Journal of Pharmaceutical and Biomedical Analysis 122 (2016) 81–89

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

^{13}C solid-state NMR analysis of the most common pharmaceutical excipients used in solid drug formulations, Part I: Chemical shifts assignment

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 8 January 2016
Accepted 12 January 2016
Available online 22 January 2016

Keywords:
Excipients
Solid drug forms
Solid state NMR
GIPAW

ABSTRACT

Solid-state NMR is an excellent and useful method for analyzing solid-state forms of drugs. In the ^{13}C CP/MAS NMR spectra of the solid dosage forms many of the signals originate from the excipients and should be distinguished from those of active pharmaceutical ingredient (API). In this work the most common pharmaceutical excipients used in the solid drug formulations: anhydrous α-lactose, α-lactose monohydrate, mannitol, sucrose, sorbitol, sodium starch glycolate type A and B, starch of different origin, microcrystalline cellulose, hypromellose, ethylcellulose, methylcellulose, hydroxyethylcellulose, sodium alginate, magnesium stearate, sodium laurilsulfate and Kollidon® were analyzed. Their ^{13}C CP/MAS NMR spectra were recorded and the signals were assigned, employing the results (R^2: 0.948–0.998) of GIPAW calculations and theoretical chemical shifts. The ^{13}C ssNMR spectra for some of the studied excipients have not been published before while for the other signals in the spectra they were not properly assigned or the assignments were not correct. The results summarize and complement the data on the ^{13}C ssNMR analysis of the most common pharmaceutical excipients and are essential for further NMR studies of API-excipient interactions in the pharmaceutical formulations.

1. Introduction

Solid dosage forms are the most popular methods of drug delivery due to their many advantages such as convenience of administration, accuracy and reproducibility of a dosing, increased drug stability and facility of mass production.

Excipients, by definition, are pharmacologically inactive substances included in the formulation, used as a carrier of active pharmaceutical ingredients (APIs). In the case of the solid drug forms excipients are mostly used as fillers or diluents, allowing convenient and accurate dispensation of an API in a dosage form. Excipients can be very useful in the manufacturing process, aiding in the handling of the active substances. They may also have an impact on a number of desirable properties of the solid dosage form, including suitable hardness, low friability and proper size. In practice, there are several most frequently used excipients in the solid drug formulations belonging to various chemical classes; most of them are organic compounds, usually carbohydrates.

In the field of pharmaceutical analysis the most essential techniques are those which allow analyzing the drug directly in its final pharmaceutical formulation, with no need of sample preparation. NMR spectroscopy is one of the most informative analytical techniques providing data on the structure, dynamics and interactions of chemical compounds [1,2]. This makes the solid-state NMR (ssNMR) one of the most valuable methods which could be applied in many ways in pharmaceutical analysis of solid dosage forms. Numerous applications of ssNMR can be found in the literature and include identification of API [3,4], polymorphic analysis [5,6], drug stability, interactions between API and excipients, quantitative analysis and drug manufacturer identification [7].

This last application can be particularly helpful in the identification of counterfeit drugs. Many of the fake drugs contain the same concentration of an API as the original ones. This makes the identification of the counterfeit drugs an even more complicated and challenging task. On the other hand, drug manufacturers are not obliged to provide data on the quantitative excipients composition in the solid drug forms. The confidentiality of some excipient

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http://dx.doi.org/10.1016/j.jpba.2016.01.032
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composition information is required to protect the manufacturer's intellectual property and hinders the production of fake drugs. As a result the counterfeit drugs usually differ from the original ones in the excipient composition. Therefore analytical techniques like ssNMR that provide information not only about the API but also qualitative and quantitative data about the excipients used in the drug formulation are particularly useful, as they help to distinguish between the original and fake products [8].

Although in the last years extensive development of ssNMR techniques has been achieved, even simple, popular and easy to perform one-dimensional spectra registered using the cross-polarization (CP) under magic angle spinning (MAS) can be very informative on the qualitative and quantitative composition of the pharmaceutical product.

Proper signal assignment is mandatory to perform a detailed ssNMR analysis. GIPAW calculations of chemical shielding constants were previously successfully used to solve the problem of the signal assignment in the case of the APIs [1,3,5]. Calculations of the NMR parameters can be particularly helpful in the spectral interpretation, confirmation of experimental NMR parameters and assessment of experimental feasibility, as well as may provide a flexible way to study the dependence of NMR parameters upon structure. The usefulness of those theoretical calculations in the ssNMR analysis of excipients is presented in this article.

Although the ssNMR data on some of the pharmaceutical excipients were reported previously, usually the excipients were not the main objects of those studies. In many cases there were no assignments in the ^{13}C ssNMR spectra, or the assignments were questionable. Moreover, the ssNMR spectra of the excipients were registered for the samples under various magnetic fields and using different MAS spinning frequencies, which resulted in the inhomogeneity of the already published data.

The aim of the study was to perform a detailed analysis of the most common pharmaceutical excipients used in the solid drug formulations, including proper signal assignment. To achieve this goal, the GIPAW calculations of the NMR parameters were employed. This methodology has been proven to be very successful in performing the unequivocal signal assignment of API and in many cases it is a method of choice, since the 2D experiments in the ssNMR are not as popular as in the case of solution NMR, yet in some cases can be very useful [9].

2. Materials and methods

2.1. Materials

In this study the anhydrous α-lactose; α-lactose monohydrate; mannitol; sucrose; sorbitol; sodium starch glycolate type A and sodium starch glycolate type B; potato starch; corn starch; microcrystalline cellulose (Avicel® PH-101; hypromellose; ethylcellulose; methylcellulose; hydroxyethylcellulose; sodium alginate; magnesium stearate; sodium laurilsulfate; Kollidon® 25; manufactured by the Sigma–Aldrich) (St. Louis, MO, USA) were used.

2.2. Solid-state NMR measurements

Solid-state ^{13}C CP/MAS NMR spectra were recorded on a Bruker DSX 400 spectrometer (Bruker BioSpin, Rheinstetten, Germany) operating at 400.61 MHz (^{1}H) and 100.13 MHz (^{13}C), powder samples were spun at 10 kHz in a 4 mm ZrO_2 rotor using a double air-bearing probehead (Bruker PH MAS VTN 400WB BL4). Acquisition was performed with a standard CP pulse sequence with ramped CP scheme and two-pulse phase modulation decoupling scheme, using 3.2 μs proton 90° pulse, 2 ms contact time and repetition times ranging from 5 s to 1200 s. The decoupling field strength was set to 78 kHz. Glycine was used for the Hartmann–Hahn matching procedure and as an external standard; ^{13}C chemical shifts were referenced to glycine CO at 176.5 ppm. Chemical shifts were calibrated relative to TMS. For all the experiments 0.755 Hz digital FID resolution, 32 K time domain and 24 752 Hz spectral width were applied.

2.3. GIPAW CASTEP calculations

The quantum-chemical calculations of geometry, energy and NMR shielding constants were carried out with the CASTEP program [10,11] implemented in the Materials Studio 6.1 software [12]. Geometry optimizations and calculations of NMR chemical shielding were performed using the plane wave pseudopotential formalism and the Perdew–Burke–Ernzerhof (PBE) exchange-correlation functional, defined within the generalized gradient approximation (GGA) and the dispersion-interaction contributions were considered using the Tkatchenko–Scheffler (TS) method [13] for density functional theory dispersion correction (DFT-D). All the calculations were done with ultrasoft pseudopotentials calculated on the fly; the quality of calculations was set to fine as implemented in the CASTEP standards. CASTEP default values for the geometry convergence criteria were used. The kinetic energy cutoff for the plane waves was set to 550 eV. Brillouin zone integration was performed using a discrete $2 \times 1 \times 3$ (for anhydrous α-lactose), $3 \times 2 \times 1$ (for mannitol), $3 \times 1 \times 2$ (for α-lactose monohydrate), $2 \times 2 \times 1$ (for sucrose) and $1 \times 1 \times 3$ (for sorbitol) Monkhorst-Pack k-point sampling for a primitive cell. The computation of shielding tensors was performed using the gauge-including projector-augmented wave (GIPAW) method of Pickard and Mauri [14]. In the calculations, the experimental X-ray structures (refcodes EYOCUQ01 for anhydrous α-lactose, DMANTL09 for mannitol, LACTOS11 for α-lactose monohydrate, SUCROS16 for sucrose, GLUCIT03 for sorbitol) from the Cambridge Structural Database (CSD) [15] were used. In the calculations the positions of all atoms were optimized, while the cell parameters were fixed to their experimental values. To compare the theoretical and experimental data, the calculated chemical shielding constants (σ_{iso}) were converted to chemical shifts (δ_{iso}), using the following equation: $\delta_{iso} = (\sigma_{Gly} + \delta_{Gly}) - \sigma_{iso}$, where σ_{Gly} and δ_{Gly} stand for the shielding constant and the experimental chemical shift, respectively, of the glycine carbonyl carbon atom (176.5 ppm).

3. Results and discussion

On the basis of chemical structure, the studied excipients were divided into four groups (1) disaccharides and sugar alcohols (2) starch and its derivatives (3) cellulose and its derivatives and (4) various other ones.

3.1. Disaccharides and sugar alcohols (Fig. 1, Table 1)

This group is the only one of the studied excipients for which the crystal structures are available. Therefore, it was possible to perform the GIPAW calculations and on the basis of their results to suggest proper assignments of the resonances in ^{13}C CP/MAS NMR spectra.

Naturally occurring mono- and disaccharides, as well as their derivatives, are frequently used as excipients. Lactose is the most widely used diluent in the tablet formulation process. It does not react with most drugs, whether used in hydrous or anhydrous form. There is notable agreement that five well-accepted lactose forms exist in the solids [16]. These consist of a single hydrated form, α-lactose monohydrate, and three dehydrated forms: β-lactose, stable anhydrous α-lactose and unstable hygroscopic anhydrous

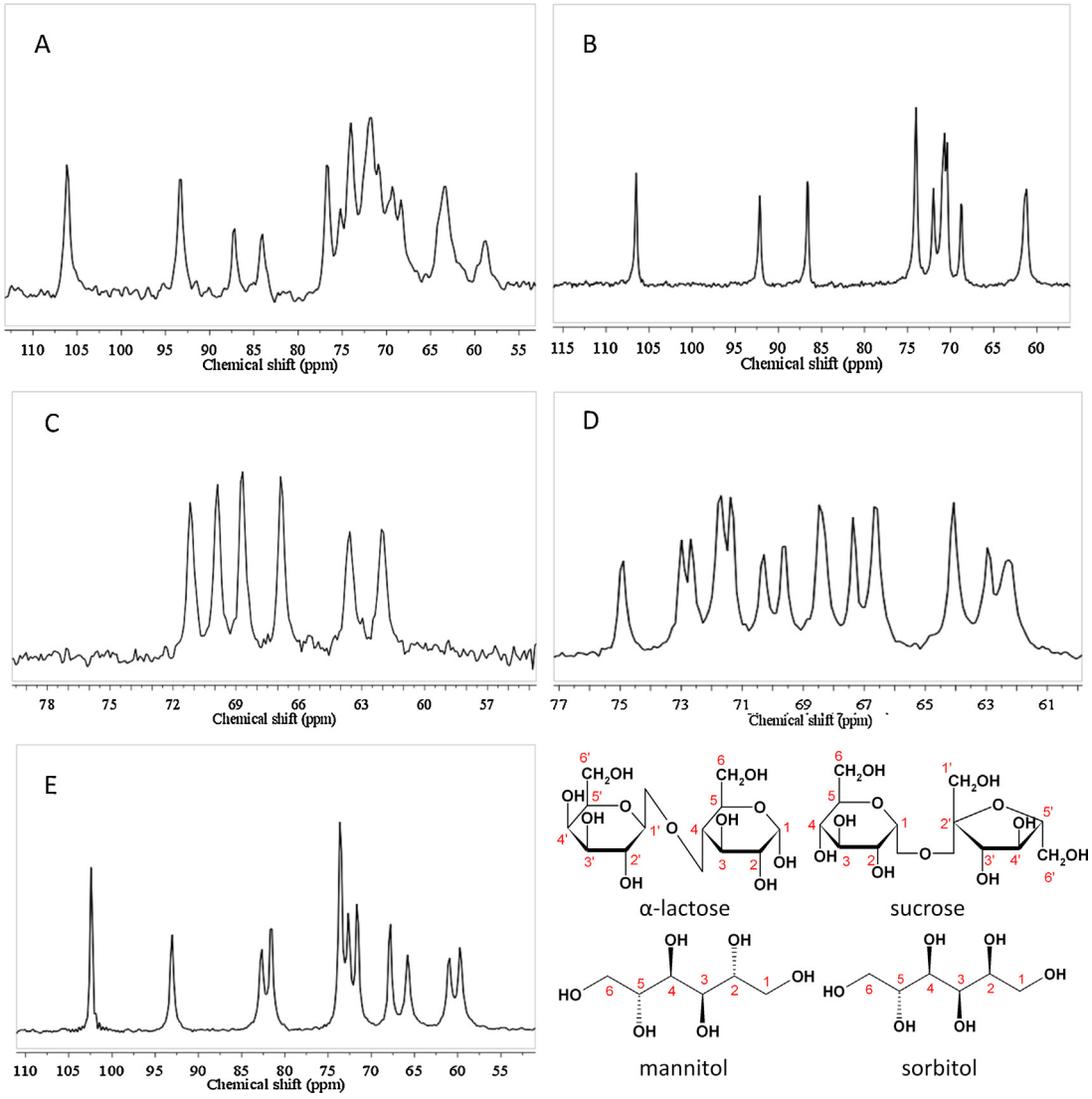

Fig. 1. ^{13}C CP/MAS NMR spectra of the anhydrous α-lactose (A), α-lactose monohydrate (B), mannitol (C), sorbitol (D) and sucrose (E).

α-lactose. The most popular polymorphic forms of lactose that are used as excipients are α-lactose monohydrate and anhydrous α-lactose.

^{13}C CP/MAS NMR spectra of lactose polymorphs were reported before [16]. though without the signal assignment. Despite the conformational similarities between the α-lactose anhydrous and α-lactose monohydrate, the ^{13}C CP/MAS NMR spectra of those two polymorphs differ significantly due to the differences in the crystal arrangements. In the case of α-lactose monohydrate ^{13}C CP/MAS NMR spectrum the signals are narrow due to the presence of only one molecule in the asymmetric unit ($Z' = 1$). In the crystals of α-lactose monohydrate the water molecule plays a role of both double hydrogen bond donor and acceptor (it is involved in four hydrogen bonds) and links the two molecules of α-lactose.

In the ^{13}C CP/MAS NMR spectrum of anhydrous α-lactose the signals are significantly broader and more overlapped. This is caused by the presence of two molecules in the asymmetric unit ($Z' = 2$). However, due to the significant role of hydrogen bond network in the stabilization of this structure, the overlapping signals do not necessarily originate from the corresponding atoms of those two molecules in the asymmetric unit cell (i.e., the signal at 70.99 ppm originates from the carbon atoms 4′ and 2 of the same molecule). Therefore, proper assignment of the peaks in anhydrous α-lactose was much more challenging and probably that is why it was not published before. Fortunately, the crystal structures of those two forms were previously deposited in Cambridge Structural Database (CSD), which allowed to perform the GIPAW calculations and assign the peaks in both spectra. Theoretical and experimental results were found to be in excellent agreement.

Since the α-lactose monohydrate when overheated converts to the anhydrous form, ssNMR can be used to determine whether or not the storage conditions of this excipient were proper.

Sucrose is believed to exist only in one stable-monoclinic hemihedral form [17]. Despite the great significance of this compound, to the best of our knowledge the signals in the ^{13}C CP/MAS NMR spectrum of crystalline sucrose have not been assigned properly yet. The first attempt to resolve this matter was made by Pfeffer et al. [18] who registered the ^{13}C CP/MAS NMR spectrum of partially deuterated crystalline samples of sucrose and compared its assignment with the solution spectra. Those authors left some peaks in the ^{13}C CP/MAS NMR spectra unassigned due to the ambiguous results of the employed methodology.

More recently, Lee and Da Chang [17] proposed the assignment of some signals in the ^{13}C ssNMR spectra of crystalline sucrose; however, their results were not consistent with those obtained by Pfeffer et al. [18].

Table 1
^{13}C CP/MAS chemical shifts (δ, ppm) of the studied excipients.

Anhydrous α-lactose		α-Lactose monohydrate		Sucrose		Mannitol		Sorbitol	
^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$
1	93.32	1	92.16	1	93.06	1	62.01	1a	66.63
2	70.99	2	70.99	2	73.59	2	71.16	2a	72.70
3	74.02	3	74.02	3	72.65	3	66.84	3a	72.94
4	84.08	4	86.61	4	67.82	4	68.70	4a	67.35
5	71.83	5	70.42	5	73.59	5	68.89	5a	70.30
6	58.84	6	61.35	6	59.72	6	63.58	6a	62.92
1′	106.11	1′	106.51	1′	65.79			1b	64.07
2′	71.83	2′	70.72	2′	102.04			2b	74.92
3′	76.68	3′	72.01	3′	82.69			3b	71.68
4′	70.99	4′	68.75	4′	71.64			4b	68.41
5′	75.16	5′	74.02	5′	81.58			5b	69.63
6′	63.42	6′	61.20	6′	60.98			6b	62.31
1a	93.32							1c	64.07
2a	71.83							2c	71.68
3a	71.83							3c	68.41
4a	87.23							4c	71.41
5a	74.02							5c	66.63
6a	63.42							6c	62.31
1′a	106.11								
2′a	74.02								
3′a	74.02								
4′a	68.39								
5′a	76.68								
6′a	63.42								

Taking advantage of the good quality crystal structure of sucrose deposited in CSD GIPAW calculations were performed and according to the obtained results a new assignment was suggested, based on the very good agreement between the experimental data and results of theoretical calculations. The coefficient of determination (R^2) between the calculated and experimentally obtained chemical shifts of suggested assignment was found to be significantly higher than that for Pfeffer's assignment (0.996 vs. 0.972; respectively).

Owing to their chemical similarity, sorbitol and its stereoisomer mannitol are characterized by similar values of their chemical shifts for the signals in the ^{13}C CP/MAS NMR spectra. Mannitol exists in four crystalline forms, three anhydrous forms: α, β and δ and a hemihydrate one [19]. The δ form is enantiotropically related to α and β forms. The object of this study was the most stable β form, which is the only polymorph described in the European Pharmacopeia (Ph. Eur.). The results of the calculations of the chemical shielding constants confirmed the ^{13}C CP/MAS NMR spectra assignment published by Grindley et al. [20].

The signals in the ^{13}C CP/MAS NMR spectrum of mannitol are significantly narrower than those in the spectrum of sorbitol. This is a result of a different crystal structure arrangement and the number of units in the crystal unit cell (Z'). In the case of mannitol $Z' = 1$, which corresponds with the presence of six signals in its ^{13}C CP/MAS NMR spectrum. In the case of sorbitol $Z' = 3$, therefore its ^{13}C CP/MAS NMR spectrum is much more complicated and the signals were not previously assigned. Taking advantage of the deposited in CSD crystal structure and using the results of the GIPAW calculations the signal assignments of those two excipients were performed, basing on the theoretically obtained chemical shifts values.

The results of the GIPAW calculations which were essential to perform the signal assignment can be found in the supplementary materials (Table S1).

3.2. Starch and its derivatives (Fig. 2, Table 2)

Opinions on the possible use of ^{13}C ssNMR analysis to differentiate the samples of starch by its origin are divided. Some authors [21]. using ambiguous resolution enhancement methods, like large negative line broadening (LB = −100), try to distinguish the starch of different origin by the differences in the chemical shift values of the overlapping signals in the 95–105 ppm region. Others point out that the starch is a natural mixture of amylose and amylopectin, combined in different proportions, and suggest that the starch origin can be determined by comparing the spectrum of an excipient with a series of spectra of the mixtures of amylose and amylopectin in different proportions [22]. This however can be very misleading since the amylose and amylopectin contents in the starches of different origin are not constant and depend on many factors, including the place of cultivation and plant variety.

According to Ph. Eur., the origin of starch can be confirmed by the microscopic analysis of the particle size or by the observation of opalescence of water suspension. In this study any significant differences between the ^{13}C CP/MAS NMR spectra of starch, either in the chemical shift values or in the relative intensities of the signals, for the samples originating from different plant sources (corn and potato) have not been found.

Sodium starch glycolate is the cross-linked and substituted polymer of glucose. The degree of cross-linking and substitution are important factors in determining the effectiveness of this material as superdisintegrant. The effect of the introduction of large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. The effect of the cross-linking is also to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water. The optimum balance between the degree of substitution and the extent of cross-linking allows rapid water uptake by the polymer without the formation of a viscous gel that might impede dissolution. The Ph. Eur. differentiates sodium starch glycolate types A, B and C. Those types differ in the content of elemental sodium, the range of pH and other physico-chemical properties which affect their pharmaceutical application.

It is possible to synthesize sodium starch glycolate from a wide range of native starches, but in practice potato starch is used since it gives the product with the best disintegrating properties. The Ph. Eur. specifies potato starch as the basis of types A and B of sodium starch glycolate. The degree of substitution in sodium starch glyco-

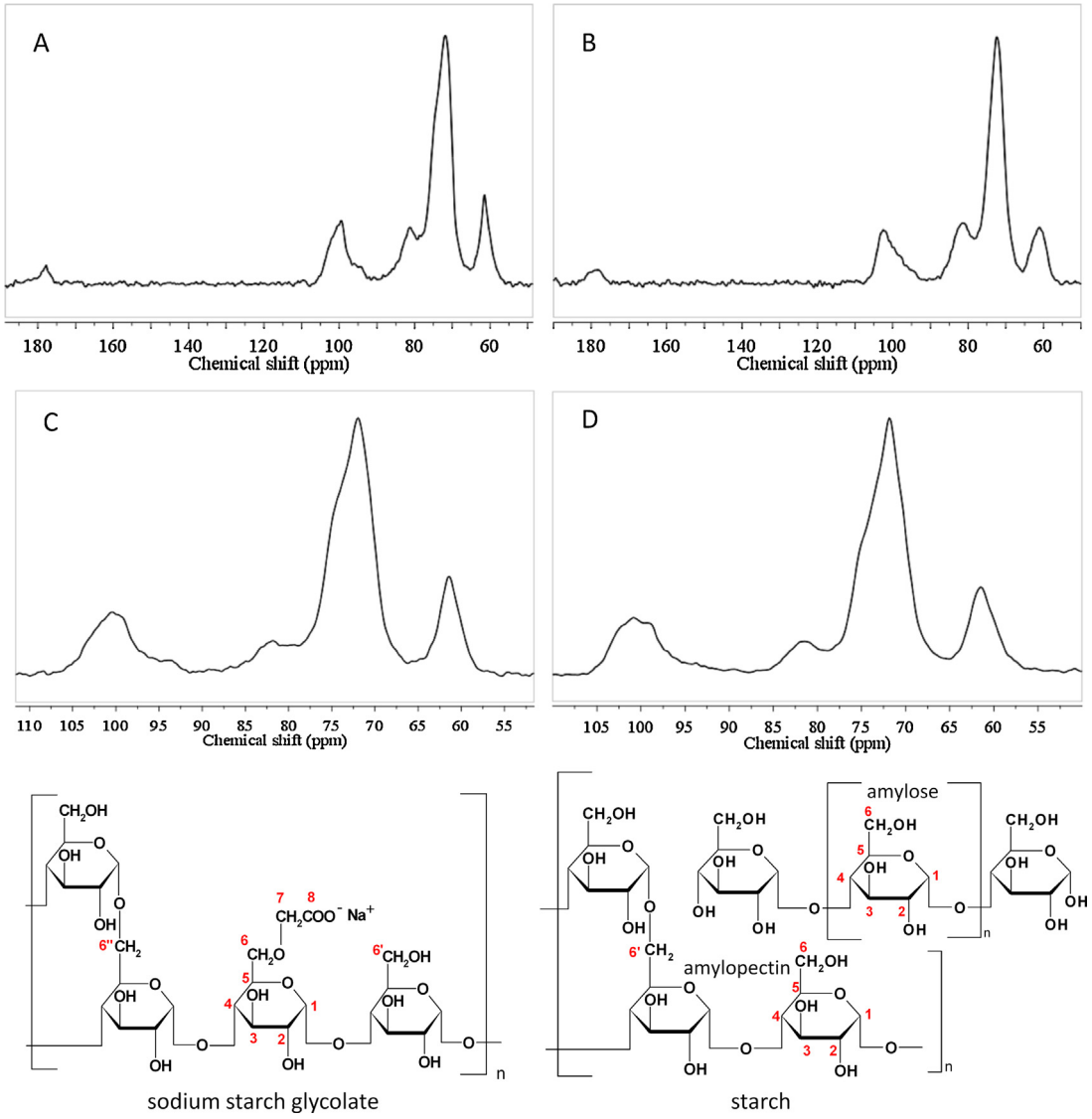

Fig. 2. ^{13}C CP/MAS NMR spectra of the sodium starch glycolate type A (A), sodium starch glycolate type B (B), potato starch (C) and corn starch (D).

Table 2
^{13}C CP/MAS chemical shifts (δ, ppm) of the studied excipients.

Corn starch		Potato starch		Sodium starch glycolate type A		Sodium starch glycolate type B	
^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$
6,6′	61.43	6,6′	61.43	6,6,6″,7	61.47	6,6,6″,7	61.13
2,3,5	71.81	2,3,5	71.98	2,3,5	71.87	2,3,5	72.33
4	81.46	4	81.83	4	81.18	4	81.21
1	100.84	1	100.32	1	99.52	1	102.50
				8	177.82	8	178.27

Table 3
^{13}C CP/MAS chemical shifts (δ, ppm) of the studied excipients.

Microcrystalline cellulose		Hypromellose		Ethylcellulose		Hydroxyethylcellulose		Methylcellulose	
^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$
6[a]	63.43	10	18.93	8	15.59	6,7,8	61.06	6	60.72
6	65.42	6,7,8	60.47	6,7	68.50	5	70.31	2,3,5	74.39
5	72.54	2,3,5,9	74.58	2,5	75.40	2,3	74.19	4	83.97
2,3	75.14	4	84.08	3,4	83.03	4	82.06	1	103.72
4[a]	84.78	1	103.49	1	102.78	1	102.83		
4	89.14								
1	105.31								

[a] Signals originating from the fiber surface and the amorphous material.

Table 4
^{13}C CP/MAS chemical shifts (δ, ppm) of the studied excipients.

Sodium alginate		Kollidon® 25		Magnesium stearate		Sodium laurilsulfate	
^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$	^{13}C atom	$\delta_{CP/MAS}$
5	65.56	3	18.64	18	14.37	12	14.41
2,3	68.43	2	31.72	17	25.01	11	24.12
2′,3′,5′	71.73	2′	36.12	3	28.26	3	27.47
4′	75.59	4	43.07	2,4–15	33.28	2,4–10	32.98
4	80.89	1′	51.03	16	38.74	1	69.05;70.30
1,1′	101.36	1	176.25	1	179.38–185.96		
6,6′	176.39						

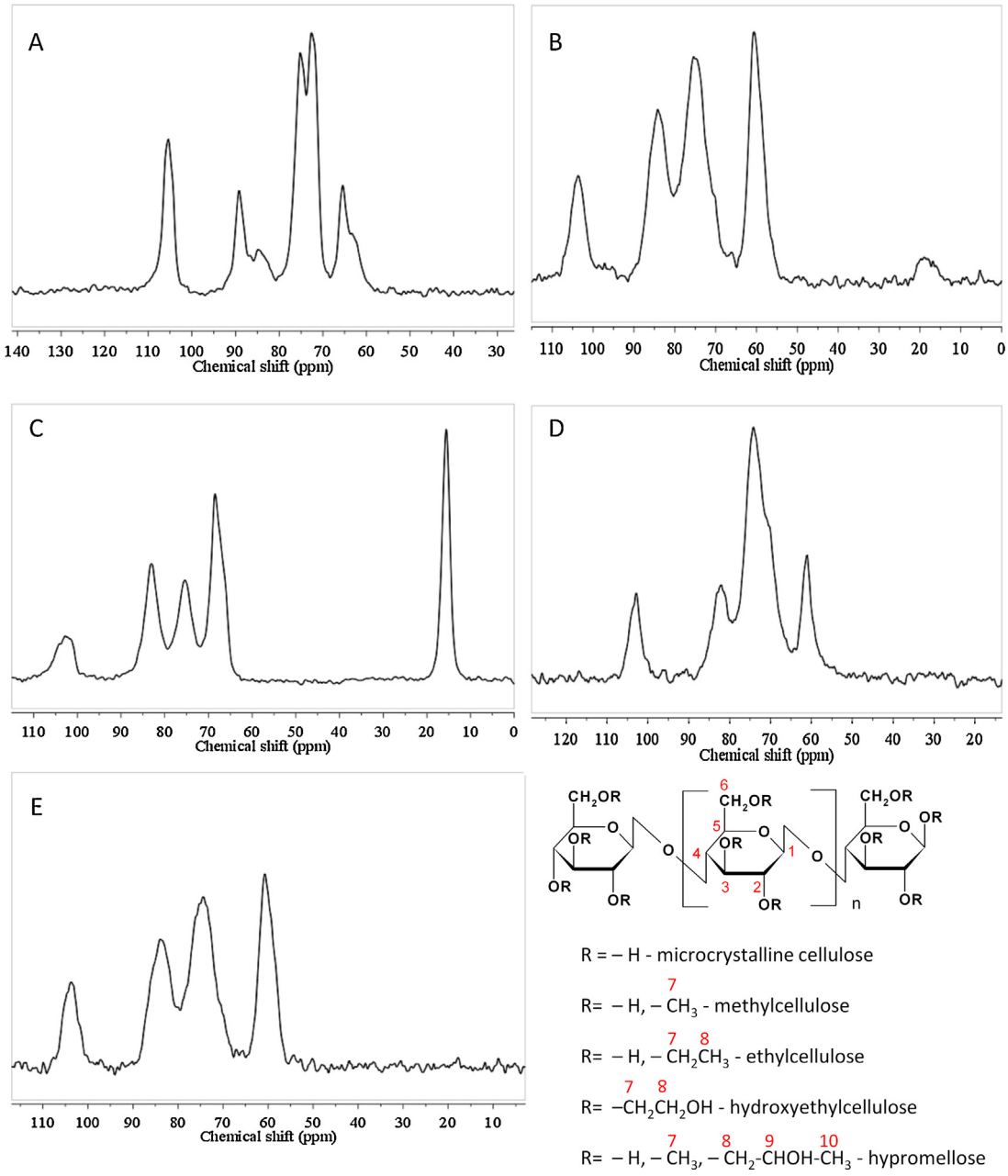

Fig. 3. ^{13}C CP/MAS NMR spectra of the microcrystalline cellulose (Avicel® PH-101) (A), hypromellose (B), ethylcellulose (C), hydroxyethylcellulose (D) and methylcellulose (E).

late is in the range from 0.23 to 0.32, as compared with a maximum possible value of 3 (i.e., when all three hydroxy groups in the glucose units would be substituted). The degree of substitution is not explicit in the Ph. Eur. monographs, but it is related to the assay value (i.e., the sodium content of the dried and alcohol washed substance). Sodium starch glycolate type B is characterized by the apparently lower pH, and hence a lower degree of substitution than type A.

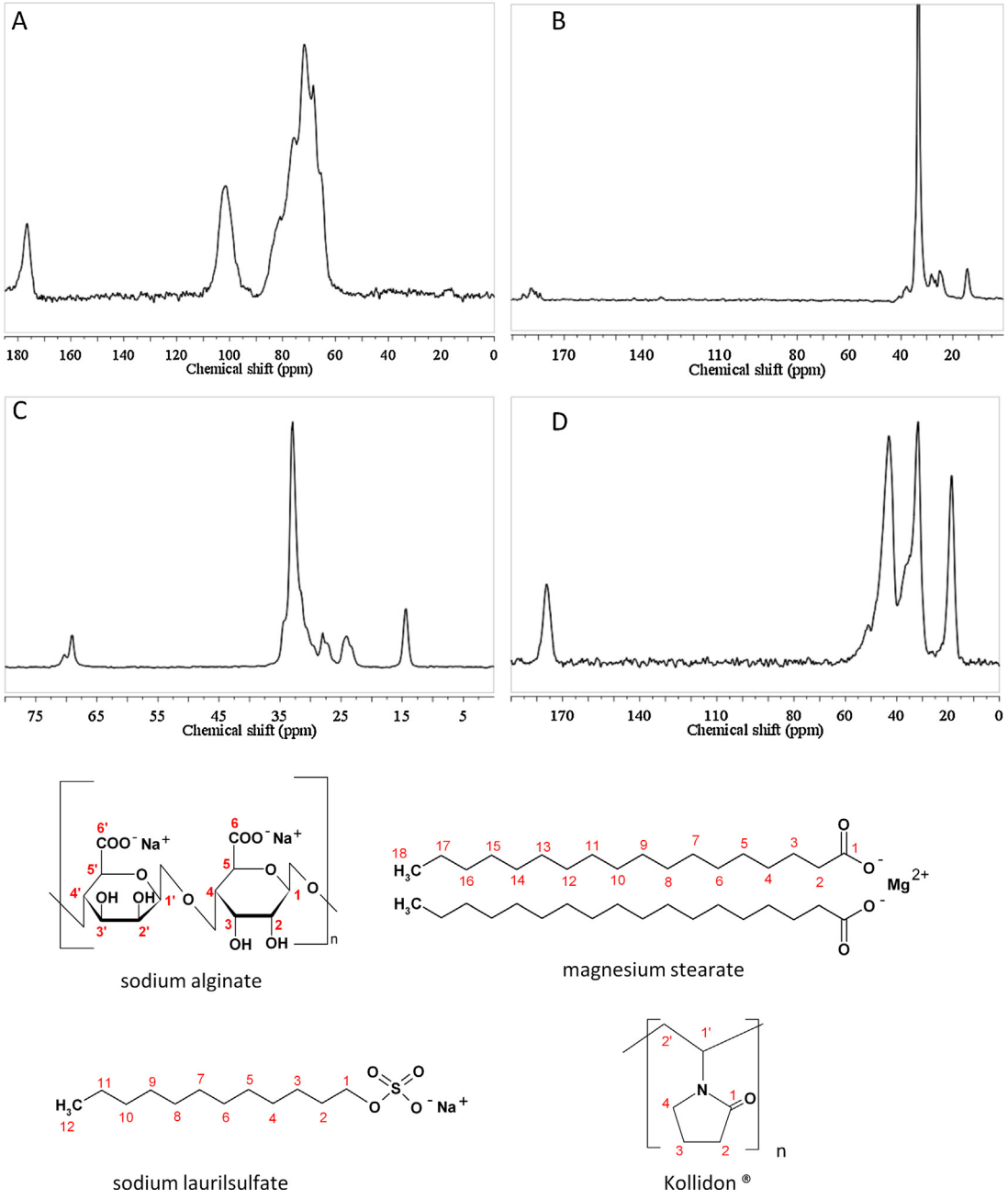

Fig. 4. ^{13}C CP/MAS NMR spectra of the sodium alginate (A), magnesium stearate (B), sodium laurilsulfate (C) and Kollidon® 25 (D).

To the best of our knowledge, the ^{13}C ssNMR spectra of sodium starch glycolate have not been published yet, although the ^{23}Na ssNMR was used to characterize this popular excipient [23]. Therefore, the ^{13}C CP/MAS NMR spectra of sodium starch glycolate types A and B were registered and are presented in Fig. 2.

Since the studied samples of sodium starch glycolate types A and B have been manufactured from the potato starch, it is not surprising that there are some similarities between their ^{13}C CP/MAS NMR spectra, including the shapes and the number of signals in the range of 70–85 ppm. However, there are also some significant differences between the ^{13}C CP/MAS NMR spectra of the potato starch and sodium starch glycolate, which can be explained as a result of starch substitution. The most apparent one is the existence of an extra signal at 178 ppm in the spectrum of sodium starch glycolate. This signal was assigned as originating from the carboxylic groups introduced by substitution.

There are also some noticeable differences between the ^{13}C CP/MAS NMR spectra of sodium starch glycolate type A and B. First of all, the intensities and shapes of the signals at 61 ppm are different for those two types. In the case of type A, characterized by a higher degree of substitution, this signal is more intensive and narrower. Those two types differ also in the shapes of the broad signals at 95–105 ppm.

3.3. Cellulose and its derivatives (Fig. 3, Table 3)

Microcrystalline cellulose is one of the most commonly used pharmaceutical excipients for direct tableting. Differences in flow properties and tableting characteristics can be attributed to differences in the moisture content and particle size distribution, and microcrystalline cellulose is typically available as grades that are classified according to these parameters. Multiple grades of

microcrystalline cellulose varying in mean particle size and water content were the object of studies of Sperger and Munson [24]. Those authors did not observe any significant differences between the spectra of different grades or between lots of the same grade. Although in this study the microcrystalline cellulose of different grades have been used, no differences between our spectra and the previously published ones have been found.

In the spectra of ethylcellulose a single and narrow signal at 15.61 ppm can be observed. The signal is characteristic of this excipient and can be used to distinguish it from the other excipients from this group. The signal assignment in the ^{13}C CP/MAS NMR spectra was performed on the basis of the ^{13}C NMR solution spectra recently published by the Es-haghi et al. [25]. and the ^{13}C CP/MAS NMR spectrum of ethylcellulose has not been published before.

The spectra of hydroxyethylcellulose, hypromellose [24] and methylcellulose [26] registered using the samples purchased from the same manufacturer have been published and assigned recently and correspond with those registered in this study.

3.4. Varia (Fig. 4, Table 4)

Currently, there are several types of commercially available products of polyvinylpyrrolidone (PVP) on the market that meet current Ph. Eur. monographs standards. Kollidon® is a brand name for highly cross-linked modification of PVP. Kollidon® products consist of soluble and insoluble grades PVP of various molecular weights and particle sizes. They are used as dry binders, film-formers, stabilizers in suspensions, dispersants for pigments, enzyme stabilizers and bioavailability improvers. Kollidon® 25 due to its high water absorption properties is commonly added as an excipient to a tablet formulation to facilitate its breakage or disintegration. The ^{13}C ssNMR spectrum of this material has not been published before. To the best of our knowledge, so far only the PVP 40 [27] and PVP 90 [28] ^{13}C CP/MAS NMR spectra have been published and the signals have been assigned. The material of our studies differs from the previously studied samples of PVP in the average molecular weight (Mw), which for our sample was in the range of 28,000–34,000 instead of 40,000 for PVP 40 and 360,000 for PVP 90. Despite the diversity in the Mw, the spectra of different types of PVP are similar. Therefore, in our opinion, ^{13}C ssNMR cannot be used to determine the type of PVP which was used as an excipient.

The magnesium stearate of pharmaceutical grade is composed of the salts of stearic, palmitic and other fatty acids derived from natural sources. To fulfill the requirements of Ph. Eur. the content of stearic acid in the fatty acid fraction should be minimum 40.0% and the sum of stearic acid and palmitic acid in the fatty acid fraction should be minimum 90.0%. As a result, the quantitative composition of this excipient can vary and depends on the methods and materials used in its preparations. Magnesium stearate can form a variety of hydrates upon exposure to humidity. Consequently, most of the commercial supplies for this lubricant contain a mixture of various hydrates in unknown ratios. Therefore, some differences between the ^{13}C CP/MAS NMR spectra of this excipient originating from different manufacturers are anticipated. In the ^{13}C CP/MAS NMR spectrum of magnesium stearate the most intensive signal originates from the methylene groups. To the best of our knowledge, the ^{13}C CP/MAS NMR spectra of this excipient have not been published before.

A similar situation concerns sodium laurilsulfate, which according to the Ph. Eur. is a mixture of sodium alkyl sulfates (minimum 85.0%), consisting chiefly of sodium dodecyl sulfate. The influence of the source variability on solid oral dosage form development was the object of studies [29] which revealed its impact on the solubilization, granulation process, and tablet dissolution. This heterogeneity of the composition of this excipient results in differences between the ^{13}C ssNMR spectra of the samples of different origin. In this study some extra signals could be observed which were not present in the spectra of pure sodium dodecyl sulfate [30]. The spectrum of sodium alginate has been published and assigned recently [24].

4. Conclusions

Pharmaceutical excipients are a very heterogeneous group of compounds or their mixtures. Some of them (α-lactose, α-lactose monohydrate, sorbitol, mannitol, sucrose) are described in the Ph. Eur. as single polymorphs, for which the good quality crystal structures have already been obtained. For those excipients the ^{13}C ssNMR spectra are repetitive and do not differ when registered for the samples of different origin.

The other excipients (magnesium stearate, sodium laurilsulfate) are the mixtures of various polymorphic forms or even mixtures of various compounds. Since the Ph. Eur. allows a relatively high degree of variability in their quantitative composition, the differences between the ^{13}C ssNMR spectra registered for the samples of different origin are expected.

Some differences between the ^{13}C ssNMR spectra for the samples of different origin may also be noticed in the cases of natural (starch, cellulose derivatives) and synthetic (PVP, ethylcellulose, hypromellose, hydroxyethylcellulose) macromolecules. However, as it was shown above, this does not occur in all cases. Excipients from this group are the mixtures of compounds with different Mw and form the particles of different shapes and different size distributions. Therefore, in the ^{13}C ssNMR spectra of their samples broad and overlapping signals are usually observed.

In this work the most common pharmaceutical excipients used in the solid drug formulations have been analyzed. Their solid-state NMR spectra have been assigned, employing GIPAW calculations, if possible (e.g., available XDR data).

For some of the studied excipients (ethylcellulose, Kollidon® 25, magnesium stearate, sodium starch glycolate) ^{13}C ssNMR spectra have not been published before whereas for the other (anhydrous α-lactose, α-lactose monohydrate, sorbitol) the signals in the spectra were not assigned or the assignments were not correct (sucrose).

The results of this work summarize the data on the ^{13}C ssNMR analysis of the most common pharmaceutical excipients. These data may serve as a convenient guide for solid drug formulations and popularize solid-state NMR as a tool in pharmaceutical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpba.2016.01.032.

References

[1] E. Pindelska, A. Sokal, L. Szeleszczuk, D.M. Pisklak, W. Kolodziejski, Solid-state NMR studies of theophylline co-crystals with dicarboxylic acids, J. Pharm. Biomed. Anal. 100 (2014) 322–328.
[2] M.A. Zielińska-Pisklak, D.M. Pisklak, I. Wawer, ^{1}H and ^{13}C NMR characteristics of β-blockers, Magn. Reson. Chem. 49 (2011) 284–290.
[3] E. Pindelska, L. Szeleszczuk, D.M. Pisklak, Z. Majka, W. Kolodziejski, Crystal structures of tiotropium bromide and its monohydrate in view of combined solid-state NMR and GIPAW studies, J. Pharm. Sci. 2015 (104) (2015) 2285–2292.
[4] D.M. Pisklak, M. Zielińska-Pisklak, Ł. Szeleszczuk, I. Wawer, ^{13}C cross-polarization magic-angle spinning nuclear magnetic resonance analysis of the solid drug forms with low concentration of an active ingredient-propranolol case, J. Pharm. Biomed. Anal. 93 (2014) 68–72.
[5] E. Pindelska, L. Szeleszczuk, D.M. Pisklak, A. Mazurek, W. Kolodziejski, Solid-state NMR as an effective method of polymorphic analysis: solid dosage forms of clopidogrel hydrogensulfate, J. Pharm. Sci. 104 (2015) 106–113.

[6] J.E. Pacilio, J.T. Tokarski, R. Quiñones, R.J. Iuliucci, High-resolution solid-state NMR spectroscopy: characterization of polymorphism in cimetidine a pharmaceutical compound, J. Chem. Educ. 91 (2014) 1236–1239.
[7] M. Zielińska-Pisklak, D.M. Pisklak, I. Wawer, Application of ^{13}C CPMAS NMR for qualitative and quantitative characterization of carvedilol and its commercial formulations, J. Pharm. Sci. 101 (2012) 1763–1772.
[8] I. Wawer, M. Pisklak, Z. Chilmończyk, ^{1}H, ^{13}C, ^{15}N NMR analysis of sildenafil base and citrate (Viagra) in solution, solid state and pharmaceutical dosage forms, J. Pharm. Biomed. Anal. 38 (2005) 865–870.
[9] A.C. Pinon, A.J. Rossini, C.M. Widdifield, D. Gajan, L. Emsley, Polymorphs of theophylline characterized by DNP enhanced solid-state NMR, Mol. Pharm. 12 (2015) 4146–4153.
[10] M.D. Segall, P.J.D. Lindan, M.J. Probert, C.J. Pickard, P.J. Hasnip, S.J. Clark, M.C. Payne, First-principles simulation: ideas, illustrations and the CASTEP code, J. Phys. Condens. Matter 14 (2002) 2717–2744.
[11] J.R. Yates, C.J. Pickard, F. Mauri, Calculation of NMR chemical shifts for extended systems using ultrasoft pseudopotentials, Phys. Rev. B 76 (2007) 024401.
[12] Materials Studio v 6.1Copyright Accelrys Software Inc. (2013).
[13] A. Tkatchenko, M. Scheffler, Accurate molecular van der Waals interactions from ground-state electron density and free-atom reference data, Phys. Rev. Lett. 102 (2009) 073005.
[14] C.J. Pickard, F. Mauri, All-electron magnetic response with pseudopotentials: NMR chemical shifts, Phys. Rev. B 63 (2001) 2451011–2451013.
[15] F.H. Allen, The Cambridge Structural Database: a quarter of a million crystal structures and rising, Acta Cryst. B 58 (2002) 380–388.
[16] J.H. Kirk, S.E. Danna, C.G. Blatchford, Lactose A definitive guide to polymorph determination, Int. J. Pharm. 334 (2007) 103–114.
[17] T. Lee, G. Da Chang, Sucrose conformational polymorphism: a jigsaw puzzle with multiple routes to a unique solution, Cryst. Growth Des. 9 (2009) 3551–3561.
[18] P.E. Pfeffer, L. Odier, R.L. Dudley, Assignment of ^{13}C CPMAS NMR spectra of crystalline methyl β-D-glucopyranoside and sucrose using deuterium labelling and interrupted proton decoupling, J. Carbohyd. Chem. 9 (1990) 619–629.
[19] M.G. Cares-Pacheco, G. Vaca-Medina, R. Calvet, F. Espitalier, J.J. Letourneau, A. Rouilly, E. Rodier, Physicochemical characterization of D-mannitol polymorphs: the challenging surface energy determination by inverse gas chromatography in the infinite dilution region, Int. J. Pharm. 475 (2014) 69–81.
[20] T.B. Grindley, M.S. McKinnon, R.E. Wasylishen, Towards understanding ^{13}C NMR. chemical shifts of carbohydrates in the solid state. The spectra of d-mannitol polymorphs and of dl-mannitol, Carbohyd. Res. 197 (1990) 41–52.
[21] H. Tang, B.P. Hills, Use of ^{13}C MAS NMR to study domain structure and dynamics of polysaccharides in the native starch granules, Biomacromolecules 4 (2003) 1269–1276.
[22] N.W.H. Cheetham, L. Tao, Solid state NMR studies on the structural and conformational properties of natural maize starches, Carbohydr. Polym. 36 (1998) 285–292.
[23] S. Edge, A.M. Belu, U.J. Potter, D.F. Steele, P.M. Young, R. Price, J.N. Staniforth, Chemical characterisation of sodium starch glycolate particles, Int. J. Pharm. 240 (2002) 67–78.
[24] D.M. Sperger, E.J. Munson, Analysis of structural variability in pharmaceutical excipients using solid-state NMR spectroscopy, AAPS PharmSciTech 12 (2011) 821–833.
[25] H. Es-haghi, S.M. Mirabedini, M. Imani, R.R. Farnood, Preparation and characterization of pre-silane modified ethyl cellulose-based microcapsules containing linseed oil, Colloid. Surf. A 447 (2014) 71–80.
[26] F.A. Aouada, M.R.D. Moura, W.T. Lopes Da Silva, E.C. Muniz, L.H.C. Mattoso, Preparation and characterization of hydrophilic spectroscopic, and kinetic properties of hydrogels based on polyacrylamide and methylcellulose polysaccharide, J. Appl. Polym. Sci. 120 (2011) 3004–3013.
[27] Y. Aso, S. Yoshioka, Molecular mobility of nifedipine-PVP and phenobarbital-PVP solid dispersions as measured by ^{13}C-NMR spin-lattice relaxation time, J. Pharm. Sci. 95 (2006) 318–325.
[28] C.A. Oksanen, G. Zografi, Molecular mobility in mixtures of absorbed water and solid poly(vinylpyrrolidone), Pharm. Res. 10 (1993) 791–799.
[29] D. Qiang, J.A. Gunn, L. Schultz, Z. Li, Evaluation of the impact of sodium lauryl sulfate source variability on solid oral dosage form development, Drug Dev. Ind. Pharm. 36 (2010) 1486–1496.
[30] B.K. Lavine, S. Hendayana, Y. He, W.T. Cooper, Solid-state NMR studies of ionic surfactants adsorbed on cyanopropyl bonded phases: implications for micellar liquid chromatography, J. Colloid Interface Sci. 179 (1996) 341–349.