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Investigation of Carbohydrates and Their Derivatives as Crystallization Modifiers

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1. Introduction

Development in the field of pharmaceutical administration has resulted in the discovery of highly sophisticated drug delivery systems that allow for the maintenance of a constant drug level in an organism. Contrary to these revolution biopharmaceutical results, over the last ten years, the number of poorly soluble drugs has steadily increased. Estimates state that 40% of the drugs in the pipelines have solubility problems. Progress in high throughput screening methods leads to an even greater amount of newly discovered drugs, but a lot of them have poor water solubility. Literature states that about 60% of all drugs coming directly from synthesis are nowadays poorly soluble. Meanwhile the five key physico-chemical properties, such as pK_a , solubility, permeability, stability and lipophilicity, in early compound screening should be optimized. Compounds with insufficient solubility carry a higher risk of failure during discovery and development, since insufficient solubility may compromise other property assays, mask additional undesirable properties, influence both pharmacokinetic and pharmacodynamic properties of the compound and finally may affect the developability of the compound. Poor solubility in water correlates with poor bioavailability. If there is no way to improve drug solubility, it will not be able to be absorbed from the gastrointestinal tract into the bloodstream and reach the site of action (Junghanns & Müller, 2008; Payghan et al., 2008).

Modification/optimization of unfavourable physico-chemical properties of these drugs is possible through increasing their water solubility or improving permeability. There are many ways to solubilize certain poorly soluble drugs. But these methods are limited to drugs with certain properties in regard to their chemistry or, for example, to their molecular size or conformation.

Aqueous solubility can be increased by chemical exchange: (i) salts, co-crystals or solvates formation (affects also chemical stability, polymorphism, technological workability);

(ii) substitution by hydrophilic groups (effect of drugs with small molecules can be decreased); (iii) prodrug preparation (hydrolyzable amides or semiesters with polybasic acids). In general, the following structural modifications are the best way to improve permeability: (i) replacement of ionisable groups by non-ionizable groups; (ii) increase of lipophilicity; (iii) isosteric replacement of polar groups; (iv) esterification of carboxylic acid; (v) reduction of hydrogen bonding and polarity; (vi) reduction of size; (vii) addition of a non-polar side chain; (viii) preparation of prodrugs. Generally, these strategies are based on a few fundamental concepts: change of ionizability, lipophilicity, polarity or change of hydrogen bond donors or acceptors. Both approaches interact logically.

Based on these facts, pre-formulation/formulation can be another and mostly successful strategy for improving aqueous solubility and/or permeability and subsequently bioavailability. For example, selection of a suitable salt, particle size reduction (till nano size) connected with an increase of the surface area, change of polymorphic forms, selection of appropriate excipients to function as solubilizers/transporters (surfactants or pharmaceutical complexing agents, permeability enhancers) can be used for the oral dosage form (Kerns & Di, 2008).

It is well-known that crystalline materials obtain their fundamental physical properties from the molecular arrangement within the solid, and altering the placement and/or interactions between these molecules can, and usually does, have a direct impact on the properties of the particular solid. Currently, solid-state chemists call upon a variety of different strategies when attempting to alter the chemical and physical solid-state properties of active pharmaceutical ingredients (APIs), namely, the formation of salts, polymorphs, hydrates, solvates and co-crystals (Seddon & Zaworotko, 1999; Datta & Grant, 2004; Grepioni & Braga, 2007; Schultheiss & Newman, 2009).

Currently, salt formation is one of the primary solid-state approaches used to modify the physical properties of APIs, and it is estimated that over half of the medicines on the market are administered as salts (Bighley et al., 1996; Stahl & Wermuth, 2002; Gu & Grant, 2003.). However, a major limitation within this approach is that the API must possess a suitable (basic or acidic) ionizable site. In comparison, co-crystals (multi-component assemblies held together by freely reversible, non-covalent interactions) offer a different pathway, where any API regardless of acidic, basic or ionizable groups, could potentially be co-crystallized. This aspect helps to complement existing methods by reintroducing molecules that had limited pharmaceutical profiles based on their non-ionizable functional groups. Since the primary structure of a drug molecule does not change in co-crystals, their development in terms of the regulation "New Chemical Entities (NCEs)" of the U.S. Food and Drug Administration (FDA) as well as European Commission Regulation (EC) No. 258/97 carries fewer risks and takes much less time; nevertheless stability and bioequivalent studies are still necessary. In addition, the number of potential non-toxic co-crystal formers (or co-formers) that can be incorporated into a co-crystalline reaction is numerous, *e.i.* pharmaceutical excipients, amino acids, food additives, nutraceuticals, see for example the GRAS list (Generally Regarded as Safe) or the EAFUS Database (Everything Added to Food in the United States), both published by the FDA.

It should be made clear that no one particular strategy offers a solution for property enhancement of all APIs. Each API must be examined and evaluated on a case-by-case basis in terms of molecular structure and desired final properties (Schultheiss & Newman, 2009).

2. Polymorphism

The term "polymorphism" (from Greek: *polys* = many, *morfé* = form) was first used by Mitscherlich in 1822. He noticed that one compound of a certain chemical composition can crystallize into several crystal forms (Mitscherlich, 1822). Polymorphism is an ability of substances to exist in two or more crystal modifications differing from each other by structure and/or molecule conformation in the crystal lattice. The concept of polymorphism is often confounded with isomorphism or pseudopolymorphism. These concepts are interconnected but there are great differences between them.

In contrast to polymorphism when one substance able to form different crystal modifications is considered, in case of isomorphism two or more different substances that have just similar structure but form the same crystal modifications are considered. Such substances can even form so-called isomorphous series. Most often they originate as a result of co-crystallization of isomorphous substances from the mixture of their saturated solutions. A typical example is sulphates: magnesium sulphate, zinc sulphate and nickel sulphate crystallizing as heptahydrates. Also pseudopolymorphism should be distinguished from polymorphism. The concept of pseudopolymorphism is used for crystalline forms which also comprise solvent molecules as an integral part of their structure. These pseudopolymorphs are sometimes called solvates or hydrates if the solvent is water (Rodríguez-Spong et al., 2004).

The fundamental forms of solid substances can be classified into polymorphs, solvates/desolvated solvates and amorphous substances. A co-crystal can be defined as a multiple-component crystal, in which two or more molecules that are solid under ambient conditions coexist through a hydrogen bond (see Fig. 1 and Fig. 2). Polymorphism can be

Figure 1. API solid form classification based on structure and composition. (Ref. Sekhon, 2009) (Taken and adapted with the permission of the author.)

classified depending on the fact if the molecule occurs in different conformations or is the same. If the molecule can have different conformations that crystallize differently and so the molecule is flexible, conformation polymorphism is observed. If the molecule is rigid, does not have any conformations and polymorphs differ only by their packing in the crystalline structure, this is the case of package polymorphism (Sharma et al., 2011).

Polymorphism should be distinguished from crystal morphology that represents crystallization of a substance from different solvents with a change of the form but without modification of the crystalline structure.

Figure 2. Schematic illustration of polymorphism of solid compounds. (Ref. Kratochvíl, 2009) (Taken and adapted from the presentation "Pharmaceutical Co-crystals" with the permission of the author.)

In the pharmaceutical practice it is conventional to collectively call all polymorphs, solvates and polymorphs of the same API as solid forms or polymorphs in the extended meaning and designate them by, for example, Roman numerals or letters. It should be taken into consideration that designation of polymorphs is often non-uniform; it originates historically; therefore it is possible that two different polymorphs will be designated by different authors in the same way. A problem of pharmaceutical producers is polymorphic transitions in organic systems that are often hysteresis, badly defined and solvent-mediated. Polymorphic transitions can occur at all technological stages of drug production (at final API crystallization, wet granulation, micronization, tableting or in ready tablets, for example, under the influence of auxiliaries – excipients). At drug registration, national regulation authorities demand description of all solid forms and possible phase transitions of the drug as well as a prescribed guarantee of the product polymorphic purity from pharmaceutical companies. At present approximately 85% of pharmaceutical products are solid formulations; therefore no manufacturer can afford to ignore the issue of polymorphism.

2.1. Crystallization

During crystallization a self-assembly supramolecular process takes place when randomly oriented molecules assemble into internally structured crystals (Kratochvíl, 2007). There are several ways of crystallization: (i) by evaporation of solvent; (ii) by addition of antisolvent (product precipitation); (iii) by cooling of solution; (iv) by change of pH; (v) by addition of a compound that will produce the desired product by a chemical reaction; (vi) by lyophilisation, sublimation or cooling of melt (Kratochvíl, 2010). The first two possibilities were used in the experimental part.

The process of crystal formation is a complicated kinetic process which, if we simplify, is composed of nucleation, subsequent crystal growth around the formed crystal nuclei and growth termination. This happens at precipitation of a solid substance in the crystalline form from solution or at solidification of a substance.

The basis of nucleation is the quickest formation of the crystal nucleus. By constant sequence of molecules addition molecular aggregates, clusters, originate. The aggregates spontaneously impact and thus disintegrate but also grow. When they achieve the critical size, they become nuclei that do not disintegrate spontaneously but, to the contrary, only grow into a crystal. Nuclei can be classified into primary and secondary. Primary nucleation is further divided into homogenous and heterogeneous. Homogenous nucleation is characterized by formation of nuclei as a result of random impacts of aggregates somewhere in the solution volume without the presence of any foreign matter. By contrast, heterogeneous nucleation is assisted by foreign matters, for example, a stirrer. Secondary nucleation is also called seeded nucleation – small crystals (nuclei, seeds) of a desired crystal are added to the original solution. Seeding is successfully applied for systems where polymorphous behaviour cannot be excluded. Seeding of the system with a desired polymorph assures that an undesired polymorph will not be formed. After formation of the nucleus the system pass to the second mentioned crystallization phase. In this phase growth of crystals from the formed nucleus continues. If an API is crystallized with a co-crystallization partner, for example excipient or another API, with co-crystals formation, such process is called co-crystallization.

2.2. Properties of solid forms

For polymorphic drugs, the most thermodynamically stable polymorph is usually preferred. This polymorph normally assures reproducible bioavailability for the whole period of the pharmaceutical shelf life under different storing conditions that are possible in practice. A significant advantage is that production of such a polymorph is mostly easier controlled on an industrial scale. But in some cases a metastable crystalline form or an amorphous form is preferred due to patent and medical reasons. This happens when a higher concentration of an API in the system or faster dissolution of poorly soluble substances is required. Certain substances are used in the amorphous form also due to the fact that a crystalline form of the compound was not obtained. When an amorphous form or a metastable crystalline polymorph is used, especial attention is to be paid to safety assurance and the effectiveness of the drug for the whole shelf life period. These aspects are to be assured also for storing conditions in other climatic zones.

Though the biological effect of an API is induced by interaction of the drug molecule with a target receptor when cell natural chemistry is influenced primarily by conformation changes, it is important in what solid phase the drug is administered to the patient. That means that not only the molecular but also the crystalline structure of an API is essential. The crystalline structure influences not only chemical and physical stability but also the drug dissolution rate and so can affect markedly the drug bioavailability. On the other hand, an amorphous form may have a considerably higher dissolution rate than the most stable polymorph. Great differences in the solubility and the dissolution rate of polymorphs can be a reason of significant differences in their distribution in the organism. Low plasma concentration can theoretically cause incomplete occupation of respective membrane receptors at the site of action (they are blocked by a substrate), or biological activity can change from agonist to antagonist or vice versa.

However, the dissolution rate is not the only important parameter of the difference between polymorphs. There can be also differences in crystal size and shape that influence milling, tableting, filtration, looseness and other important technological parameters. There are also differences in chemical reactivity, thermal stability, hygroscopicity, density, hardness, etc.

Thus it can be stated that different arrangement and conformation change of molecules in the crystal structure lead to differences in properties as follows: (i) mechanical (hardness, compactness, etc.); (ii) surface (surface energy, interfacial tension, etc.); (iii) kinetic (dissolution values, stability, etc.); (iv) spectroscopic (electronic, vibrational state transition, etc.); (v) thermodynamic (melting point, sublimation, enthalpy, entropy, etc.); (vi) packing properties (molar volume a density, hygroscopicity, etc.) (Brittain, 2009).

2.3. Multi-component solids

Usually solid crystal substances can exist as mono-component or multi-component. Mono-component systems contain, as evident from the name, only one component, and multi-component systems consist of two or more components. In pharmaceuticals this is a crystal composed of an API and an additional molecule that determines the type of the multi-component system, pseudopolymorph. As illustrated in Fig. 1, the additional molecule of hydrates is water; of solvates, a solvent; of salts, an ionizable component; and of co-crystals, a co-crystallization partner (Stahly, 2007; Kratochvíl, 2010). All these systems can be polymorphic (see Fig. 1 and Fig. 2). Due to the breadth of the topic and the focus of this paper on preparation of co-crystals, only co-crystals will be described in more details.

3. Co-crystals

The term "co-crystal" (also written as cocrystal) originates from "a composite crystal" (Desiraju, 2003). The term and the definition of co-crystal is a subject of topical debate. In principle this is a multi-component system of host and guest type; both components are solid in pure state and under ambient conditions. There are a lot of definitions; for example, Stahly defines co-crystals as molecular complexes that contain two or more different

molecules in the same crystal structure (Stahly, 2007). Bhogala and Nangia define co-crystals as multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions (Bhogala & Nangia, 2008). Childs and Hardcastle define co-crystals as a crystalline material made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule (Childs & Hardcastle, 2007). The simplest definition of co-crystals was proposed by Bond: "synonym for multi-component molecular crystal" (Bond, 2007). Also the definition of Aakeröy and Salmon can be recognized. They describe co-crystal as stoichiometric structurally homogeneous multi-component crystalline material of host-guest type that contains two or more neutral building blocks (discrete neutral molecular species that are solids at ambient conditions) that are present in definite amounts whereas all solids containing ions, including complex transition-metal ions, are excluded (Aakeröy & Salmon, 2005). Jones defines co-crystal as a crystalline complex of two or more neutral molecular constituents bound together in the crystal structure through non-covalent interactions, often including hydrogen bonding (Jones et al., 2006) and Zaworotko says that co-crystals are formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions (Vishweshwar et al., 2006a).

The host is an API, and the guest is a co-crystallization partner (an excipient or another API). Note that according to the definition by Aakeröy and Salmon co-crystals are different from solvates by the fact that the host and the guest of co-crystals are in the solid phase, while solvates contain both a solid phase and a solvent (or its residual), *i.e.* a liquid phase. However, there is still the problem of a boundary between the salt and the co-crystal, because according to the last mentioned definition of Aakeröy and Salmon, ions as co-crystal components are excluded, so on Fig. 3 only the first example of two is a co-crystal according to the mentioned definition. The borderline between salts and co-crystals is blurred and can be distinguished by the location of the proton between an acid and a base. This state can be denoted as salt-co-crystal continuum (Childs et al., 2007).

Several types of co-crystals can be distinguished: (i) "simple" co-crystals; (ii) solvated (hydrated) co-crystals – the co-crystal contains a component that is liquid at ambient temperature; (iii) salt co-crystals – the host is an ionized form; (iv) solvated salt co-crystals; (v) polymorphs of all previous types of co-crystals.

3.1. Properties of co-crystals

Pharmaceutical co-crystals, that is, co-crystals that are formed between an API and pharmaceutically acceptable (GRAS) compounds (co-crystal formers, counterions) that are solid under ambient conditions, represent a new paradigm in API formulation that might address important intellectual and physical property issues in the context of drug development and delivery.

Co-crystals can be understood as "addition compounds" or "organic molecular compounds". They are attractive to the pharmaceutical industry, because they offer opportunities to modify the chemical and/or physical properties of an API without the need to make or break covalent

bonds (see Fig. 4). The term "non-covalent derivatization" was coined for this approach. Co-crystals of an API with excipients become very important as a tool to tune solubility and absorption. The application of co-crystal technologies has only recently been recognised as a way to enhance solubility, stability and the intellectual property position with respect to development of APIs (Vishweshwar et al., 2006b; Sekhon, 2009; Schultheiss & Newman, 2009).

Co-crystallization with pharmaceutical excipients does not affect pharmacological activity of an API but can improve physical properties, such as solubility, hygroscopicity and compaction behaviour (Aakeröy et al., 2007; Rodríguez-Hornedo et al., 2007; Trask, 2007; Sun & Hou, 2008; Zaworotko, 2008). Co-crystals with the same active pharmaceutical ingredient will have strikingly different pharmaceutical properties (melting point, solubility, dissolution, bioavailability, moisture uptake, chemical stability, etc.), depending on the nature of the second component. Some of co-crystals formed had higher and some lower melting points as compared to their pure components, for example, succinic acid (Mp=135.3), urea (Mp=188.9), co-crystal of succinic acid-urea (Mp=149.9) (Walsh et al., 2003).

Example 1

Example 2

Figure 3. Possible multi-component systems: co-crystals, salt co-crystals and derived multi-component solids. (Ref. Schultheiss & Newman, 2009; reprinted and adapted with permission from Schultheiss N., Newman A. Pharmaceutical co-crystals and their physicochemical properties. *Crystal Growth & Design* 2009, 9(6): 2950–2967. Copyright 2009 American Chemical Society.)

Figure 4. Frequency of occurrence of organic molecular co-crystals in the Cambridge Structural Database from 1988 to 2007. For the purposes of this graph, co-crystals are distinct from solvates, hydrates and simple salts. (Ref. Childs & Zaworotko, 2009; reprinted with permission from Childs S.L., Zaworotko M.J. The reemergence of cocrystals: The crystal clear writing is on the wall introduction to virtual special issue on pharmaceutical cocrystals. *Crystal Growth&Design* 2009, 9(10): 4208-4211. Copyright 2009 American Chemical Society.)

Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility (Vishweshwar et al., 2006a). Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility increase/decrease, change of dissolution rate, stability, hygroscopicity and compressibility without alternating their pharmacological behaviour (Ranganathan, 1999; Fleischman et al., 2003; Almarsson & Zaworotko, 2004; Childs et al., 2004; Peterson et al., 2006; Hickey et al., 2007; Žegarać et al., 2007; Schultheiss & Newman, 2009).

The use of co-crystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest (Fleischman et al., 2003; Jones et al., 2006; McNamara et al., 2006; Peterson et al., 2006; Vishweshwar et al., 2006a). Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen, sulfadimidine, etc. (Vishweshwar et al., 2005; Vishweshwar et al., 2006b; Caira, 2007; Rodríguez-Hornedo et al., 2007; Babu et al., 2008; Sarma et al., 2008). Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool (Vishweshwar et al., 2003). The co-crystal of piracetam-L-tartaric acid showed improved hygroscopic properties

(Viertelhaus et al., 2009). Co-crystal forming abilities of two anti-HIV drugs (lamivudine and zidovudine) were studied to investigate the general applicability (Bhatt et al., 2009). Trimer co-crystals of *cis*-itraconazole-succinic acid were prepared and characterized by the possibility of achieving the higher oral bioavailability normally observed for amorphous forms of water-insoluble drugs (Remenar et al., 2003). The novel pharmaceutical co-crystal norfloxacin saccharinate dihydrate and its co-crystal, norfloxacin saccharinate–saccharin dihydrate were reported (Velaga et al., 2008).

3.2. Design of co-crystals

Co-crystallization is a result of competing molecular associations between similar molecules, or homomers, and different molecules, or heteromers. Instead, both components (host and guest) utilise prominent intermolecular non-covalent interactions such as hydrogen bonding, van der Waals forces and π - π stacking interactions to combine and yield a uniform crystalline material. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single-component crystals and their polymorphs) or with different molecular components (multiple-component crystals or co-crystals) in the crystalline state (Jayasankar et al., 2006; Sekhon, 2009). The components in a co-crystal exist in simple definite stoichiometric ratios, e.g., 1:1, 1:2, 2:1, etc. Co-crystals have different crystal structures than the pure components, contain different intermolecular packing patterns and as such they often exhibit different physical properties than the pure components. Unlike salt formation, co-crystallisation does not rely on ionisation of the API and the counterion to make a solid. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API (Aakeröy & Salmon, 2005; Miroshnyk et al., 2009).

The formation of a salt or a co-crystal can be predicted from pK_a value of an acid (A) and a base (B). Salt formation generally requires a difference of about 3 pK_a units between the conjugate base and the conjugate acid (A) *i.e.* $[pK_a(B) - pK_a(A) \geq 3]$ (Etter, 1990; Whitesides & Wong, 2006; Sekhon, 2009). In cases when $\Delta pK_a = pK_a(B) - pK_a(A) = 0-3$, the transfer of proton is ambiguous, and we can talk about the salt–co-crystal continuum (Childs et al., 2007).

Co-crystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio, the solvents, the temperature, the pressure, the crystallization technique, etc. Common functional groups, such as carboxylic or amino acids, amides, alcohols and carbohydrates are typically found to interact with one another in co-crystals (see Fig. 5) (Miroshnyk et al., 2009; Sarma et al., 2011; Qiao et al., 2011). Etter has studied hydrogen bonds in co-crystals and uses them as design elements. The hydrogen bond general rules are the following: (i) all good proton donors and acceptors are used in hydrogen bonding, (ii) if six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen

bonds, and (iii) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds with one another. In addition, the selectivity of hydrogen bonding in co-crystals was demonstrated by using pyridines (Etter, 1991; Sarma et al., 2011).

Based on the above mentioned facts co-crystal prediction includes the following steps: (i) determining whether a given set of two or more molecular components will undergo co-crystallization; (ii) identifying the primary intermolecular interactions, e.g., hydrogen-bond motifs that will exist within a particular co-crystal structure; and (iii) envisioning the overall packing arrangement in the resulting co-crystal structure (Trask, 2007).

Design and preparation of pharmaceutical co-crystals is a multi-stage process that can be schematically described in the following steps: (i) selection and research of APIs; (ii) selection of co-crystal formers; (iii) empirical and theoretical guidance; (iv) co-crystal screening; (v) co-crystal characterisation; (vi) co-crystal performance (Miroshnyk et al., 2009; Qiao et al., 2011).

Figure 5. Possible formation of hydrogen bonds between synthons used in crystal engineering: acid-acid (a), acid-amine (b), acid-amide (c), acid-imide (d), amide-amide (e), and alcohol-ether (f).

3.3. Synthesis of co-crystals

A pharmaceutical co-crystal is a single-crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former (Vishweshwar et al., 2006). Co-crystal former may be an excipient or another drug (Rodríguez-Hornedo et al., 2007). Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offers a chance to increase the number of forms of an API.

Crystalline forms can be generated by means of kinetically or thermodynamically controlled crystallization processes. Synthesis/processing of co-crystals can be accomplished via a number of methods, including slow solvent evaporation crystallization from solution, solvent-reduced (e.g. slurring, solvent-drop grinding) and solvent-free (e.g. grinding, melt), high throughput crystallization and co-sublimation techniques (Shekunov & York,

2000; Morissette et al., 2004; Trask & Jones, 2005; Trask et al., 2005a; Trask et al., 2005b; Trask et al., 2006; Stahly, 2007; Berry et al., 2008; Takata et al., 2008; Friščić & Jones, 2009; Schultheiss & Newman, 2009; Qiao et al., 2011). Typically co-crystals are prepared by slow solvent evaporation that is only viable if compatible solubility in a given solvent exists between the components comprising the potential co-crystal. The potential benefits, disadvantages and methods of preparation of co-crystals were reported (Blagden et al., 2007). Solvent drop grinding has been reported to be a cost-effective, green, and reliable method for discovery of new co-crystals as well as for preparation of existing co-crystals. A slurry crystallization technique was used in co-crystal screening of two non-ionizable pharmaceutical host compounds, stanolone and mestanolone, with 11 pharmaceutically acceptable guest acids, and the results demonstrated the importance not only of hydrogen bonding but also of geometric fit in co-crystal formation (Takata et al., 2008). In addition to these classical techniques of co-crystal synthesis, also more sophisticated methods can be mentioned such as electrochemical crystallization, gel crystallization, vapour-diffusion crystallization, cryogenic grinding (cryomilling), microporous membranes crystallization, supercritical fluids crystallization and sonocrystallization (Dahlin et al., 2011; Hsu et al., 2002; Forsythe et al., 2002; He & Lavernia, 2001; Di Profio et al., 2007; Tong et al., 2001; Ruecroft et al., 2005). The combinations and variations of the above techniques may be used to cause co-crystal formation (McMahon et al., 2007). It is evident that many of the reported co-crystals appear to be the result of serendipity, although several groups have successfully exploited crystal engineering principles for design and synthesis of co-crystals.

4. Characterization of co-crystals

Co-crystal characterisation is an important constituent part of co-crystal research. The basic techniques of analysis of co-crystals involve especially solid state analysis methods (Zakrzewski & Zakrzewski, 2006; Dohnal et al., 2010), *i.e.* vibration-rotation spectroscopy, solid state NMR, thermal analysis, microscopy techniques and X-ray diffraction. The most often used solid-state analytical techniques will be discussed below.

4.1. Spectroscopy of vibration-rotation transitions

According to the used part of infrared (IR) spectra (energy), near infrared spectroscopy (NIR), middle infrared spectroscopy (MIR), Raman scattering and terahertz (THz) spectroscopy are distinguished.

4.1.1. NIR Spectroscopy

Photons in NIR region have the highest energy and can therefore vibrationally excite molecules into even higher excited vibrational states than the first level, *i.e.* the second, the third and others. These transitions are called overtones. Absorption of radiation in the NIR region is usually based on higher energy transitions between vibrational levels of molecules, namely combination transitions and overtones and not fundamental transitions, which are dominant in mid infrared region (MIR). NIR spectrometers are not so demanding of applied

materials, as are the instruments working in the mid infrared region, due to different radiation frequencies used in the NIR spectrometry. Acquisition of NIR spectra requires several seconds and can be performed during manufacturing process. Therefore, the NIR spectroscopy is still more often applied as a tool of process analytical technology. In co-crystal analysis NIR spectroscopy is commonly used as a screening method of the first choice (Pekárek & Jampílek, 2010).

4.1.2. MIR spectroscopy and Raman scattering

The aim is not only to present the basic principles of both methods, but also to compare them. Raman spectroscopy and mid-infrared spectroscopy are both widely used in the pharmaceutical industry for the solid-state characterization because of their specificity. MIR region is the most important region in terms of analytical application. It is a region, where the majority of the so-called fundamental vibrations appear, *i.e.* the vibrational transitions from the basic to the first excited vibrational state. Vibrational spectroscopy provides key information about the structure of molecules. Positions and intensities of bands in a vibrational spectrum can be used to determine the structure of a molecule or to determine the chemical identity of a sample. With sufficient experience it is possible to identify chemical compounds or monitor intermolecular interactions by evaluating changes in positions and intensities of Raman bands which is extremely useful for the above mentioned purposes.

The mid-infrared and Raman spectra (with the exception of optical isomers) of a drug substance or any chemical compound are unique. Raman spectroscopy is a vibrational spectroscopy method which complements mainly the mid-IR spectroscopy. The intensity of bands in IR spectra is proportional to the dipole moment change occurring during the given type of the vibrational motion. Modes with a large change in the dipole moment having intensive bands in the IR spectra generally provide low-intensity bands in Raman spectra. Conversely, vibrations of non-polar functional groups provide intense bands in Raman spectra and weak bands in infrared spectra. (Zakrzewski & Zakrzewski, 2006; Pekárek & Jampílek, 2010). An important advantage of Raman spectroscopy over IR spectroscopy is the possibility to measure aqueous solutions. This advantage can be used in identification of APIs in aqueous solutions, emulsions or suspensions.

4.1.3. THz spectroscopy

This technique covers a wide interval, which can be roughly defined, for example, by frequencies of 100 GHz and 3 THz, which corresponds to wavelengths between 3 and 0.1 mm, *i.e.* wave numbers from 3 to 100 cm⁻¹. Hence THz region partially overlaps with far-infrared region. The characteristic frequency of 1 THz can be equivalently expressed in other spectroscopic units. The decisive factor for expansion of this method was the development of optical femtosecond lasers being an integral part of the most current laboratory and commercial THz spectrometers. Attractiveness of the THz field lies in the scale of the specific options for application of electromagnetic radiation of these frequencies. Application options in pharmaceutical analysis are mainly spectroscopy and imaging.

Solid substances often exhibit specific interactions in the THz region. While some crystals are transparent in this range, many others show low-frequency oscillations of the crystal structure (called phonon bands) with characteristic frequencies being determined by short-range inter-atom interactions and even arrangement of atoms at long distances (Kadlec & Kadlec, 2012). Similar to NIR and mid-IR spectroscopy, in THz spectroscopy reflectance (less often) and transmittance measurements are used.

It is known that vibrational modes of amorphous and crystalline substances are very different. This was experimentally proven, for example, in THz spectra of samples of crystalline and amorphous saccharides (Walther et al., 2003). The absence of sharp vibrational modes that can be observed in the crystalline form was later also confirmed in THz spectra of indomethacin (Strachan et al., 2004).

Determination of tablet coating thickness and determination of particle size belong among special applications of THz spectroscopy. Radiation in THz region has the lowest energy, which can cause changes mainly in rotational energy of molecules therefore it has the lowest (destructive) influence on measured co-crystals.

4.2. Solid state nuclear magnetic resonance

Solid state NMR (ssNMR) spectroscopy is not used for routine analyses in pharmacy because of its demands, but its role in pharmaceutical development is indispensable. It has very wide application. The most important applications can be divided into the following groups (Havlíček, 2010): (i) API structural analysis; (ii) polymorphism; (iii) co-crystal analysis; (iv) dosage form analysis; (v) solvate analysis; (vi) salt analysis.

Among the most widely used ssNMR techniques CP/MAS NMR belongs. It has three modifications: cross polarization (CP), magic angle spinning (MAS) and high-power heteronuclear decoupling. With this arrangement the sensitivity and line broadening problems were overcome, and high-resolution ssNMR was brought in practical use.

Solid-state NMR is capable of providing detailed structural information about organic and pharmaceutical co-crystals and complexes. ssNMR non-destructively analyzes small amounts of powdered material and generally yields data with higher information content than vibrational spectroscopy and powder X-ray diffraction methods. Particularly, its ability to prove or disprove molecular association and possibility to observe structural features (such as hydrogen bonding) are great advantages of this method. These advantages can be utilized in the analysis of pharmaceutical co-crystals, which are often initially produced using solvent drop grinding techniques that do not lend themselves to single-crystal growth for X-ray diffraction studies (Vogt et al., 2009).

4.3. Thermal analysis

Thermal analysis is a broad term referring to methods (see Table 1), which measure physical and chemical properties of a substance, a mixture of substances or also of a reaction mixture as a function of temperature or time during a controlled temperature programme. Most of

these methods monitor corresponding system properties (mass, energy, size, conductivity, etc.) as dynamic functions of temperature.

For co-crystal analysis mainly differential scanning calorimetry (DSC) and its modifications, differential thermal analysis (DTA) and thermogravimetry analysis (TGA), are of great importance. For special cases a very useful method is thermally stimulated current (TSC). DSC and DTA are the most applied methods of thermal analysis in pharmaceutical development. In DSC, the sample is subjected to linear (or modulated) heating, and the heat flow rate in the sample is proportional to the actual specific heat and is continuously measured. Very interesting and useful modifications of DSC are hyperDSC, microDSC and modulated DSC (Krumbholcová & Dohnal, 2010).

Method name	Tracked value
Differential thermal analysis (DTA)	temperature difference between the studied and the standard sample
Differential scanning calorimetry (DSC)	thermal energy provided for compensation of temperature between the studied and the standard sample
Thermogravimetry analysis (TGA)	weight change
Thermomechanical analysis (TMA)	change in a mechanical property (module, hardness)
Dilatometry	change in volume
Effluent gas analysis	volume of the studied gas
Pyrolysis	pyrolysis products
Thermal luminescence analysis	emission of light
Electric conductivity analysis	change in electric conductivity

Table 1. List of the most common methods of thermal analysis. (Ref. Krumbholcová & Dohnal, 2010).

4.3.1. Thermally stimulated current

This special thermal method uses a so-called molecular mobility, which provides information about the structure of substances, about dynamic parameters ΔH and ΔS and the relaxation (release) time τ . In TSC the substance is heated to a temperature T_P in an electric field with intensity E_P for a period of time t_P , which is sufficient for differently moving particles of the studied substance to reach identical orientation in the electric field. In this state, the sample is rapidly cooled to a temperature T_0 , which ensures zero motion of the particles. The effect of the electric field is then also deactivated, and the substance is then kept at temperature T_0 for time t_0 . The temperature then linearly increases, and the substance returns to the previous balance, and depolarization current I_D is recorded as a function of temperature. Each depolarization peak is characterized by temperature $T_{\max}$ with intensity

$I_{\max}$. This technique is particularly suitable for substances with polar character. It can distinguish polymorphs or co-crystals, which cannot be determined by classical DSC (Krumholcová & Dohnal, 2010).

4.4. X-Ray diffraction

X-Ray diffraction is one of the basic solid state analytical techniques labelled as the "gold standard". It is used not only for characterization and identification of crystalline substances but also for their discrimination.

Two basic methods are discerned according to the type of the analysed sample. They are:

1. Diffraction on single crystal (single-crystal X-ray diffraction, SCXRD),
2. Powder diffraction (X-ray powder diffraction, XRPD).

Name	single-crystal X-ray diffraction	X-ray powder diffraction
Abbreviation	SCXRD	XRPD
Sample – type	Single crystal	Powder
Sample – amount	1 single crystal with size of 0.1 – 1 mm	100 – 500 mg
Sample – preparation	Selection of a suitable single crystal and its fixation onto the goniometric head.	Filling of the holder cavity or possibly milling.
Sample – consumption	Non-destructive	Non-destructive
Measurement time	Hours/days	Minutes/hours
Analysis of obtained data	Complete information about the molecule, conformation, bond lengths, chirality, spatial arrangement of molecules in the crystal, interactions between molecules, determination and location of solvents.	„Fingerprint" of the crystal structure
Principle of the method	Monochromatic light falls on a single crystal, and because only one lattice diffracts, it is necessary to rotate the crystal to obtain the desired set of reflections (the principle of four-circle diffractometer).	Monochromatic radiation impacts a polycrystalline material and all lattices that meet the diffraction condition diffract at the same time.
Practical application	Crystallographic studies: determination of the complete structure of an API, a protein, a complex, etc.	Mainly industrial, screening and control method for characterization of crystalline materials.

Table 2. Comparison of basic diffraction methods. (Ref. Brusová, 2010).

Their basic characteristics, advantages and disadvantages are summarized in Table 2. The X-ray structural analysis methods, which use single-crystal samples, often allow a complete determination of crystallographic characteristics. Diffraction on a single-crystal yields intensities of diffractions on individual configurations of the crystallography planes, individually for each of their orientation, and the number of the detected maxima is very high, in orders of $10^2 - 10^4$. In the powder diffraction, on a debyeogram or a diffractogram there at most 100 lines can be distinguished. In addition, each diffraction line is a superposition of diffractions of all inequivalent and equivalent planes (Hušák et al., 2007; Kratochvíl et al., 2008).

5. Carbohydrates and their derivatives as crystallization modifiers

As discussed above, pharmaceutical co-crystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Various co-crystals of APIs were prepared by reason of intellectual property protection, for example, imatinib (see Fig. 6, structure I) with co-crystal carbohydrate formers such as α -D-glucopyranose, D-fructofuranose and *N*-methyl-D-glucamine (meglumine) (Král et al., 2010); agomelatine (see Fig. 6, structure II) with carbohydrate counterions such as D-sorbitol, aspartame, phenyl- β -D-glucopyranoside, D-glucoheptono-1,4-lactone, D-(+)-trehalose, lactose, α -D-glucopyranose, saccharose, *N*-methyl-D-glucamine and D-(+)-glucosamine hydrochloride (Ferencova et al., 2012); or to improve permeability, for example, alendronate (see Fig. 6, structure III), ibandronate (see Fig. 6, structure IV) or risedronate (see Fig. 6, structure V) with a number of carbohydrates as co-crystal formers (Jampílek et al., 2009; Haroková, 2010; Havelková, 2010; Hrušková, 2010; Jampílek et al., 2010; Kos, 2010; Oktábec et. al, 2010; Kos et al., 2011; Ťažká 2011; Havelková, 2012; Oktábec, 2012).

Figure 6. APIs used as host of carbohydrate formers.

The present study deals with the design and an effort to prepare co-crystals/new entities, generally new solid phases, of the above discussed bisphosphonates III-V. These

compounds were investigated in detail, and a lot of valuable knowledge concerning generation of solids was obtained. Bisphosphonates (BPs) can be denoted as top-selling APIs. BPs are the most widely used and the most effective bone resorption inhibitors currently available for treatment of Paget's disease, tumour-associated bone disease and osteoporosis. All BPs have high affinity for bone mineral as a consequence of their P-C-P backbone structure, which allows chelation of calcium ions (Ebetino et al., 1998). Following release from bone mineral during acidification by osteoclasts, BPs appear to be internalized specifically by osteoclasts, but not other bone cells. The intracellular accumulation of BP leads to inhibition of osteoclast function due to changes in the cytoskeleton, loss of the ruffled border (Carano et al., 1990; Sato et al., 1991) and apoptosis (Hughes et al., 1995; Selander et al., 1996; Ito et al., 1999; Reszka et al., 1999). The ability of BPs to inhibit bone resorption depends on the presence of two phosphonate groups in the P-C-P structure, which appears to be required for interaction with a molecular target in the osteoclast as well as for binding bone mineral (Rogers et al., 1995; van Beek et al., 1998; Rogers et al., 2000). BPs as pyrophosphate analogues are a group of drugs that are widely used in practice. There are several injectable bisphosphonates: etidronate, pamidronate and zoledronate, which may be administered every three months or yearly. Peroral BPs alendronate and risedronate are taken daily, weekly or monthly, and ibandronate is approved to be taken monthly. Oral bioavailability of these BPs is very low (their gastrointestinal absorption is about 1%) due to their high hydrophilicity (Ezra & Golomb 2000).

A number of various patented solid forms of each API from this group can be found, which, for example, complicates their utilization for generic formulation from the intellectual property point of view. Eiermann et al. prepared crystalline forms of ibandronate (**IV**) B and A (Eiermann et al., 2006a; Eiermann et al., 2006b). Lifshitz-Liron et al. obtained forms C, D, E, F, G, H, J, K, K2, K3, Q, Q1, Q2, Q3, Q4, Q5, Q6, QQ, R, S and T (Lifshitz-Liron et al., 2006). Muddasani et al. prepared polymorphs I and II (Muddasani et al., 2007), and Devarakonda et al. generated ibandronate forms III-XXXI (Devarakonda et al., 2010). Ten different polymorphic and pseudo-polymorphic forms of sodium risedronate (**V**) identified as A, B, B1, BB, D, E, F, G and H and a semi-crystalline form were described (Cazer et al., 2001; Aronhime et al., 2003a; Aronhime et al., 2003b; Richter et al., 2007). The crystal structures of four different hydrates (monohydrate, dihydrate, hemipentahydrate and variable hydrate) and an anhydrate of sodium risedronate (**V**) have been elucidated and discussed by Redman-Furey (Redman-Furey et al., 2005) and Gossman (Gossman et al., 2003). Recently three new phases were found and named J, K and M (Bruning et al., 2011).

This paper deals with investigation of various types of carbohydrates and their derivatives as crystallization modifiers applied to crystal study concerning the BP family. Carbohydrates were used due to their hydroxyl moieties, which are able to interact with a phosphoric group and/or a nitrogen atom in the alkyl chain or heterocycle. Carbohydrates also provided a unique excellent system of hydroxyl moieties in different stereochemical modifications. These hydroxyl groups can be straightly modified, for example, by alkylation/arylation, and the structure of the carbohydrate molecule obtains absolutely different three-dimensional/space properties.

Figure 7. Structures of sugar alcohols used as potential co-crystal/crystallization formers.

Figure 8. Structures of furanoses used as potential co-crystal/crystallization formers.

Figure 9. Structures of hexoses used as potential co-crystal/crystallization formers.

Thus mixtures of BPs with various sugar alcohols, furanoses, pyranoses and gluco-, manno- and galactopyranoside derivatives, some amino carbohydrates and disaccharides (see Figs. 7-11) as counterions were designed in an effort to prepare new crystalline forms or co-crystals/new entities. Mixtures of BPs and carbohydrates in different ratios and under various conditions were prepared. All the prepared mixtures (solid compounds) were characterized using some of the above mentioned solid state analytical techniques (Haroková, 2010; Havelková, 2010; Hrušková, 2010; Kos, 2010; Oktábec et. al, 2010; Kos et al., 2011; Ťažká 2011; Havelková, 2012; Oktábec, 2012).

Figure 10. Structures of pyranosides used as potential co-crystal/crystallization formers.

5.1. Generation of samples

All the evaluated samples with ratios 1:1 (A), 1:2 (B) and 1:3 (C) were prepared by means of dissolution of bisphosphonate monosodium salt and the excipient in water, subsequently mixed (1 h) and slowly evaporated at ambient temperature. To some samples with ratios 1:2

and 1:3 methanol was slowly added dropwise as an anti-solvent. The solid precipitated compound was filtered and dried at ambient temperature, samples 1:2 (D) and 1:3 (E), and the remaining liquid part was slowly evaporated at ambient temperature, samples 1:2 (F) and 1:3 (G). All generated solid compounds were subsequently screened by means of FT-NIR and FT-Raman spectroscopy. If a sample differing from the starting materials was found, it was additionally characterized by the below mentioned methods (Jampílek et al., 2009; Haroková, 2010; Havelková, 2010; Hrušková, 2010; Jampílek et al., 2010; Kos, 2010; Oktábec et. al, 2010; Kos et al., 2011; Ťažká 2011; Havelková, 2012; Oktábec, 2012).

Figure 11. Structures of disaccharides used as potential co-crystal/crystallization formers.

5.2. Used solid-state analytical techniques

Near infrared spectra were recorded using a Smart Near-IR UpDrift™, Nicolet™ 6700 FT-IR Spectrometer (Thermo Scientific, USA). The spectra were obtained by accumulation of 128 scans with 4 cm⁻¹ resolution in the region of 12800–4000 cm⁻¹. FT-Raman spectra were accumulated by an FT-Raman spectrometer RFS 100/S (Karlsruhe, Bruker, Germany). The spectra were obtained by accumulation of 256 scans with 4 cm⁻¹ resolution in the back scattering geometry with the laser wavelength of 1064 nm. ³¹P CP/MAS NMR Spectra were recorded on a Bruker AVANCE 500 MHz spectrometer (Karlsruhe, Bruker, Germany). The ³¹P CP/MAS spectra were measured in 4 mm rotor at 10 kHz with 2 ms contact time. ³¹P chemical shift of NH₄H₂PO₄ (0 ppm) was used as an external reference for ³¹P chemical shift. The ¹³C CP/MAS spectra were measured in 4 mm rotor at 13 kHz with 2 ms contact time. Carbon chemical shifts were referenced to the signal for TMS via a replacement sample of glycine (176 ppm for the carbonyl group signal). The XRPD patterns were obtained on a PANalytical X'PERT PRO MPD diffractometer with Cu Kα radiation (45 kV, 40 mA). The powder samples were measured on Silica plate holder. Data were recorded in the range

2–40° 2 θ , with 0.01° 2 θ step size and 50 s/step scan speed. For the measurement of differential scanning calorimetry (DSC) curve an instrument DSC Pyris 1 (PerkinElmer, USA) was used. Maximum sample weight was 3.5 mg, and the standard Al sample pan was used. The record of the DSC curve was in the range of 50–300 °C at the rate of 10.0 °C/min under a nitrogen atmosphere.

5.3. Crystal products of carbohydrates with alendronate and ibandronate

Although a number of carbohydrates were tested as potential co-crystal/crystallization formers, no change in the crystal structure of the used alendronate sodium salt (**III**) was obtained. The starting material was always obtained.

Mixtures of ibandronate monosodium salt (**IV**) with twenty-eight carbohydrates were generated by means of thermodynamically and/or kinetically controlled crystallization processes. Polymorph B of ibandronate monosodium salt monohydrate (sodium hydrogen {1-hydroxy-3-[methyl(pentyl)amino]-1-phosphonopropyl}phosphonate, **IV**) was used as a starting material (Eiermann, 2006a), which is the most common in pharmaceutical formulations. It is a white powder, freely soluble in water and practically insoluble in organic solvents.

From all the tested agents, only phenyl- β -D-galactopyranoside (see Fig. 10, structure **24**) yielded noteworthy products with BP **IV**. The rest of the tested carbohydrates, except phenyl- β -D-glucopyranoside (see Fig. 10, structure **21**) and 2-naphthyl- β -D-galactopyranoside (see Fig. 10, structure **25**), generated again the starting polymorph B. The mentioned two carbohydrates **21** and **25** provided mixtures of polymorphs A+B, as shown in Table 3. Samples of **IV-24** in ratios 1:1 (**A**), 1:2 (**B**) and 1:3 (**C**) were prepared by mixing and subsequent evaporation at ambient temperature. In all three samples a change in the NIR spectra can be observed in the range of 5,300–4,800 cm⁻¹. The spectra of samples **IV-24/B** and **IV-24/C** are very similar, only slightly different from sample **IV-24/A**, probably due to the lower crystallinity of sample **IV-24/A**, which causes broader bands in the spectrum. As samples **IV-24/A-C** were prepared in the same way, it can be concluded that increasing concentration of compound **24** influences the sample crystallinity.

Comp.	A	B	C	D	E	F	G
IV-21	B	B	B	B	B	A+B	A+B
IV-24	new	new	new	B	B	new	new
IV-25	B	B	B	B	B	A+B	A+B

Table 3. Samples of ibandronate (**IV**) and used carbohydrates **21**, **24** and **25** in ratios 1:1, 1:2 and 1:3 prepared by evaporation at ambient temperature (**A**, **B**, **C**), samples in ratios 1:2 and 1:3 prepared by methanol precipitation (**D**, **E**) and samples in ratios 1:2 and 1:3 prepared by addition of methanol and evaporation of liquid part at ambient temperature (**F**, **G**). (Ref. Oktábec et al., 2010; Havelková, 2012).

Based on the NIR spectra of samples of **IV-24/D** and **IV-24/E** in ratios 1:2 and 1:3 precipitated by methanol and filtered, it can be concluded that both samples contain only

form B of compound **IV**. The same characteristic bands in the range of 5,300–4,800 cm^{-1} as for samples **IV-24/A-C** can be observed for samples **IV-24/F** and **IV-24/G** in ratios 1:2 and 1:3 after addition of methanol, filtration of the obtained precipitate and evaporation at ambient temperature. Based on this fact it can be concluded that addition of methanol does not influence generation of a new unknown solid phase, because the same products were yielded with and without methanol addition. Slow evaporation seems to be important, *i.e.* thermodynamically controlled crystal modification is probable. The presence of carbohydrate **24** is fundamental for generation of a new entity. The samples **IV-24/A-C** and **IV-24/F**, **IV-24/G** were also characterized by means of the FT-Raman spectrometry and ^{31}P CP/MAS NMR spectroscopy for verification of this hypothesis. Both methods confirmed the presence of new solid phases.

From the above mentioned results (Table 3) it is evident that ibandronate (**IV**) provided a new solid phase only with phenyl- β -D-galactopyranoside (**24**). These samples, **IV-24/A-C** and **IV-24/F**, **IV-24/G**, were generated under the thermodynamic conditions (slow evaporation at ambient temperature) without or with methanol. It can be concluded that the presence of the co-crystal/crystallization former and the thermodynamic conditions were essential for generation of the new solid phase. Note that only β -D-pyranosides with substituted hydroxyl moiety in $\text{C}_{(1)}$, position 2 of the tetrahydropyran ring, *e.i.* in the equatorial position, showed interactions with BP **IV**. Although phenyl- α -D-pyranosides were not evaluated, it is possible to suppose that α -D-pyranosides possess probably a disadvantageous configuration of $\text{C}_{(1)}$ hydroxyl moiety.

Based on the above discussed results it can be also stated that substitution of $\text{C}_{(1)}$ hydroxyl with the aromatic group is necessary for interactions, because *e.g.* methyl- β -D-galactopyranoside (**23**) contrary to phenyl- (**24**) or naphthyl- β -D-galactopyranoside (**25**) provided no modification of the starting polymorph of compound **IV**. This hypothesis is supported by the fact that phenyl- β -D-glucopyranoside (**21**) afforded also the change of polymorph B to form A of BP **IV**. It can be assumed that naphthyl is too bulky compared to the phenyl ring. Nevertheless from all the evaluated substituted pyranosides only phenyl- β -D-galactopyranoside (**24**) yielded the new solid phase of compound **IV**. As non-covalent interactions are important for generation of crystal forms, the space configuration of all the hydroxyl moieties is probably essential for interactions between BP **IV** and carbohydrate **24**. As illustrated in Fig. 10, where basic spatial configuration of substituted pyranosides is shown, different interactions between phenyl- β -D-galactopyranoside (**24**) and phenyl- β -D-glucopyranoside (**21**) are probably caused by opposite orientation of hydroxyl moiety in $\text{C}_{(4)}$ in position 5 of the tetrahydropyran ring. In compound **21** this hydroxyl moiety is *trans*-oriented (in equatorial configuration) to the hydroxymethyl group in $\text{C}_{(5)}$ in position 6 of the tetrahydropyran ring, while in compound **24** it is *cis*-oriented (in axial configuration), which at the same time guarantees space proximity to the pyran oxygen. Pyranoside **24** possesses *cis*-orientation of hydroxyl moieties in $\text{C}_{(3)}$ and $\text{C}_{(4)}$ in positions 4 and 5 of the tetrahydropyran ring together with the phenoxy moiety in $\text{C}_{(1)}$ in position 2 of the tetrahydropyran ring. This fact together with *cis*-orientation of the hydroxymethyl group in $\text{C}_{(5)}$ in position 6 probably results in essential three-point interaction of neighbouring

hydroxyl moieties between compound **24** and BP **IV** that is completed by interactions of the adjacent phenoxy moiety and pyran oxygen in comparison with carbohydrate **21**, see Fig. 10.

5.4. Crystal products of carbohydrates with risedronate

The semi-crystalline risedronate monosodium salt sodium 1-hydroxy-1-phosphono-2-(pyridin-3-yl-ethyl)phosphonate, (**V**) was used as a starting material (Richter et al., 2007). It is a white powder, freely soluble in water and practically insoluble in organic solvents. The sodium hemipentahydrate, which is the marketed form A, is the most stable of all these forms at ambient conditions (298 K, 50% room humidity) (Cazer et al., 2001).

From all the tested agents only phenyl- β -D-galactopyranoside (**24**) with risedronate (**V**) yielded noteworthy products. Other tested carbohydrates yielded either risedronate form A (in most cases), form H (in the case of the samples with *myo*-inositol (see Fig. 7, structure **4**), D-lyxofuranose (see Fig. 8, structure **9**), phenyl- β -D-glucopyranoside (**21**) and naphthyl- β -D-galactopyranoside (**25**) prepared by addition of methanol and evaporation of the liquid part at ambient temperature) or impure form B in the case of the sample with β -D-allopyranose (see Fig. 9, structure **13**) precipitated by methanol. A rapid change in solubility equilibrium and fast precipitation (kinetically controlled crystallization process) caused generation of different form B (samples **V-13/D** and **V-13/E**), while slow evaporation, *i.e.* thermodynamically controlled crystallization, led to preparation of stable polymorphs A or H. β -D-Allopyranose (**13**) modifies the environment from which compound **V** was crystallized, but this carbohydrate was not detectable in the final crystalline form. Based on this fact it can be concluded that the addition of methanol as an anti-solvent is crucial for generation of this different/uncommon solid form.

Different interactions of BP **V** with carbohydrate **13** are probably caused by the opposite orientation of hydroxyl moieties in C₍₁₎ and C₍₃₎ in positions 2 and 4 of the tetrahydropyran ring in comparison with α -D-gluco-, α -D-manno- and α -D-galactopyranose (**10–12**). The β -position of the hydroxyl moiety in C₍₁₎ of β -D-allopyranose (**13**) possesses also *cis*-orientation (axial configuration, see Fig. 9) with respect to the pyran oxygen in position 1 of the tetrahydropyran ring. As bonds influencing generation of crystalline forms are formed by non-binding interactions (e.g. by *H*-bonds, ionic bonds, van der Waals forces (dispersion attractions, dipole-dipole, dipole-induced dipole interactions) and hydrophobic interactions), the steric arrangement of hydroxyl moieties on pyranose skeletons is important for formation of interactions, as discussed above.

Samples of **V-24/A–C** were prepared by mixing saturated aqueous solutions and subsequent evaporation of water at ambient temperature. All three samples contained polymorph A of risedronate (**V**) (the most thermodynamically stable form). Samples **V-24/D** and **V-24/E** precipitated by methanol and filtered yielded again polymorph A of compound **V**. Samples **V-24/F** and **V-24/G** were generated by addition of methanol and filtration of the obtained precipitate with following evaporation at ambient temperature. Samples **V-24/F** and **V-24/G** were absolutely different from all the above mentioned samples. A change in the NIR

spectra of samples **V-24/F** and **V-24/G** was observed in the range of 7,100–4,900 cm^{-1} . Both samples were also characterized by means of FT-Raman spectrometry and ^{31}P and ^{13}C CP/MAS NMR spectroscopy for verification of the above mentioned hypothesis. Sample **V-24/G** was a mixture of polymorph A and the amorphous form of **V**, but sample **V-24/F** was confirmed as a new crystalline form of BP **V**. Therefore solid **V-24/F** was additionally characterized by means of XRPD (Fig. 12) and also by DSC. A XRPD pattern corresponds to a crystalline sample. Visual comparison of the measured pattern with those published previously (Aronhime et al., 2003; Bruning et al., 2011) revealed that a new solid phase of BP **V** was formed. It is also supported by the absence of peaks of co-crystal former **24**. It can be concluded that the presence of compound **24** and slow evaporation, *i.e.* thermodynamically controlled crystallization process, with a small amount of methanol as anti-solvent provided risedronate (**V**) in an unknown form that was named as polymorph P.

Sugar alcohols did not provide any different forms or co-crystals with risedronate (**V**). The polyols used are acyclic compounds, or probably important heterocyclic oxygen is not present in the ring. In the case of *myo*-inositol (**4**), where only the different polymorph H of compound **V** was detected, *cis*-oriented hydroxyl moieties are in $\text{C}_{(1)}$, $\text{C}_{(2)}$, $\text{C}_{(3)}$ and $\text{C}_{(5)}$ or conversely oriented hydroxyl moieties are in $\text{C}_{(4)}$ and $\text{C}_{(6)}$, see Fig. 7. Contrary to the rest of the tested unsubstituted carbohydrates, only β -D-allopyranose (**13**) shows *cis*-orientation of hydroxyl moieties in $\text{C}_{(1)}$ and $\text{C}_{(5/6)}$ in positions 2 and 6 of the tetrahydropyran ring together with the pyran oxygen in position 1 and *cis*-orientation of hydroxyl moieties in $\text{C}_{(2)}$, $\text{C}_{(3)}$ and $\text{C}_{(4)}$ in positions 3, 4 and 5 of the tetrahydropyran ring, *i.e.* *cis*-orientation of three sequential hydroxyl moieties. These facts are probably essential for interactions between BP **V** and carbohydrate **13**. For example, α -D-galactopyranose (**12**) possesses 1, 4, 5, 6 *cis*-oriented pyran oxygen together with hydroxyl moieties; α -D-glucopyranose (**10**) possesses 1, 4, 6 *cis*-oriented pyran oxygen together with hydroxyl moiety; and α -D-mannopyranose (**11**) possesses 3, 4, 6 *cis*-oriented hydroxyl moieties together with pyran oxygen in position 1.

Figure 12. XRPD patterns of new solid phase **V-24/F** named as polymorph P.

According to the above mentioned hypothesis, interactions with BP **V** should be predicted only for D-lyxofuranose (Fig. 8, structure **9**) from the furanose family. D-Lyxofuranose (**9**) shows *cis*-orientation of hydroxyl moieties in C₍₂₎ and C₍₃₎ in positions 3 and 4 of the tetrahydrofuran ring together with the furan oxygen in position 1. Nevertheless, this three-point interaction of carbohydrate **9** with BP **V**, which however is not completed by other additional/secondary interactions, is not sufficient for generation of a different form or co-crystal of BP **V**, when only form H was generated using compound **9**. Probably the conformation of the tetrahydrofuran ring different from the pyranose chair conformation is also important.

Different interactions of risedronate monosodium salt (**V**) with phenyl-β-D-galactopyranoside (**24**) compared to other evaluated *O*-substituted pyranosides are probably caused by the opposite orientation of the hydroxyl moiety in C₍₄₎ in position 5 of the tetrahydropyran ring, as it is shown in Fig. 10 and discussed in Section 5.3. β-Position of the hydroxyl moiety in C₍₁₎ of β-D-glucopyranoside and β-D-galactopyranoside (as well as in β-D-allopyranose) possessing also *cis*-orientation to the pyran oxygen together with phenyl substitution of this hydroxyl moiety seems also to be an important assumption for interactions. For example, methyl-β-D-galactopyranoside (**23**) did not show any interactions with compound **V**, whereas phenyl-β-D-glucopyranoside (**21**) and naphthyl-β-D-galactopyranoside (**25**) generated polymorph H of compound **V**, and phenyl-β-D-galactopyranoside (**24**) provided a new solid phase. Aliphatic alkoxy moieties (methoxy, octyloxy) show absolutely different physico-chemical properties, *i.e.* non-binding interactions compared with the aromatic phenyl nucleus. On the other hand, a naphthyl moiety, which is comparable with a phenyl ring, does not meet steric requirements to generate a new solid phase with compound **V**. Contrary to the rest of the tested *O*-substituted pyranosides, carbohydrate **24** shows *cis*-orientation of hydroxyl moieties in C₍₃₎, C₍₄₎ and C₍₅₋₆₎ in positions 4, 5 and 6 of the tetrahydropyran ring, *i.e.* three sequential hydroxyl moieties that possess *cis*-orientation with the phenoxy moiety in C₍₁₎ in position 2 of the tetrahydropyran ring together with the pyran oxygen in position 1, as was mentioned in Section 5.3. This configuration of all the hydroxyl moieties, as illustrated in Fig. 10, is probably essential for interactions between risedronate (**V**) and phenyl-β-D-galactopyranoside (**24**).

6. Future research

Samples **IV-24/A-B** and **IV-24/F**, **IV-24/G** should be characterized by XRPD. Also some of the above mentioned samples as well as sample **V-24/F** (polymorph P) should be analyzed using single-crystal X-ray diffraction (SCXRD), *i.e.* monocrystals should be prepared for absolute characterization of their structure. Based on the above described primary screening, other carbohydrate derivatives should be synthesized, especially various substituted β-D-pyranosides, *e.g.* *O*-arylated or *O*-alkylated. For example, based on the screening of these carbohydrates, it was confirmed that the structure derived from β-D-galactopyranose could be a successful candidate for modification of a crystalline form of BPs.

In the recent past, molecular modelling and/or molecular dynamics simulates started playing an increasingly important role in detection of molecule interactions. These computational techniques allow investigating possible binding modes of compounds. Therefore the priorities are advanced simulation of interactions between carbohydrate

derivatives and various APIs and modelling/computing of physico-chemical properties of these new potential solids by means of various advanced simulating software products and subsequent transfer of the results of this systematic virtual screening to practice.

7. Conclusion

Twenty-eight carbohydrate derivatives were evaluated as formers during crystallization process of monosodium salts of alendronate (**III**), ibandronate (**IV**) and risedronate (**V**). All prepared samples were screened by FT-NIR and FT-Raman spectroscopy, and some new entities were checked by ^{31}P and ^{13}C CP/MAS NMR spectroscopy, XRPD and DSC. In the present study the relationships between the chemical structures of bisphosphonates and carbohydrates required for crystalline form change are investigated and discussed. It can be concluded that in general carbohydrates can be used as crystallization modifiers, although none of carbohydrates afforded a new solid phase with alendronate (**III**). Ibandronate (**IV**) and risedronate (**V**) generated new solid phases with phenyl- β -D-galactopyranoside (**24**). It is worth to note that both BPs **IV** and **V** contain trisubstituted nitrogen in contrast to alendronate (**III**), which can be an important factor that can cause different interactions. In case of BP **IV** it can be speculated about co-crystal generation; in case of BP **V** the new crystal form, polymorph P, is explicitly characterized. In both cases thermodynamically controlled crystallization was successful. The fundamental steric requirements to carbohydrate formers for generation of a new solid phase is β -orientation of hydroxyl moiety in $\text{C}_{(1)}$ in position 2 of the tetrahydropyran ring together with *cis*-orientation of at least three vicinal hydroxyl moieties and the pyran oxygen. β -Hydroxyl moiety in $\text{C}_{(1)}$ have to be substituted by an aromatic or heteroaromatic ring. It is also important to note that all the used carbohydrates can chelate the sodium cation in monosodium salts of BPs, and thus the sodium cation can contribute to the binding of BPs and carbohydrate with convenient conformation. The sodium cation can make the complex energetically favourable and help to retain the proper topology of the binding phosphates of BPs and the proper orientation of the hydroxyl moieties of a carbohydrate.

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