Co-crystal Screening Study of Risedronate and Unsubstituted Hexoses

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Abstract: Polymorphism of active pharmaceutical ingredients (APIs) gets increasing attention as an important physico-chemical parameter influencing bioavailability and stability of API and pharmaceuticals. Co-crystals of API with common pharmaceutical excipients become very important as a tool to tune up solubility and absorption. Bisphosphonates (e.g. alendronate, risedronate, ibandronate) are widely used in clinical practice. They are indicated for the treatment and prevention of osteoporosis. They are powerful inhibitors of bone resorption, but their gastrointestinal adsorption is only about 1% due to their high hydrophilicity. Some experiments were designed to prepare co-crystals of risedronate. In the present study various mixtures of risedronate and excipients were prepared. All the prepared mixtures (solid compounds) and/or new entities were analyzed by means of FT-NIR, FT-Raman spectroscopy and solid state NMR.

Keywords: Risedronate; Co-crystals; FT-NIR; FT-Raman; CP/MAS NMR.

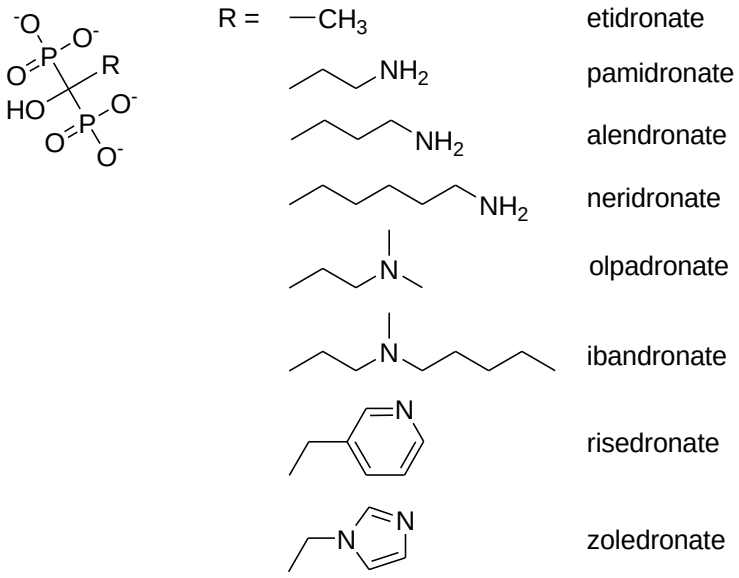
INTRODUCTION

Bisphosphonates (BPs) are the most widely used and the most effective antiresorptive agents currently available for the treatment of Paget's disease, tumor-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 [1]. Following release from bone mineral during acidification by osteoclasts, BPs appear to be internalized specifically by osteoclasts but not other bone cells [2]. The intracellular accumulation of BP leads to inhibition of osteoclast function, due to changes in the cytoskeleton, loss of the ruffled border

[2,3] and apoptosis [4-7]. The ability of BPs to inhibit bone resorption depends on the presence of two phosphonate groups in the P-C-P structure, which appear to be required for interaction with a molecular target in the osteoclast as well as for binding bone mineral [8-10].

Bisphosphonates as pyrophosphate analogues (see the general structure in Figure 1) are a group of drugs widely used in practice. There are several injectable bisphosphonates: etidronate (Didronel®), pamidronate (Aredia®) and zoledronate (Zometa®), which may be administered every three months or yearly. Peroral bisphosphonates alendronate (Fosamax®) and risedronate (Actonel®, Risendros®) are taken daily or weekly and ibandronate (Boniva®) is approved to be taken monthly. Risedronate has a chemically unique component as compared with the other bisphosphonates, which is believed to reduce the likelihood of gastro-intestinal side effects. Risedronate is more potent in blocking the dissolution of bone than etidronate and alendronate. [11]. Oral bioavailability of these bisphosphonates is very low (their gastrointestinal absorption is about 1%) due to their high hydrophilicity [12].

Figure 1. Structures of clinically used bisphosphonates.



In general, structural modifications are the best way to improve permeability: *i*) ionisable groups to 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 nonpolar side chain; *viii*) preparation of prodrugs. Generally these strategies are based on a few fundamental concepts: reduction of ionizability, increase of lipophilicity, reduction of polarity or reduction of hydrogen bond donors or acceptors. Thus, it is important to assess permeability early and to build permeability improvement into the synthetic plan from the beginning. This could rescue a chemical series that has great potential and improve drug exposure in animal pharmacology and pharmacokinetic studies [13].

Formulation is other strategy for improving permeability and bioavailability. For example, permeability enhancers, surfactants or pharmaceutical complexing agents can be used in oral dosage form [13].

The application of co-crystal technologies has only recently been recognised as a way to enhance solubility, stability and the IP position with respect to the development of APIs. Unlike salt formation, co-crystallisation does not rely on ionisation of the API and the counterion to make a solid. Instead, both components utilise prominent intermolecular

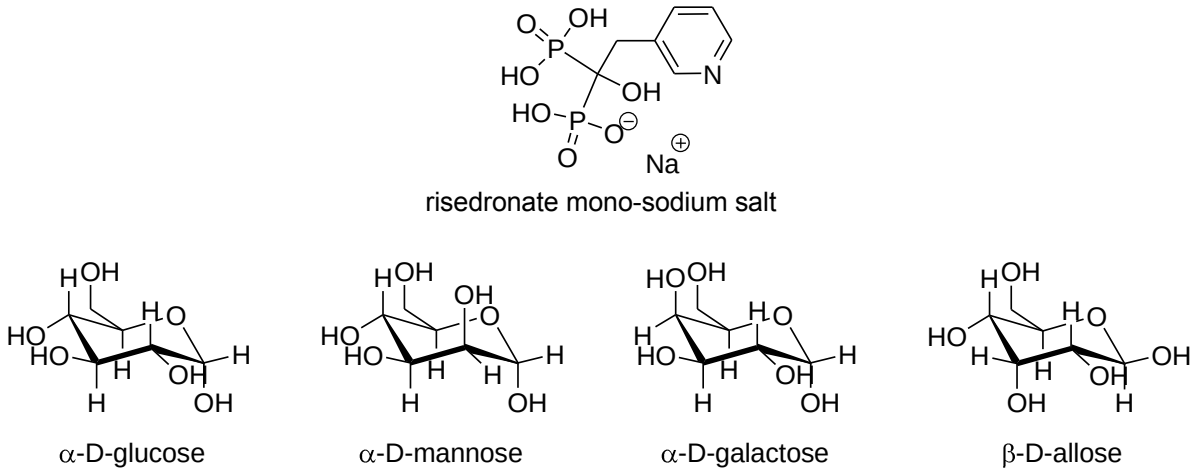
interactions, such as hydrogen bonding, to combine and yield a uniform crystalline material. Combining an API with a pharmaceutically acceptable agent in this guest/host manner has become an increasingly attractive route for developing pharmaceutical products. For example, co-crystallisation offers an alternative when salt screening is either unsuccessful or impossible (due to lack of ionisation sites) to improve the physical properties of a drug. Furthermore, exploring the co-crystallisation potential around an API increases the intellectual property protection over a particular drug product; thus, reducing the risk of costly litigation and market erosion. A recent development in the field has not only seen co-crystallisation as an alternative to salt studies, but has also seen its combination with salts to yield co-crystals of salts [14]. Co-crystals of API with common pharmaceutical excipients become very important [15,16].

Due to the above mentioned facts some experiments were designed to prepare co-crystals of risedronate as a base for possible super generics. In the present study various mixtures of risedronate and excipients (more hydrophobic adducts) in different ratios and under various conditions were prepared. All the prepared mixtures (solid compounds) and/or new entities were characterized by means of the Fourier transform near-infrared (FT-NIR) spectroscopy. Potential new co-crystals were also characterized by means of the FT-Raman spectroscopy and the solid-state NMR.

RESULTS AND DISCUSSION

Various excipients and/or pharmaceutically acceptable agents were evaluated as potential counterions: α-D-glucose, α-D-mannose, α-D-galactose and β-D-allose. All the studied excipients are illustrated in Figure 2. The evaluated samples were prepared by means of dissolution of risedronate and hexose and subsequent reverse obtaining of solid compounds that were characterized using the FT-NIR spectroscopy (diffuse reflectance method, DRIFT).

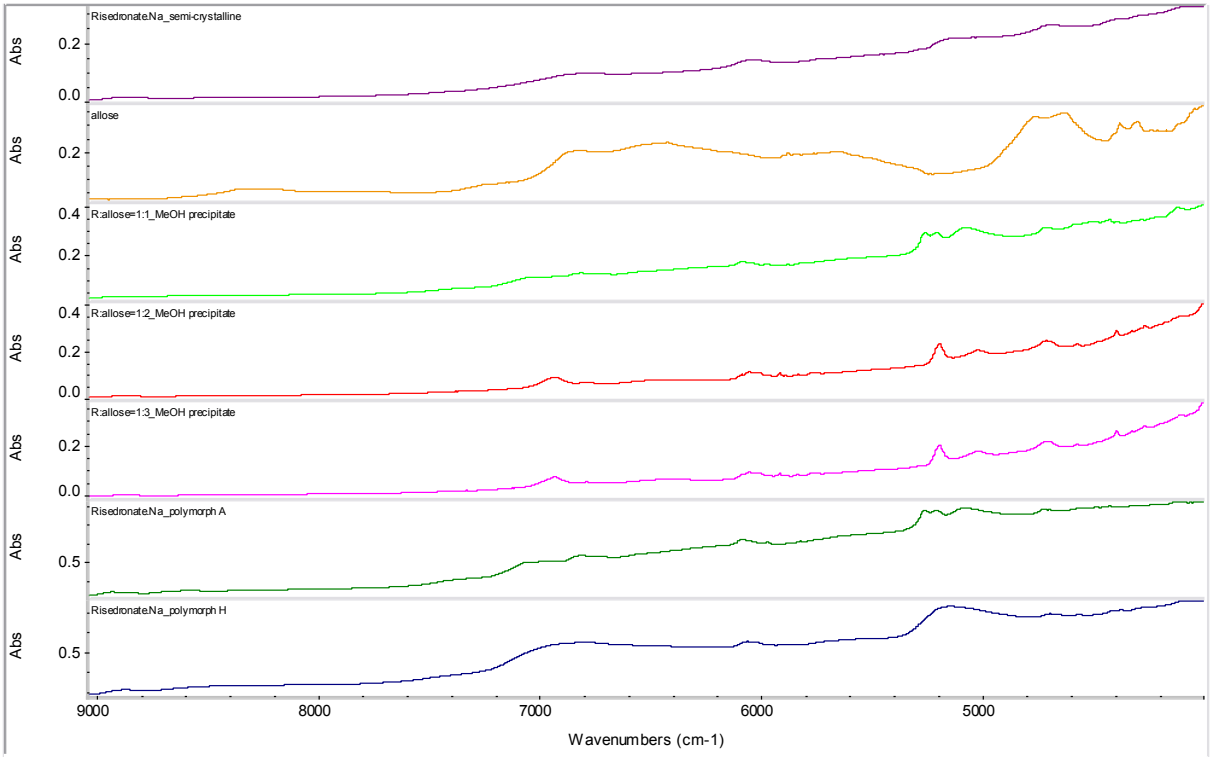
Figure 2. Structure of the starting compounds.



Optical sensing methods represent an important methodology in the modern analytical chemistry. The Fourier transform near-infrared (FT-NIR) spectroscopy is a fast and non-destructive modern analytical technique that offers many advantages for a broad range of applications, e.g. in pharmaceutical development and quality control and process analytical technology. A near-infrared spectral region (1100-2500 nm) is used for the analytical determination of chemical parameters in multiple matrices and industrial products. This has been due to the specific characteristics of this spectral region, the availability of modern instrumentation and the development of advanced chemometric approaches [17].

From all tested agents only β-D-allose generated interesting products. All products of risedronate and β-D-allose in ratios 1:1, 1:2 and 1:3 generated by slow evaporation at laboratory temperature contained risedronate polymorph A, the most thermodynamic stable risedronate form. All products of risedronate and β-D-allose in ratios 1:1, 1:2 and 1:3 generated by slow evaporation (at laboratory temperature) of methanolic solution after precipitate filtration contained only risedronate polymorph H, which is also a thermodynamic stable risedronate form.
Risedronate and β-D-allose in ratio 1:1 generated also risedronate polymorph A by methanol precipitation, but adducts in ratios 1:2 and 1:3 generated by methanol precipitation yielded risedronate in unknown form, probably a potential co-crystal, see Figure 3. Both NIR spectra seem to be similar, therefore both products were also characterized by FT-Raman spectrometry and ^{13}C and ^{31}P CP/MAS NMR spectroscopy, see Figures 4 and 5. Both methods confirmed the difference of both products from known risedronate standards. The carbohydrate component in these products also showed spectral changes in comparison with the allose standard.

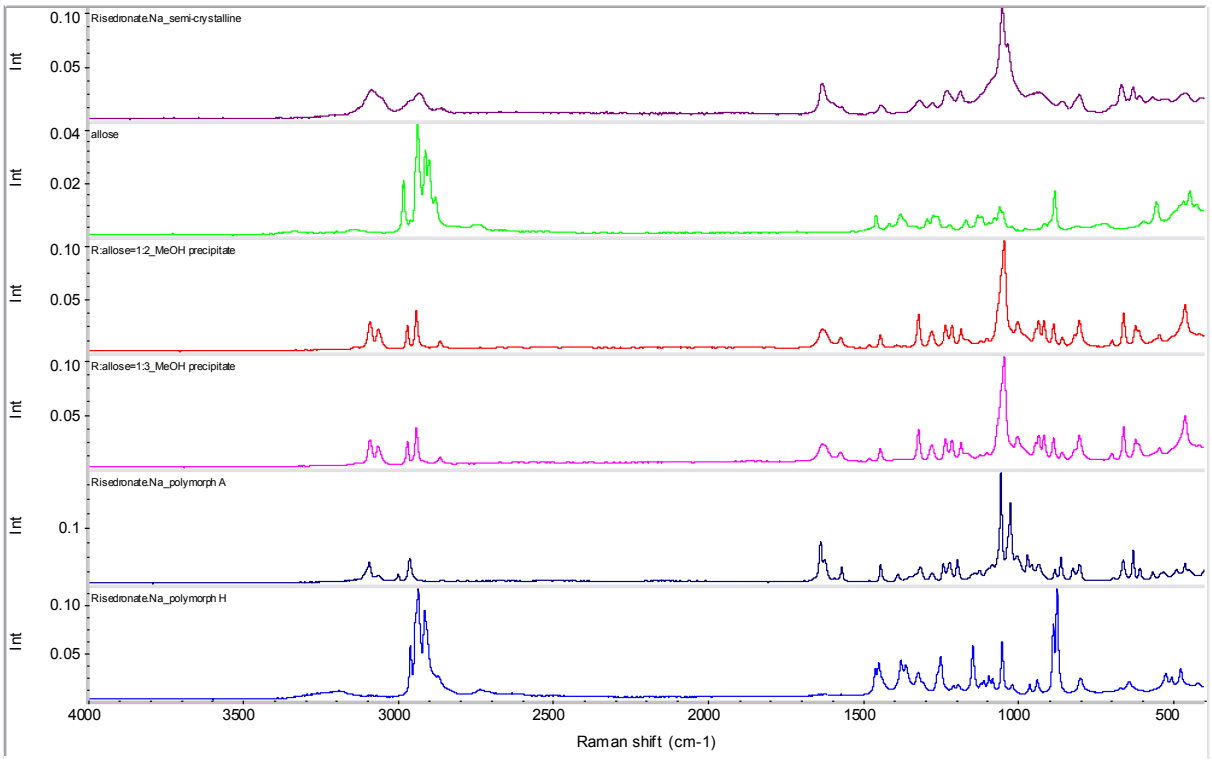
Figure 3. NIR spectra of the starting semi-crystalline risedronate mono-sodium salt, β-D-allose, methanol precipitates of risedronate and β-D-allose in ratios 1:1, 1:2 and 1:3 and stable crystalline modifications of risedronate form A and form H.



Different interactions of allose with risedronate compared to other hexoses are probably caused by opposite orientation of hydroxyl moiety in $C_{(3)}$ in position 4 of the tetrahydropyrane ring. In mannose, glucose and galactose this hydroxyl moiety is equatorial orientated, whereas the hydroxyl moiety in $C_{(3)}$ of allose is axially oriented, *i.e.* it heads under the ring plane. As bonds in co-crystals are formed by non-binding interactions, e.g. by *H*-bonds, the steric arrangement of hydroxyl moieties on hexose skeletons seems to be important for co-crystal generation.

Contrary to the rest of tested hexoses, only allose shows *cis*-orientation of hydroxyl moieties in $C_{(2)}$, $C_{(3)}$ and $C_{(4)}$ in positions 3, 4 and 5 of the tetrahydropyrane ring, *i.e.* three sequential hydroxyl moieties. This fact is probably fundamental for interactions between allose and mono-sodium salt of risedronate.

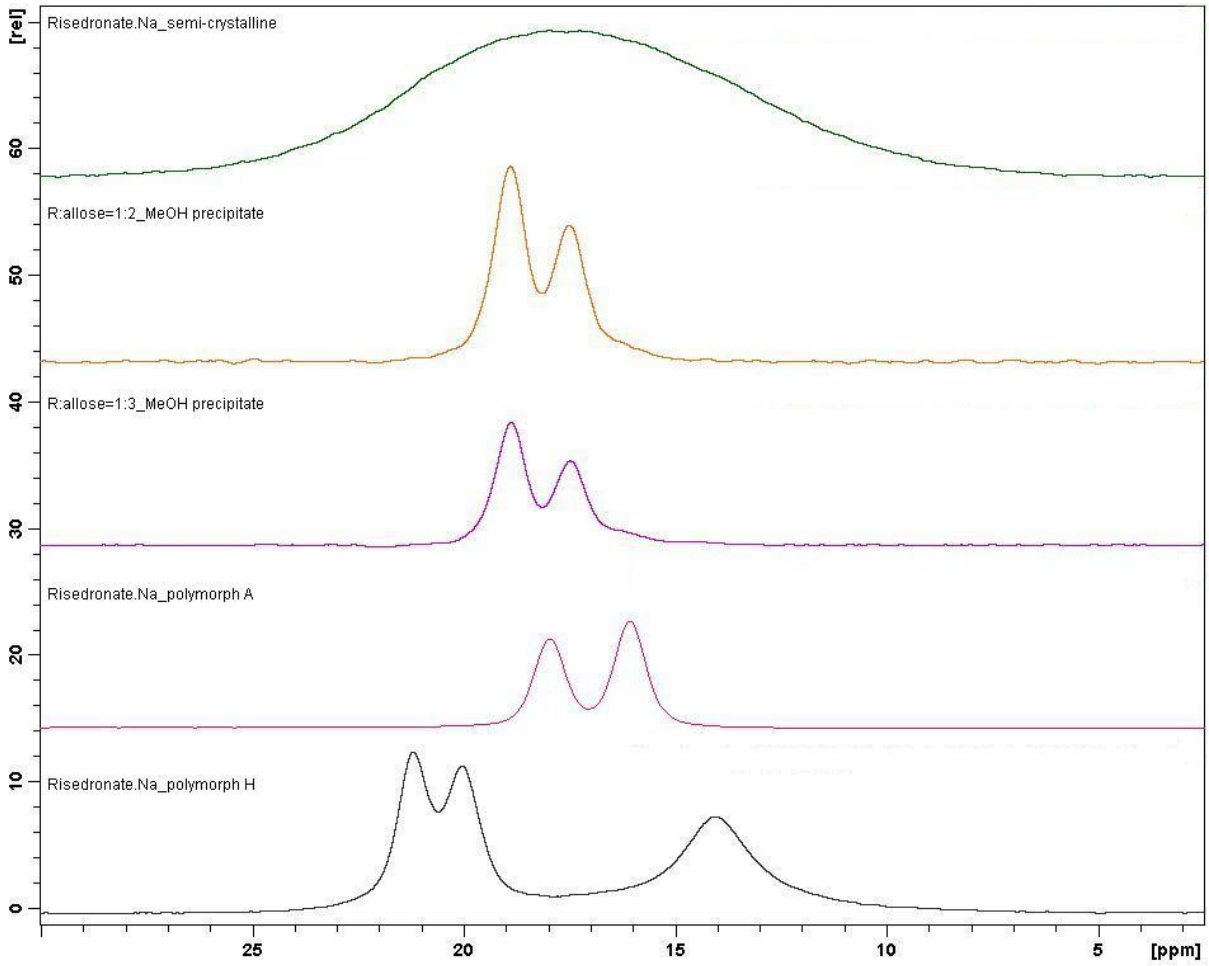
Figure 4. Raman spectra of the starting semi-crystalline risedronate mono-sodium salt, β-D-allose, potential co-crystals (both methanol precipitates) of risedronate and β-D-allose in ratios 1:2 and 1:3 and stable crystalline modifications of risedronate form A and form H.



EXPERIMENTAL

All excipients were purchased from Aldrich. All the evaluated samples in ratios 1:1, 1:2 and 1:3 were prepared by means of dissolution of semi-crystalline risedronate mono-sodium salt and an excipient in water, subsequently mixtured and slowly evaporated at laboratory temperature. To other samples in ratios 1:1, 1:2 and 1:3 methanol was added as anti-solvent. The solid precipitated compound was filtered and dried at laboratory temperature and the remaining liquid part was slowly evaporated at laboratory temperature. All generated solid compounds were subsequently characterized using the spectroscopic methods.
Near infrared spectra were recorded using a Smart Near-IR UpDrift™, Nicolet™ 6700 FT-IR Spectrometer (Thermo Scientific, USA). FT-Raman spectra were accumulated by FT-Raman spectrometer RFS 100/S, Bruker, Germany. ^{13}C and ^{31}P NMR Spectra were recorded on a Bruker AVANCE 500 MHz.

Figure 5. Comparison of ^{31}P CP/MAS NMR spectra of the starting material risedronate mono-sodium salt (semi-crystalline), both methanol precipitates of risedronate and β-D-allose in ratios 1:2 and 1:3 and stable crystalline modifications of risedronate form A and form H.



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