMR, 19F MAS NMR a faktorová analýza
10:45 - 11:00	*přestávka na kávu*
11:00 - 11:30	**Kobera Libor** *ÚMCH AV ČR* Strukturní analýza borových farmaceutických substancí pomocí NMR spektroskopie pevného stavu
11:30 - 12:00	**Policianová Olívia** *ÚMCH AV ČR* ssNMR charakterizácia farmaceutických disperzných systémov API-polymér s predpokladom zvýšenia biodostupnosti málorozpustných liečiv
12:00 - 13:00	*oběd*
13:00 - 13:30	**Starovoytová Larysa** *ÚMCH AV ČR* Vliv příměsí na mechanismy formování polymerních globulí
13:30 - 14:00	**Svobodová Jana** *ÚMCH AV ČR* NMR spektroskopie peptidů v roztoku
14:00 - 14:30	*přestávka na kávu*
14:30 - 15:00	**Spěváček Jiří** *ÚMCH AV ČR* Studium fázového přechodu klubko-globule ve vodných roztocích poly(n-vinylkaprolaktamu) a směsí poly(n-vinylkaprolaktam)/poly(n-isopropylmethakrylamid) NMR metodami
15:00 - 15:30	**Kříž Jaroslav** *ÚMCH AV ČR* MR studie preasociačních stavů blokového kopolymeru PEO-PPO-PEO a jejich interakce s částečně hydrofobními látkami
15:30	*zakončení*
16:00	*neformální diskuse*

Abstrakta P1

NMR krystalografie komplexu: Na[3-cobalt(III) bis(1,2-dicarbollide)]-poly(ethylen oxid)

J. Brus

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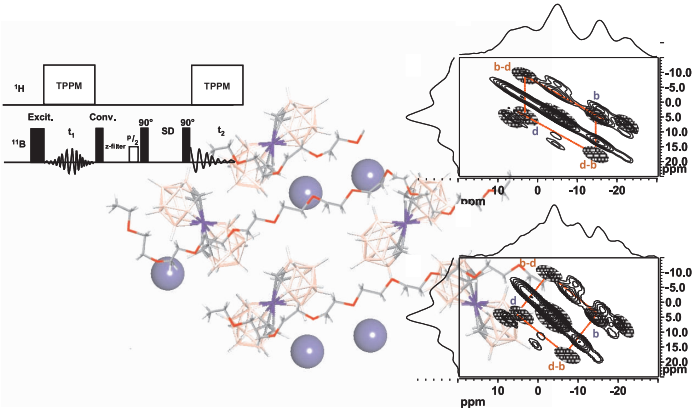
Recently we have tried to apply the concept of NMR crystallography (that was originally designed to describe the structure of powdered microcrystalline systems) on partially ordered nanostructured polymeric composites. In this respect a wide range of multidimensional multinuclear and multiple-quantum ss-NMR experiments combined with the refinement of WAXS patterns was applied. Complete 3D structure of the polymer composite poly(ethylene oxide)-[3-cobalt(III) bis(1,2-dicarbollide)](-1) (PEO-NaCoD) was finally refined [1]. In general, the investigated polymer composite provides an interesting example of systems comprising both one-half spins (1H, 13C) and half-integer spins (11B, 23Na), in which highly ordered molecular arrangement coexists with the high-amplitude molecular-level motion (5-fold jumps of carboran clusters and 30-degree libration of PEO segments). The CoD-clusters are uniformly and molecularly dispersed within the PEO matrix. Metallacarborane anions freely rotate along the B10-B10` axis. The polymeric matrix does not contain crystalline domains typical for pure high-molecular weight PEO. There are two types of PEO segments. The first one is involved in dihydrogen bonding with boron clusters, and the second one forms the complex with sodium ions. All the cations are uniformly organized within the composite. They are effectively separated from CoD-anions and immobilized by PEO chains. This example thus demonstrates that the concept of NMR crystallography can be applied not only on highly crystalline small-size or medium-size organic substances, such as pharmaceutical solids, but also on the nanostructured polymer systems exhibiting relatively high-amplitude motions. On the other hand, this example shows certain limitations following from relatively low resolution of ss-NMR experiments in 1H dimension. This fact suggests the application of heteronuclear X-Y correlation experiments involving 13C, 11B and 23Na. The experiments providing measurements of 11B-13C(23Na,11B) heteronuclear dipolar contacts, however, require extensive validation and optimization. Preliminary results of this effort are also presented



[1] P. Matejicek, J. Brus, A. Jigounov, J. Plestil, M. Uchman, K. Prochazka, M. Gradzielski, Macromolecules 2011 DOI:10.1021/ma200502t

Abstrakta P2

Polymorfismus aktivních farmaceutických ingrediencí, 13C CP/MAS NMR, 19F MAS NMR a faktorová analýza

Martina Urbanova, Jiri Brus, Olivia Policianova, Libor Kobera

Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Heyrovsky sq. 2, 162 06 Prague 6, Czech Republic

1) Current pharmaceutical research encounters with the problem of low solubility of many active ingredients (APIs). To overcome this limitation the poorly water-soluble drugs are formulated as solid dispersions in matrices of hydrophilic polymers. In these new dosage formulations, besides the notoriously discussed polymorphism and a bit mysterious pseudopolyamorphism, precise structural characterization of APIs is complicated by their interactions with macromolecules of excipients. In this presentation a time-saving method for identification of various forms of pharmaceutical substances in solid polymer dispersions is introduced. The method is demonstrated on a moderately-sized active pharmaceutical ingredient (Atorvastatin, C33H35FN2O5) exhibiting extensive polymorphism and pseudopolyamorphism. The API was incorporated in the matrix of polvinylpyrrolidone (PVP) forming uniformly dispersed nanosized domains. Size of domains, approximately tens of nanometers, was estimated by measuring T1(1H) and T1 (1H) relaxation times. The proposed strategy of structural characterization of the API in PVP is based on the processing of the 19F MAS NMR spectra of various polymeric formulations by multivariate analysis (singular value decomposition algorithm). It was found out that molecular arrangement of APIs in the nanosized domains dispersed in polymer matrices is affected by the interactions with neighboring macromolecules and new non-crystalline forms of the API are created. It is demonstrated, that 19F MAS NMR spectra reflect the changes in the extent of interactions with polymer matrix, and by using factor analysis the different non-crystalline modifications of the API in solid polymeric dispersions can be distinguished and identified. On the other hand, extreme attention must be paid to correctly assess the impact of electrostatic forces or differences in magnetic susceptibility of the polymer matrix on the pattern of 19F MAS NMR spectra of the API. Dramatic changes in 19F MAS NMR spectra of well-defined forms of the API induced by different filler compounds were observed. The factor analysis of the recorded spectra, however, can eliminate and separate these effects. Consequently the subtle structural differences in the molecular arrangement of the API in the nanosized domains dispersed in polymer matrices can be traced. The proposed strategy thus provides a powerful tool for the analysis of new formulations of fluorinated pharmaceutical substances in polymer matrices.

2) Despite recent advances in solid-state NMR spectroscopy, structural characterization of amorphous and disordered active pharmaceutical ingredients (APIs) is a complex problem that required combination of many experimental approaches. In some cases even small changes in the structure result in significant variation in drug dissolution rate or stability. Exact identification of different solid-state forms and their disordered is crucial to anticipate changes in the performance of the pharmaceutics material. In this paper, we investigated trospium chloride, which has a considerable degree of disorder integrated in the mixture of two very similar forms. The situation is so confusing that it is not even clear whether we can talk about different forms, mixtures of various crystal forms or a single modification with variable extent of molecular disorder. This state indicates slight changes observed in the 13C CP/MAS NMR spectra, which are very difficult interpret. In this context we tried to solve this problem combining 13C CP/MAS NMR data with factor analysis. Only combination of solid-state NMR spectroscopy and factor analysis could be distinguished two crystal forms and more disordered forms of trospium chloride.

Abstrakta P3

Strukturní analýza borových farmaceutických substancí pomocí NMR spektroskopie pevného stavu

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In recently years, boronic acid and organoboron compounds have been used in pharmaceutical industry as enzyme inhibitors, neutron capture agents for cancer therapy or antibody mimics that recognize biologically important saccharides as well as molecular sensor or receptors. Some 20 years ago, simple alkyl or arylboronic acids were used as a serine protease inhibitor. Since then, many boronic acid compounds with an appropriate peptide sequences have been designed and synthesized for the development of more potent and selective inhibitors. Next significant potential of boronic acid compounds lies in the development of feedback controlled delivery systems for insulin because boronic acids compound form reversible complexes with sugars. As a result, boronic acids and related molecules have now evolved as major players in synthetic and medicinal chemistry.
Very important, for finally using as a medicinal product, is precise description of structural homogeneity and purity. Excellent tool for structural analysis is solid state NMR spectroscopy. Organoboronic compounds description is possible by NMR measurements of included nuclei such as 13C, 11B etc. High sensitivity and abundance of boron nucleus is suitable for measurement and consequently analysis of NMR spectra. On the other hand, quadrupolar character of boron nuclei complicates detail analysis. However, the solution provides the MQ/MAS NMR experiment and using of relatively new techniques called biaxial shearing. This combination enhances the spectral resolution and thereby helps correctly analyze and describe structure units. In our contribution we will demonstrate our attempts to structure determination of organoboron compounds by 11B MQ/MAS NMR spectroscopy. In particularly, applications of two-dimensional multiple-quantum experiments with biaxial shearing that provides detail information about local geometry of measured compounds and easier determine their structure arrangement

Abstrakta P4

ssNMR charakterizácia farmaceutických disperzných systémov API-polymér s predpokladom zvýšenia biodostupnosti málorozpustných liečiv

Olívia Policianová

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In this contribution a solid-state NMR study of structure and segmental dynamics of solid dispersions of active pharmaceutical ingredients (API) in polymer matrix is presented. In many clinical studies it has already been demonstrated that higher efficiency of APIs significantly reduces menace of many diseases. API has higher efficiency when has good bioavailability and ultimately good dissolution, solubility in human fluids and good permeability in gastrointestinal tract (GIT). Unfortunately a lot of pharmaceutical substances exhibit low solubility in water. That is why current pharmaceutical research focuses on increasing solubility and bioavailability of these substances. Among many procedures how to improve dissolution rates of poorly water-soluble drugs, the transformation from their crystalline state to more soluble amorphous, nanocrystalline solid dispersion and/or solid solution represents one of the most promising ways. In our work we focussed our attention on the study of structural properties of APIs in the prepared solid polymer dispersions exhibiting increased solubility and polymeric matrix influence (various molecular weight of polymer matrix) on the above-mentioned prepared systems. The acetylsalicylic acid was used as a model of APIs with low solubility. Several procedures were used to combine this model compound with polymeric nontoxic water soluble matrix (PEG, PVP, HPMA). In some cases the observed drug-polymer interaction significantly enhanced dissolution rates of the APIs. Structural reasons of the increased solubility in solid dispersions and polymeric matrix influence on these systems were extensively probed by a wide range of ssNMR experiments including 13C CP/MAS NMR, 1H DQ-BABA and relaxation experiments. The obtained results are comprehensively discussed in this contribution. In particular, the extent of mutual interaction is thoroughly examined.

Abstrakta P5

Vliv příměsí na mechanismy formování polymerních globulí

Larisa Starovoytovaa , Julie Šťastná

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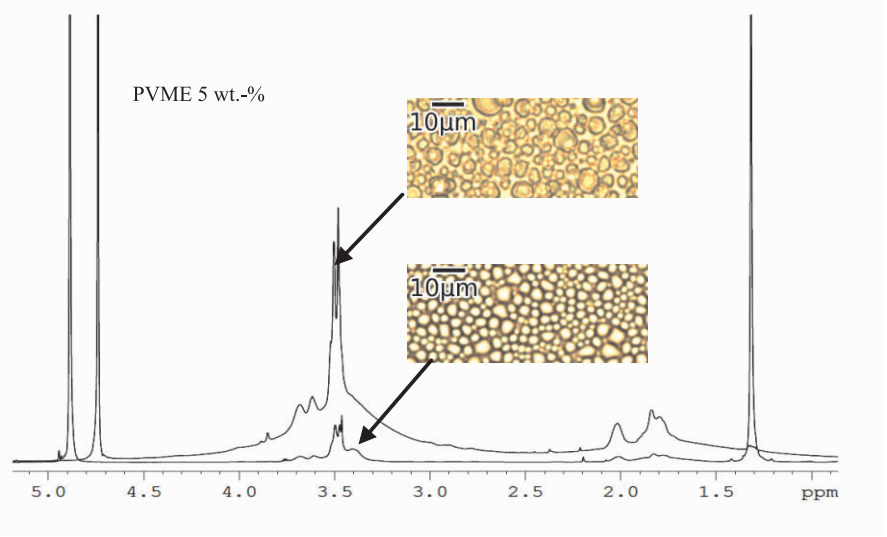
Charles University, Faculty of Mathematics and Physics, V Holešovičkách 2, 180 00 Prague Czech Republic

Hlavním účelem projektu je výzkum kinetiky formováni globulí a jejích stability v různých polymerních systémech za přítomností příměsí. Pomocí NMR dokážeme charakterizovat změny v interakcích polymer-rozpouštědlo, polymer-příměs, rozpouštědlo-příměs, popsat kinetiku procesu přechodu: schopnost uzamknout a následně uvolnit molekuly příměsi z polymerních globulí. Cílem je najit parametry, které mají vliv na změnu LCST a zjistit mechanismy formováni globulí, jejich stability a reverzibility v závislosti na stavbě polymerů nebo hydrofobnosti příměsi. Na základě porovnáni výsledků z NMR a z optického mikroskopu lze usoudit že hydrofobní příměsi preferují interakci s polymerem a tímto zvyšují celkovou hydrofobnost řetězců. Výsledkem tvorby takového komplexu je nižší teplota přechodu, jádro polymerních globulí je pevnější a voda je vyloučena z globulí již v procesu její vzniku



NMR spektroskopie peptidů v roztoku

Jana Svobodová

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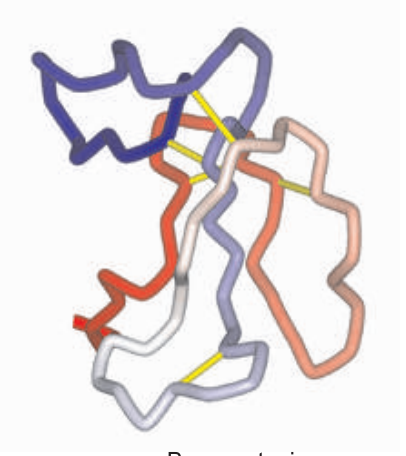
Nuclear magnetic resonance (NMR) spectroscopy is a powerful tool in biology and is widely used in studies of structure determination of proteins, peptides and amino acids fragments at atomic resolution, since the NMR data can be recorded in solution. NMR aplications include investigations of dynamic features of the molecular structures, as well as studies of structural, thermodynamic and kinetic aspects of interactions between proteins and other solution component, which may either be other macromolecules or low-molecular-weight ligands.

The aim of the work is to find and determine the structures, interactions and dynamics of stochiometric complexes between selected synthetic peptides with similar structure elements to found in AChR (acetylcholine receptor) subunits and long neurotoxins (e.g. alpha-Bungarotoxin). The solution structures of the complexes are solved using multi-dimenzional NMR spectroscopy (COSY, TOCSY, NOESY). NMR results will be suggested new possible correlations between kinetics, solution structures and dynamics for these complexes which can be considered as a general rule for the design of peptidyl protein ligands



α-Bungarotoxin

Studium fázového přechodu klubko-globule ve vodných roztocích poly(n-vinylkaprolaktamu) a směsí poly(n-vinylkaprolaktam)/poly(n-isopropylmethakrylamid) NMR metodami

Jiří Spěváček[a], Hana Kouřilová[b], Larisa Starovoytova[a], Lenka Hanyková[b]

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Charles University, Faculty of Mathematics and Physics, V Holešovičkách 2, 180 00 Prague Czech Republic

Je známo, že termoresponzivní polymery vykazují ve vodném roztoku přechod klubko-globule doprovázený agregací a tvorbou tzv. mesoglobulí. Termosenzitivita činí tyto polymery zajímavé pro různé biolékařské a technologické aplikace, např. jako polymery pro uvolňování léčiv. Mezi termoresponzivní polymery patří i poly(N-vinylkaprolaktam) (PVKL), který má poměrně značný aplikační potenciál, protože je biokompatibilní a vykazuje fázový přechod blízko fyziologické teploty. Ve srovnání s akrylamidovými polymery jeho termoresponzivní chování zatím bylo studováno mnohem méně. V přednášce budou prezentovány některé nové výsledky získané pomocí metod NMR spektroskopie při studiu vodných (D2O) roztoků PVKL a směsí PVKL/poly(N-isopropylmethakrylamid) (PIPMAm). Tyto směsi, kde obě polymerní složky vykazují termoresponzivní chování, jsme studovali s cílem zjistit, zda přítomnost druhé polymerní složky ovlivňuje fázový přechod dané složky. Oba typy zkoumaných systémů byly byly studovány v širokém oboru polymerních koncentrací (c = 0.1-30 váh.%) a polymerní směsi i pro různá složení.

Tvorba globulárních struktur vede u většiny polymerních segmentů k markantnímu rozšíření NMR signálů [1]. Z teplotních závislostí integrovaných intenzit v NMR spektrech vysokého rozlišení byly získány teplotní závislosti fázově-separovaného podílu (podíl monomerních jednotek s podstatně redukovanou pohyblivostí) a následně pak i termodynamické parametry (H, S) fázového přechodu. Informace o chování molekul vody při fázovém přechodu byly získány z měření spin-spinové relaxační doby molekul HDO. Výsledky budou diskutovány i z hlediska srovnání s jinými termoresponzivními polymery (PIPMAm, poly(N-isopropylakrylamid, polyvinylmetyléter).

Poděkování: Autoři děkují za podporu GA ČR (projekt 202/09/1281).

[1] J. Spěváček, Curr. Opin. Colloid Interface Sci. 14, 184 (2009)

NMR studie preasociačních stavů blokového kopolymeru PEO-PPO-PEO a jejich interakce s částečně hydrofobními látkami

Jaroslav Kříž

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Blokové kopolymery ethylenoxidu a propylenoxidu typu (EO)m(PO)n(EO)m jsou známy tím, že nad kritickou teplotou (CMT) tvoří ve vodě micely schopné solubilizovat hydrofobní látky. Jak jsme ukázali, již několik stupňů pod CMT vznikají preasociační stavy s pozměněnou konformací PO bloku a porušeným jeho hydratačním obalem. Tyto stavy resp. jejich závislost na teplotě mohou být podle naší studie ovlivněny malými přídavky přímo neinteragujících částečně hydrofobních látek. Studovali jsme vliv sloučenin typu (CH3)kCH3-kCOCH3, kde k=1,2,3 na preasociační stavy kopolymeru Pluronic L64. Pomocí 1H a zvláště 13C NMR spekter, příčných a podélných relaxací, PFG difusních měření a NOESY spekter bylo prokázáno, že teplota i aktivační energie konformační změny stejně jako CMT klesá se vzrůstajícím k, tedy rostoucí hydrofobicitou příměsi. Ta ke kopolymeru zřejmě není nijak stabilněji vázána, ale je schopna přechodnými interakcemi rozrušovat hydratační obal jeho propylenoxidového bloku.

Postery

NMR crystallography of boron compounds

Jiri Brus, Libor Kobera, Pavel Matejicek, Jiri Czernek, Martina Urbanova, Olivia Policianova

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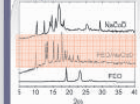
ss-NMR of [Co bis(dicarbollide)-PEO]

1. Introduction

Polymer-drug solid dispersions are currently considered as promising formulations of low soluble pharmaceutical ingredients (API). Inhibitor of HIV protease [3-cobalt(III) bis(1,2-dicarbollide)]$^{-}$(-1) (NaCoD) dispersed in poly(ethylene oxide) matrix represents one of them. Multinuclear ss-NMR combined with XRPD was applied to describe structure and dynamics of this polymeric composite.

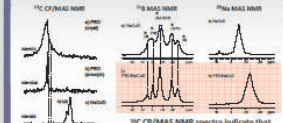
2. XRPD



XRPD data - the narrow reflections - demonstrate long-range periodic order of CoD clusters in polymer matrix of PEO (the arrangement of NaCoD in original crystals disappeared).

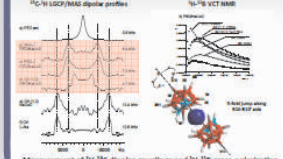
The prepared polymeric composite PEO-NaCoD can be considered as micro-(nano-)crystalline system.

3. ^{13}C, ^{11}B and ^{23}Na MAS NMR



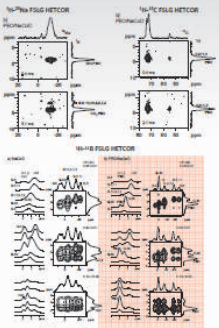
^{13}C CP/MAS NMR spectra indicate that original amorphous and crystalline phases of PEO disappeared and a new form of PEO is constituted. Mutual interactions between PEO chains and Na^{+} and CoD^{-} ions are indicated by ^{11}B, ^{23}Na MAS NMR spectra.

4. Segmental dynamics



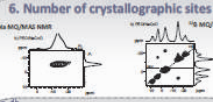
Measurement of ^{1}H-^{13}C dipolar couplings and ^{1}H-^{11}B cross-polarization rate constants indicate rotation or 5-fold jumps of CoD^{-} clusters along B10-B10' axis while PEO segments exhibit relatively low-amplitude motions with reorientation angle of C-H about 30 degrees.

5. Location of PEO, Na^{+} and CoD^{-}

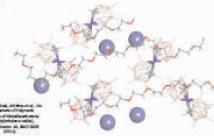


Applying a set of ^{1}H-^{13}C(^{23}Na,^{11}B) HETCOR spin-exchange experiments we obtained information on location of Na+ ions (they interact exclusively with PEO), on the size and distribution of CoD- (homogeneously dispersed wit size of domains ca 1.5-2.0 nm) and their relative orientations.

6. Number of crystallographic sites



7. Refined structure

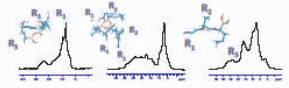


All the obtained data were used to refine periodic structure of the prepared polymer composite PEO-NaCoD.

^{11}B-^{11}B spin-exchange experiments

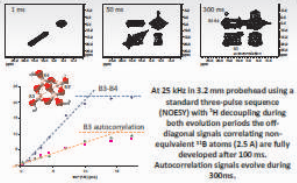
a. aim of the work

Boron compounds play an important role not only in material science but also occupy outstanding position in pharmaceutical research. Among them tripeptidic derivatives of boronic acid are known for their high therapeutic activity. These systems, however, exhibits not only extensive polymorphism, but boronic acid fragments can spontaneously undergoes condensation and dehydration forming thus various oligomers.



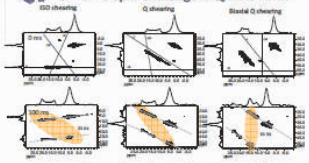
The resulting ^{11}B MAS NMR spectra are very complicated and not easy to understand. However, ^{11}B-^{11}B correlation experiments (J-coupled and dipolar coupled) offers a nice possibility to identify various oligomers of boronic acid. *(Due to the high activity of the API the correlation experiments were tested on model systems.)*

b. ^{11}B-^{11}B spin-exchange on borax



At 25 kHz in 3.2 mm probehead using a standard three-pulse sequence (NOESY) with ^{1}H decoupling during both evolution periods the off-diagonal signals correlating non-equivalent ^{11}B atoms (2.5 Å) are fully developed after 100 ms. Autocorrelation signals evolve during 300ms.

c. ^{11}B-^{11}B spin-exchange MQ/MAS NMR



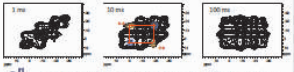
Incorporating a spin-exchange period after the triple-quantum pulse sequence the resolution of the ^{11}B-^{11}B correlation spectrum is enhanced. No autocorrelation signals evolve.

* John D. Hartman, John C. Poole, Generalized Shifted-shearing of MQMAS NMR spectra Journal of Magnetic Resonance 330 (2008) 147–151.

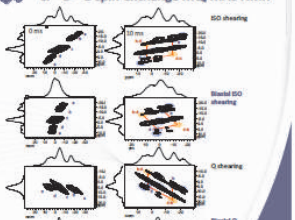
d. ^{11}B-^{11}B spin-exchange on NaCoD

Sodium metallocarborane NaCoD the complete crystal structure of which was recently refined by us is a suitable model compound to further test different ^{11}B-^{11}B spin-exchange experiments.

The proposed crystal structure of NaCoD metallocarborane derived from XRPD data and ss-NMR. GIPAW (CASTEP) calculations of ^{11}B chemical shifts exhibited deviation from experimental data ≤ 5ppm.



c. ^{11}B-^{11}B spin-exchange MQ/MAS NMR



The most suitable representation of MQ/MAS spin-exchange correlation experiments is provided by the recently developed biaxially sheared spectra*. These spectra allow for a clear separation of correlation signals.

Joint Laboratory of Solid-State NMR IMC AS CZ and JHIPC AS CZ

The research was supported by Grant 2B08021, MSM 2008-2011

Solid State NMR Spectroscopy of Boron Compounds

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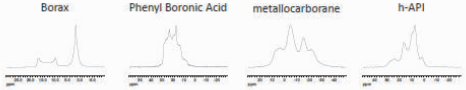
Introduction

Very important, for finally using as a medicinal product, is precise description of structural homogeneity and purity. Excellent tool for structural analysis is solid state NMR spectroscopy. Organoboron compounds description is possible by NMR measurements of included nuclei such as ^{13}C, ^{11}B etc.

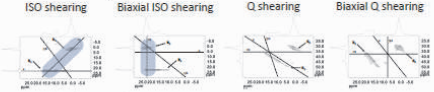
High sensitivity and abundance of boron nucleus is suitable for measurement and consequently analysis of NMR spectra. On the other hand, the quadrupolar character of boron atoms complicates detail analysis. Typical 1D MAS NMR spectra are very complicated and difficult to interpret. However, the solution provides the MQMAS NMR experiment and using of relatively new techniques called biaxial shearing. This combination enhances the spectral resolution and thereby helps correctly analyze and describe structure units.

^{11}B MAS NMR



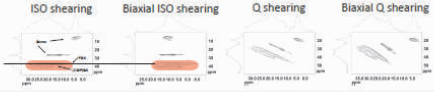
Classical & biaxial shearing

^{11}B MQ/MAS NMR of borax



^{11}B 3Q/MAS NMR of metallocaborane

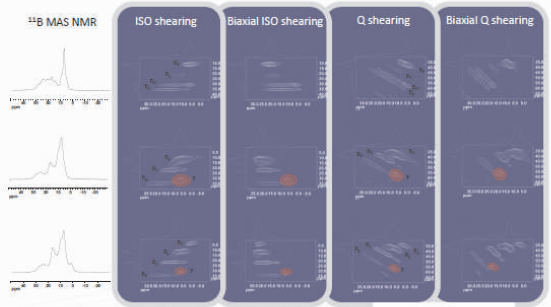
^{11}B 3Q/MAS NMR of Borax + Phenyl Boronic Acid + (2-methylpropyl) boronic acid physical mixture

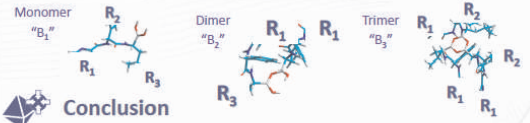


Results

^{11}B 3Q/MAS NMR of high Active Pharmaceutical Ingredients

These proteasome inhibitors systems, exhibits not only extensive polymorphism, but boronic acid fragments can spontaneously undergoes condensation and dehydration forming thus various oligomers.





Conclusion

Four possible schemes was demonstrated on this poster which may be valuable for shearing 2D MQ/MAS NMR spectra. Examination of peaks contours under different shearing schemes helps to interpret the 2D MQ/MAS NMR spectra. The suggestion arises that the choice of shearing factor should be made on a case-by-case basis. Where distinct chemical sites are well resolved, as for many model compounds, **ISO-shearing** is the best choice. Amorphous or disordered materials, on the other hand, typically give a distribution of chemical shift and/or quadrupolar parameters, and it can be more difficult to interpret MQMAS spectra to identify distinct chemical sites. Where the distribution of chemical shifts leads to greater inhomogeneous linewidths than the second-order quadrupolar broadening, eliminating chemical shift in the indirect dimension by **Q-shearing** can lead to apparently sharper spectra and therefore enhanced ability to distinguish dissimilar sites. Additional shearing in the directly detected dimension (**biaxial shearing**) can provide further cosmetic modifications of the spectra which may aid interpretation by helping to identify and characterize independent chemical sites.

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The research was supported by Grant 2B08021, MSM 2008-2011

Structural analysis of Simvastatin in polymer matrix: Combined ssNMR spectroscopy and Raman microspectroscopy

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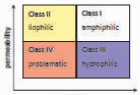
Introduction

Simvastatin is a substance used for the treatment of hypercholesterolemia. Three crystal forms Form I, II and III of Simvastatin are known. Forms II and III are stable at low temperatures [1] only and therefore inappropriate for patients. Form I is characterized by very low oral bioavailability. Thus it is important to focus on increasing the absorbency of this substance. The highest improvement in solubility and in-vitro drug release was observed in solid dispersion prepared with PVP by solvent evaporation method.[2]
In this contribution, a solid-state NMR study of structure and segmental dynamics of solid dispersions or solid solutions of Simvastatin in polymer matrix (PVP and PEG) is presented. Our aim is to find an interaction "API-excipient (polymer matrix)", relations between structure of these systems and their thermodynamic and pharmacokinetic behavior.

Reference
[1] M. Vrecer, B. Kristochel, A. Jegorov, J. Brus, J. Maloser, J. Rohlíček; Struct Chem (2010) 21:511–518.
[2] Rakesh Patel, Maddhidhal Patel; Journal of Dispersion Science and Technology, (2008) 29:150–204.

The Biopharmaceutical Classification System (BCS)

In many clinical studies it has already been demonstrated that higher efficiency of APIs significantly reduces menace of many diseases. API has higher efficiency when it 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 tissue. It classifies API into one of four classes.



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

Experimental

Preparation of model systems: Model systems of solid dispersion or solid solution were prepared by free evaporation or lyophilization of solution of Simvastatin (API) in a combination with PVP or PEG (polymeric matrix different molecular weight). These systems were prepared by the intermingle solution of Simvastatin and solution of polymer. As a solvents of this model system were used nontoxic and biodegradable compounds, which solubilize APIs and polymer matrix as water, ethanol and tert-butanol. Different ratio of API and polymer (30% API : 70% polymer and vice versa ; 50% API : 50% polymer) were tested.

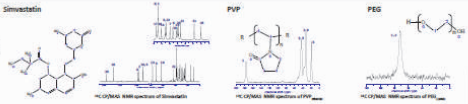
Solid-state NMR spectroscopy: Solid-state NMR spectra were measured using a Bruker Avance 500 NMR spectrometer. Magic angle spinning (MAS) frequency was 11 kHz for ^{13}C. Amplitude modulated cross-polarization (CP) of 2 ms duration was used to obtain ^{13}C CP/MAS NMR spectra. The ^{13}C scale was calibrated with glycine as external standard (176.03 ppm – low-field carbonyl signal).

Raman microspectroscopy: Raman spectra excited in the visible range with a Helle 633 nm laser on compressed sample pellets were collected on a Renishaw inVia Reflex Raman spectroscope. A research-grade Leica DM LM microscope with an objective magnification 50 was used to focus the laser beam on the sample. The scattered light was analysed by the spectrograph with a holographic grating 1800 lines mm^{-1}. A Peltier cooled CCD detector (576 × 384 pixels) registered the dispersed light.

We thank Czech Science Foundation (Grant No. P106/11/P426) and Ministry of Education, Youth and Sports of the Czech Republic (research program IMI0031) for financial support.

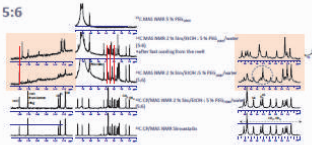
Results

Simvastatin PVP PEG

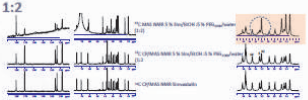


SIM dissolved in ethanol+PEG dissolved in water

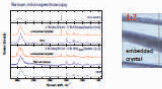
5:6



1:2



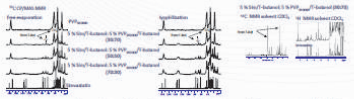
Samples were prepared by mixing solutions of PEG in water and Simvastatin in ethanol and subsequent free evaporation
•formation of solid dispersion
•from ^{13}C/CP MAS spectra in samples of solid solution is detected only Simvastatin
•PEG has very fast internal motion (both crystal and amorphous forms); ^{13}C MAS NMR spectra detect PEG and Simvastatin; from this spectra its clear interaction, and region changes in the spectra
•both types of prepared systems are heterogeneous



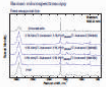
both types systems are heterogeneous
2% Sim/EtOH : 5% PEG$_{6000}$/water – 5:6
•no interaction detected by Raman spectroscopy
•optical microscopy: large embedded crystals of Simvastatin coated by PEG

5% Sim/EtOH : 5% PEG$_{6000}$/water – 1:2
•change in region about 3000 cm^{-1}: νCH$_2$ as νCH$_3$)
•new band at 1720 cm^{-1}: νC=O$_{ester}$
•optical microscopy: crystals of Simvastatin embedded in PEG

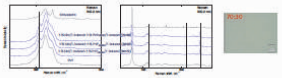
SIM+PVP dissolved in T-butanol



Samples were prepared from solutions of PVP and Simvastatin dissolved in T-butanol by free evaporation and lyophilization.
•formation of solid dispersion
•in the ^{13}C/CP MAS spectra slight signals about 120-140 ppm (region of unsaturated cyclic hydrocarbons) were found. Signals 31 and 69 ppm are residue of solvent (T-butanol). Solvent residues were confirmed by the ^{13}C NMR spectrum. From the ^{1}H NMR spectrum is apparent the decomposition of Simvastatin. There is a hypothesis of hydrolysis of Simvastatin in the environment of non-dried PVP; further measurements and experiments are necessary for its confirmation.

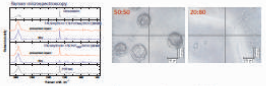


•interaction of PVP and simvastatin independent of Simvastatin content.
•new bands 2970 cm^{-1}: νCH$_3$$_{symmetric}$; 760 & 930 cm^{-1}: δCH$_{2rock}$
•optical microscopy: systems are homogenous

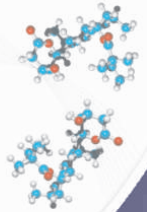


SIM+PVP dissolved in ethanol

Samples were prepared from solutions of PVP and Simvastatin dissolved in ethanol by free evaporation.
•formation of solid dispersion
•from ^{13}C/CP MAS spectra trace of interaction of PVP and Simvastatin are distinct; signals of pure Simvastatin are evident in the system 50:50 – only limit amount of Simvastatin could be incorporated into PVP; excess of Simvastatin was not incorporated to the solid solution
•the decomposition of Simvastatin not detected in the ^{1}H NMR spectrum.



optical microscopy: both systems are heterogeneous, but system 20:80 is less separated
•for system 50:50; phase separation – phase Simvastatin rich vs. PVP rich phase; interaction of PVP and Simvastatin; stronger evidence for interaction in the Simvastatin rich phase



Conclusions

In our preliminary study, we investigated the ability of Simvastatin to form a solid dispersion with polymer matrices [PVP and PEG] by ssNMR spectroscopy and Raman microspectroscopy. These methods are complementary; ssNMR spectroscopy investigates samples in bulk on a molecular level, while Raman microspectroscopy analyze mainly the surface of the sample.

Three types of samples were prepared:
i) Sim+PVP dissolved in ethanol. The system is homogenous according to NMR spectroscopy in content of Simvastatin 20%, in spite of the fact that Raman microspectroscopy distinguish two phases. Higher content of Simvastatin leads clearly to phase separated systems.
ii) Sim+PVP dissolved in T-butanol: In the system the decomposition of Simvastatin from the ^{1}H NMR spectrum was confirmed. There is a hypothesis of hydrolysis of Simvastatin in the environment of non-dried PVP.
iii) Sim dissolved in ethanol+PEG dissolved in water: The system is heterogenous. The new crystal modification probably arises.

Our study confirm that characterization of such complex systems requires a complex approach. Combination of characterization methods is necessary and a characterization by only one technique can be easily misleading.

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Determination of Structure Disorder by Solid State NMR and Factor Analysis

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Introduction

In pharmaceutical science polymorphs of active pharmaceutical ingredients (APIs) attract significant attention due to their various bioavailabilities. Generally, amorphous systems are thermodynamically less stable and any phase transformation can have significant effects on their bioavailability and/or can lead to complicated patent litigations. Moreover, the explicit characterization of amorphous solids is very difficult, especially in tablet formulations where concentration of the API is very low, and the strong signals of filler compounds prevail we are balancing on the physical and detection limits of traditionally used experimental techniques. Therefore the characterization of amorphous forms of APIs and their unambiguous identification in tablet formulations is a priority that still remains a challenge. Because approximately 20-25% of currently developed pharmaceuticals contain at least one fluorine atom, and ^{19}F isotope exhibits excellent receptivity, ^{19}F MAS NMR spectroscopy attracts growing interest. Additionally, almost none of pharmaceutical excipients contain fluorine atoms. Therefore, ^{19}F NMR spectra can be acquired very quickly even for diluted systems without the danger that ^{19}F NMR signals of the API are overlapped by the signals of filler compounds. Following these facts we developed a new and relatively time-saving procedure of the characterization of amorphous APIs in dosage forms.

Overall, we tested potential of multivariate analysis of ^{19}F MAS NMR spectra in terms of distinguishing different amorphous forms of atorvastatin as a pure active pharmaceutical ingredient, solid dispersion and atorvastatin as a low-concentration tablet formulation.

Experimental

It is well known, that atorvastatin exhibits extensive polymorphism and majority of the crystal forms are disordered and nearly amorphous. We have recrystallized atorvastatin under various conditions from different solvents (acetone, acetonitrile, water, ethanol, methanol, dimethylformamide, n-heptane). Recrystallization has been performed from solutions with cosolvents) dissolved atorvastatine-Calcium (amorphous) BIOCON) or from saturated solutions with applied mechanical grinding. Crystallization must occur very slowly and the traces of residual solvent must be removed from the resulting forms.

Systems of solid dispersion or solid solution were prepared by free evaporation or lyophilization of solution of atorvastatin with PVP (polymeric matrix). These systems were prepared by the intermingle solution of atorvastatin and solution of polymer. As a solvents of this systems were used nontoxic and biodegradable compounds, which solubilize APIs and polymer matrix as water, ethanol and tert-butanol.

Solid-state NMR spectra were measured using a Bruker Avance 500 NMR spectrometer. Magic angle spinning (MAS) frequency was 11 kHz for ^{13}C and 32 kHz for ^{19}F (2.5mm probehead). Amplitude modulated cross-polarization (CP) of 2 ms duration was used to obtain ^{13}C CP/MAS NMR spectra. Hann-echo experiments were used to acquire ^{19}F MAS NMR spectra. The ^{13}C scale was calibrated with glycine as external standard (176.03 ppm – low-field carbonyl signal). The ^{19}F scale was calibrated with PTFE (-122 ppm).

Single-Pulse Experiment

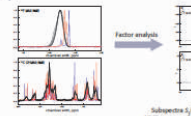
^1H-^{13}C Cross-Polarization

Factor analysis is a mathematical method which can help us to compare different data series describing the system as ^{13}C and ^{19}F NMR-MAS spectral series and x-ray diffractogram series. The factor analysis enables us to independently characterize each original series of spectra by the orthogonal base. The orthogonal base is composed from the set of so-called "subspectra" S_j. The statistical importance of each spectrum is expressed by the set of singular numbers w_j; the relative presence of the subspectrum S_j in the experimental spectrum Y_i is specified by the coefficients V_{ij}. The experimental spectrum Y_i is then given by the expression.

$$Y_i = \sum_{j=1}^{n} w_j V_{ij} S_j$$

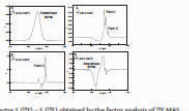
The approximation of the complete experimental series of spectra is enabled by the most significant subspectra obtained by FA. The number of independent subspectra n necessary to ensure the adequate agreement with the experimental set of spectra is a factor dimension and can be derived from the singular values .

Atorvastatin as pure API as seen by ssNMR and factor analysis

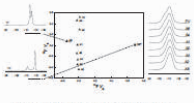


Overlay of ^{19}F MAS NMR and ^{13}C CP/MAS NMR spectra of the representative modifications of the API. The red lines mark crystalline form I; the blue lines reflect crystalline Form X, and the black lines correspond to the amorphous modifications of the API.

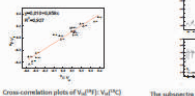
Factor analysis



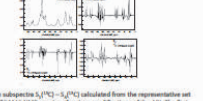
Subspectra $S_1(^{19}F) - S_3(^{19}F)$ obtained by the factor analysis of ^{19}F MAS NMR spectra of the representative modifications of the API. The first-rank subspectrum $S_1(^{19}F)$ corresponds to the superposition of signals dominating the set of ^{19}F MAS NMR spectra. Characteristic markers of crystalline forms X and Y are displayed in $S_2(^{19}F)$. The differences between the crystal forms are reflected in $S_3(^{19}F)$. The spectral differences between amorphous modifications are highlighted in the fourth-rank subspectrum $S_4(^{19}F)$.



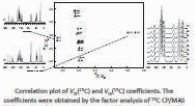
Correlation plot of $V_{i1}(^{19}F)$ and $V_{i2}(^{19}F)$ coefficients. The coefficients were obtained by the factor analysis of ^{19}F MAS NMR spectra of the representative modifications of the API. The corresponding ^{19}F MAS NMR spectra of crystalline and amorphous modifications are placed on the left and right side, respectively.



Cross-correlation plots of $V_{i1}(^{19}F)$; $V_{i2}(^{13}C)$ coefficients for amorphous samples. The correlation between the spectra ^{13}C and ^{19}F of sample was find in the result of factor analysis. The behavior of changes described by the subspectrum S_4 of the ^{13}C CP/MAS NMR series and ^{19}F MAS NMR are in a good agreement.



The subspectra $S_4(^{19}F) - S_4(^{13}C)$ calculated from the representative set of ^{13}C MAS NMR spectra of various modifications of the API. The first-rank subspectrum $S_1(^{13}C)$ corresponds to the superposition of signals dominating the set of ^{13}C CP/MAS NMR spectra. Characteristic markers of crystalline forms X and Y are displayed in $S_2(^{13}C)$. The differences between the crystal forms are reflected in $S_3(^{13}C)$. The spectral differences between amorphous modifications are highlighted in the fourth-rank subspectrum $S_4(^{13}C)$.

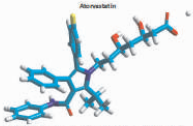


Correlation plot of $V_{i1}(^{13}C)$ and $V_{i2}(^{13}C)$ coefficients. The coefficients were obtained by the factor analysis of ^{13}C CP/MAS NMR spectra of the representative modifications of the API. The corresponding ^{13}C CP/ MAS NMR spectra of crystalline and amorphous modifications are placed on the left and right side, respectively.

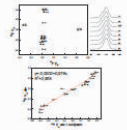
Conclusion

In the presented contribution it is demonstrated that ^{19}F MAS NMR spectroscopy combined with factor analysis (SVD algorithm) offers a fast and reliable tool to distinguish various amorphous forms of a particular fluorine-containing API in low-dose tablet formulations and API in solid dispersion. Specifically, it is shown that even relatively poorly-resolved ^{19}F MAS NMR spectra can be used to discern subtle differences between various amorphous products of the API. The proposed method also offers quantization of various mixtures of different modifications of the API.

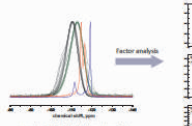
Applying the factor analysis on ^{19}F MAS NMR spectra, the sample-specific coefficients (scores, $V_{i2}(^{19}F)$) characterizing every product can be obtained. In a graphical representation these scores provide clear identification and distinction of different amorphous forms of atorvastatin. The proposed method also offers the ability to identify and quantify various mixtures of different modifications of atorvastatin. Predominantly, however, the proposed method allows the fast characterization of low-dose pharmaceutical products.



Atorvastatin as low-concentration tablet formulations and as solid dispersion

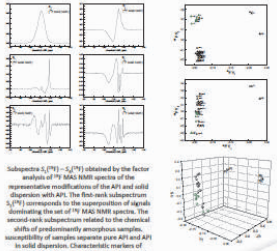


Correlation plot of $V_{i1}(^{19}F)$ and $V_{i2}(^{19}F)$ coefficients. The coefficients were obtained by the factor analysis of ^{19}F MAS NMR spectra of representative modifications of the API in low-dose tablet formulations. The corresponding ^{19}F MAS NMR spectra of crystalline and amorphous modifications are placed on the left and right side, respectively. The correlation of $V_{i2}(^{19}F)$ parameters obtained for pure forms of the API and their corresponding tablet formulations.



Overlay of ^{19}F MAS NMR spectra of the representative solid dispersion of the API. The red lines mark crystalline Form I; the blue lines reflect crystalline Form X, and the black lines correspond to the amorphous modifications of the pure API and green lines corresponds to the amorphous modifications of API in solid dispersion.

Factor analysis



Subspectra $S_1(^{19}F) - S_4(^{19}F)$ obtained by the factor analysis of ^{19}F MAS NMR spectra of the representative modifications of the API and solid dispersion with API. The first-rank subspectrum $S_1(^{19}F)$ corresponds to the superposition of signals dominating the set of ^{19}F MAS NMR spectra. The second-rank subspectrum related to the chemical shifts of predominantly amorphous samples, susceptibility of samples separate pure API and API in solid dispersion. Characteristic markers of crystalline forms X and Y are displayed in S_2 and $S_3(^{19}F)$. The spectral differences between amorphous modifications are highlighted in the fourth-rank subspectrum S_4 and $S_3(^{19}F)$.

Correlation plot of $V_{i1}(^{19}F)$ and $V_{i2}(^{19}F)$ coefficients. The coefficients were obtained by the factor analysis of ^{19}F MAS NMR spectra of the representative modifications of the API and solid dispersion with API. The corresponding ^{19}F MAS NMR spectra of crystalline are placed on the right side, and amorphous modifications are placed on the left. Green points accord solid dispersion. It is evident that the only coefficient $V_{i2}(^{19}F)$ is related to the change in chemical shift solid dispersion, which is caused by the susceptibility of the polymer matrix. Correlation plot of $V_{i1}(^{19}F)$ and $V_{i2}(^{19}F)$ coefficients is related only to changes occurring in various amorphous forms.

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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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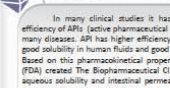
Introduction

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)



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.

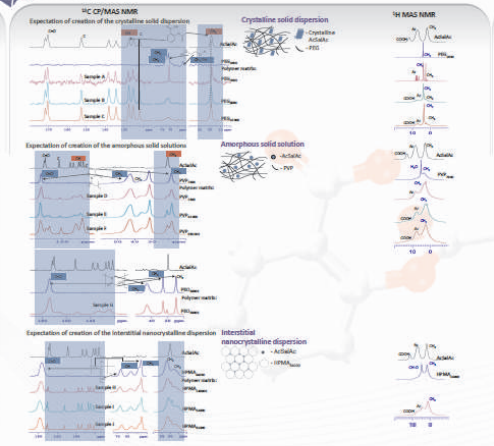
API-polymer systems

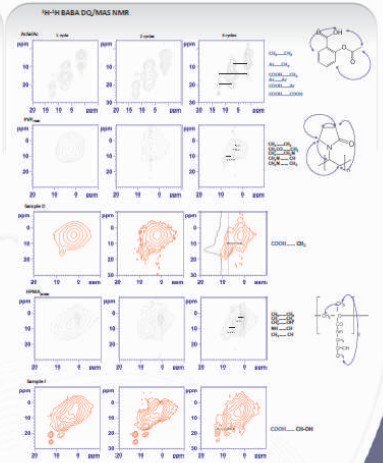
In our work we focussed our attention on the study of structural properties of APIs in the prepared solid polymer dispersions, solutions and co-crystals exhibiting increased solubility. Nowadays we are testing properties of acetylsalicylic acid (AcSalAc) as an API system with relatively low solubility. 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).

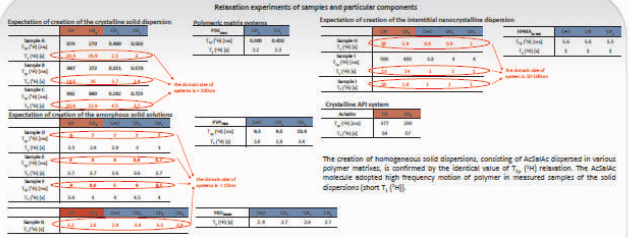
Samples of API-polymer system:

Sample A: AcSalAc/ T-but, 30 % + PEG_{1000}/ T-but, 70 %
Sample B: AcSalAc/ T-but, 30 % + PEG_{6000}/ T-but, 70 %
Sample C: AcSalAc/ T-but, 30 % + PEG_{20000}/ T-but, 70 %
Sample D: AcSalAc/ T-but, 30 % + PVP_{360}/ T-but, 70 %
Sample E: AcSalAc/ T-but, 30 % + PVP_{40000}/ T-but, 70 %
Sample F: AcSalAc/ T-but, 30 % + PVP_{360000}/ T-but, 70%
Sample G: AcSalAc/ T-but, 30 % + PEO_{100000}/ water, 70 %
Sample H: AcSalAc/ T-but, 30 % + $HPMA_{1000}$/ water, 70 %
Sample I: AcSalAc/ T-but, 30 % + $HPMA_{5000}$/water, 70 %
Sample J: AcSalAc/ T-but, 30% + $HPMA_{9500}$/ water, 70 %

Results







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_2 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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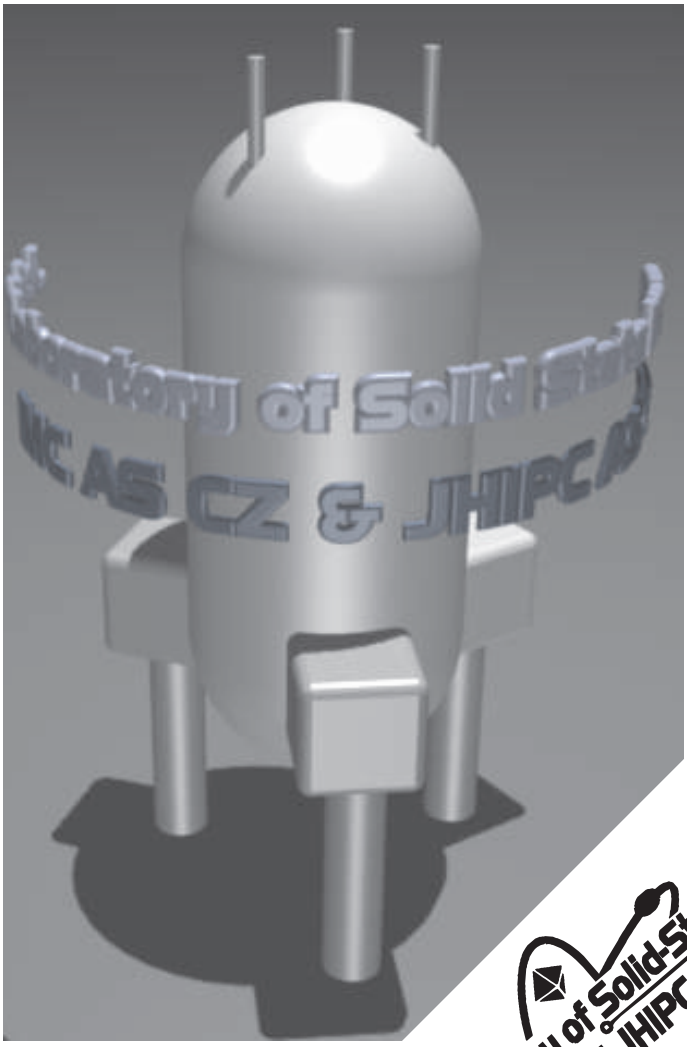

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