The polymorphism of statins and its effect on their physicochemical properties

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Abstract

Polymorphism of pharmaceutical substances has a significant impact on their physicochemical properties, durability, bioavailability and consequently on their pharmacological activity. Solid dosage forms may exist in both crystalline and amorphous forms. Amorphous varieties are characterized by higher solubility and dissolution rates, while crystalline forms show greater purity and storage stability. The choice between the crystalline or amorphous form of a drug is extremely important to ensure effective and safe pharmacotherapy. Statins — the most commonly used group of drugs in the treatment of lipid disorders — are an example of drugs that occur in many crystalline and amorphous forms. Statins belong to class II in the biopharmaceutical classification system (BCS), which means that they are poorly soluble, but permeate biological membranes well. The bioavailability of statins shows considerable variation, which is associated with the first-pass effect in the liver and the accumulation of the drug in the hepatocytes. The improvement of bioavailability after oral administration of poorly soluble medicinal substances remains one of the most challenging aspects of the drug development process. A specific polymorphic form is obtained by applying appropriate conditions during the process of its preparation under industrial conditions, including the use of a suitable solvent, a specific temperature or rate of crystallization. The article provides a comprehensive update on the current knowledge of the influence of polymorphic form on statin solubility and bioavailability. Research is still being carried out to obtain new polymorphic varieties of statins that are characterized by better physicochemical and pharmacokinetic parameters.

Key words: bioavailability, solubility, amorphic substances, crystalline forms, statins

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Introduction

Polymorphism is the occurrence of different crystalline forms of the same chemical substance. These forms differ in the geometry of a single cell that repeats in the 3 dimensions of the crystal. There are many medicinal substances that exhibit polymorphism. The same drug substance may exist in several polymorphic forms, depending on the distribution of molecules in the crystal lattice, which means individual variants may differ in their properties and activities. Therapeutic substances may also exist in amorphous forms, in which there is no regularity in the distribution of the structural elements and the molecules are arranged chaotically, like in liquids.[1,2]

Individual polymorphic forms of the same drug substance may differ in their physical properties such as chemical reactivity, solubility and dissolution rate, stability, melting and sublimation temperature, density, hardness, adsorption, hygroscopicity and refractive index.[1,2] Crystalline forms are thermodynamically more stable than amorphous varieties, which are high energy systems with a high free enthalpy. Amorphous substances demonstrate a tendency toward crystallization, which is a transition to an energy-beneficial system. The solubility and dissolution rate of crystalline forms are less than those of amorphous materials. The crystallites are also less hygroscopic. The better solubility of amorphous varieties results in their higher bioavailability, which is the fraction of the administered dose of the drug that gets into systemic circulation at a specific rate, and is a factor determining the pharmacological activity of the drug.[3]

The polymorphism of medicinal substances can be crucial in the production of a drug in the form of tablets under industrial conditions. Amorphous forms create problems at the formulation stage: they mix less and have worse rheological properties than crystalline systems.[4] Among crystalline varieties, the most readily formulated into tablets are those with a symmetrical structure (e.g., tetragonal or regular), while substances that crystallize in the monoclinic system cause problems during tablet formulation.

The literature contains several examples of drugs that can occur in crystalline as well as in amorphous forms, including indomethacin,[5] paracetamol,[6] phenobarbital and nifedipine.[7] Moreover, there are many poorly soluble drugs for which differences in polymorphic form solubility are crucial in terms of drug bioavailability, e.g., chloramphenicol palmitate, oxytetracycline, carbamazepine, ritonavir, phenylbutazone and rifaximin.[8]

Statins are the most commonly used group of drugs in the treatment of lipid disorders.[9] They are inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, which is involved in the conversion of HMG-CoA to mevalonate, the primary substrate in the synthesis of cholesterol. Inhibition of this enzyme leads to a reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride (TG), and increases the concentration of high-density lipoprotein (HDL) cholesterol.[10] Moreover, statins have various pleiotropic effects resulting from cholesterol-independent mechanisms of action, statins' ability to affect several tissue functions and the modulation of specific signal transduction pathways. The beneficial effects of statins include anti-inflammatory and antioxidant activity, improvement of endothelial function, increased bioavailability of nitric oxide and inhibition of the progression of atherosclerotic plaques.[11] Statins are classified into 3 categories based on their increasing potency and efficacy in lowering plasma LDL concentrations. First-generation statins included lovastatin, pravastatin and fluvastatin. Simvastatin and atorvastatin belong to the second generation, and rosuvastatin and pitavastatin to the third generation of statins.[12]

Many clinical studies have shown that from 13% to 75% of patients fail to achieve their target levels of LDL-cholesterol and total cholesterol.[13,14] The underlying causes of statin resistance are multifactorial. It appears that both medication-specific and patient-specific factors contribute to the variability of cholesterol-lowering activity. The effectiveness of therapy with statins differs among compounds and may be decreased as a result of variability in the pharmacokinetics of this group of drugs. This variability may be caused by the different lipophilic properties of statins and their solubility. Statins belong to class II of the biopharmaceutical classification system (BCS), which means that they are poorly soluble, but they permeate biological membranes well. For low-solubility BCS II drugs, various oral formulation technologies, including salt formation, particle-size reduction, the use of lipid vehicles and co-solvents in the form of liquid-filled capsules, complexation, and more recently amorphous solid dispersions are designed to maximize the availability of the active pharmaceutical ingredient (API) in the gastrointestinal tract. Statins are an example of drugs that exist in an amorphous state and many crystalline forms, differing in their physical properties and pharmacological activity. Therefore, the polymorphic form of certain statins may significantly impact their bioavailability and in consequence their cholesterol-lowering effects.

In the current article, a comprehensive review of the available evidence regarding the effects of polymorphic form on statins' solubility and bioavailability is presented, including the possible clinical implications.

Polymorphism of statins

Atorvastatin

Atorvastatin is one of the most widely prescribed drugs in the world, and the most widely prescribed statin.[15] It is the most effective statin in lowering cholesterol in LDL, non-HDL and other lipoproteins.[16] Atorv-

astatin is usually marketed as its calcium trihydrate salt, which allows it to be conveniently formulated in pharmaceutical formulations. Like other statins, atorvastatin belongs to BCS class II. Its molecules have a lipophilic character; it is insoluble in aqueous solutions at pH ≤4, and very slightly soluble in water and phosphate buffer at pH 7.4.[17] However, atorvastatin penetrates the intestinal membrane very easily at the intestinal pH 6–6.5, and it absorbs into the blood quickly, achieving maximal concentration (C_{max}) after 1–2 h. About 30% of the administered dosage is absorbed in this way. However, due to the first-pass effect in the liver and intestine, and elimination by the mucous membrane of the stomach and intestine before reaching systemic circulation, the absolute bioavailability of atorvastatin is 14%.[18] The bioavailability of the drug is one of the key parameters for many therapeutic indications. It is dependent on the form of the atorvastatin in the pharmaceutical formulation. More than 70 polymorphic forms of atorvastatin are known, among which crystalline forms are the majority, and at least 2 forms are amorphous (referred as "form 23" and "form 27").[19] The crystalline forms of atorvastatin have strictly defined properties; their solubility depends on the structure of the crystal network and the size of the molecules. These forms are more permanent in the thermodynamic sense than the amorphous forms; their solubility and dissolution rates are lower, which leads to lower bioactivity. On the other hand, atorvastatin in amorphous form has significantly more specific surface area, more substantial capacity to absorb solvents and is more reactive than the crystalline forms, which results in better solubility and bioavailability.[17] Several techniques are commonly used for the transformation of the crystalline drug to the amorphous state, including supercritical anti-solvent precipitation and the spray drying process.[20–22]

Numerous authors have characterized polymorphic forms of atorvastatin based on crystallographic and spectroscopic techniques. Shete et al. performed solid-state characterizations of commercial crystalline and amorphous atorvastatin samples available in the Indian market using X-ray powder diffractometry (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis, Karl Fisher titrimetry, microscopy, contact angle, and intrinsic dissolution rate (IDR).[23] The authors found that all the crystalline samples were stable form I, which had previously been characterized.[24] Amongst the amorphous atorvastatin samples, XRPD demonstrated that 5 samples were amorphous "form 27", while one matched amorphous "form 23".[25] The samples of amorphous atorvastatin had higher wettability and IDR than the crystalline samples, which may impact the performance and stability of the dosage form.[23] Kim et al. prepared amorphous atorvastatin hemi-calcium using the spray-drying and supercritical antisolvent (SAS) processes and compared its physicochemical properties and oral bioavailability with the crystalline form after administration of both forms in 25 mg/kg doses to male rats.[20,21] The oral absorption of amorphous atorvastatin calcium nanoparticles was higher compared with crystalline atorvastatin calcium, which was reflected by greater AUC and C_{max} values. The $AUC_{0-12\,h}$ of the amorphous atorvastatin was 2.1 times that of the crystalline form.[21] The enhancement in oral bioavailability of amorphous atorvastatin was attributed to a combination of higher apparent solubility and a higher dissolution rate due to its amorphous nature.

Rosuvastatin

Rosuvastatin is more effective at reducing LDL and TG levels in the blood plasma than statins of the first generation, including lovastatin or pravastatin, and its activity is 7 times greater than atorvastatin.[26] In contrast to atorvastatin, a molecule of rosuvastatin has a hydrophilic character, which determines the different pharmacokinetic properties of the drug in the body. After oral administration of rosuvastatin, C_{max} is obtained after 3–4 h, and the absolute bioavailability amounts to about 20%.[27] Rosuvastatin is converted to a slight degree (about 10%) into water-soluble derivative by the CYP2C9 isoenzyme, and its half-life amounts to about 19 h. In pharmaceuticals, rosuvastatin occurs in the form of a monohydrate calcium salt. At least 4 crystalline forms of rosuvastatin (A, B, B-1 and C) and 1 amorphous form are known. Form A is a pure crystalline compound; forms B and C are hydrated crystallines; and form B-1 is a dehydrated compound. When comparing the physicochemical properties of the crystalline forms, it was reported that forms B and C are much more soluble in water than form A and that this property may increase their bioavailability. Moreover, they are more thermostable than the amorphous form, which is less resistant to temperature changes, and in consequence less stable during the formulation process.[28,29] The amorphous form of rosuvastatin is manufactured by the spray-drying and freeze-drying processes.[30] It is present in the medication called Crestor®.

Simvastatin

Simvastatin, along with atorvastatin and rosuvastatin, is one of the most commonly used statins in Poland.[31] It is very well absorbed after oral administration (>90%) with C_{max} obtained after 1–2 h. Its bioavailability is very low (<5%), which is associated with the extensive metabolism of simvastatin by the isoenzyme CYP3A4.[27] Currently at least 3 crystalline[32] and 2 amorphous forms of simvastatin are known.[33] When comparing the amorphous forms, it was found that they significantly differ in the size of molecules, physicochemical properties and stability. These differences come from distinct methods in the produc-

tion process of amorphous forms, including cryo-milling (CM) and melting and quench-cooling (QC). Zhang et al. reported that the solubility of the amorphous forms prepared by these 2 methods was enhanced compared to the crystalline form, and that the QC form was more soluble than the CM form.[34] In terms of physical stability, a higher crystallization rate was observed for the CM form, while the QC form exhibited lower molecular mobility and higher chemical degradation.[34]

The superiority of amorphous simvastatin over the crystalline forms was confirmed by Singh et al.[35] The authors prepared an amorphous form of simvastatin by the process of fused dispersion. They observed an improvement in the dissolution rate at pH 6.8, with a maximum release of 99% of the amorphous drug in comparison to 21% release of the crystalline form. Moreover, the pharmacodynamic effect after the administration of both forms to rats with induced hypercholesterolemia was compared. Rats treated with amorphous simvastatin presented a 2.5-fold decrease in total cholesterol, a 1.5-fold increase in TG, a 1.4-fold decrease in LDL, a 2.4-fold decrease in VLDL, and a 1.3-fold increase in HDL-cholesterol compared to the rats treated with the crystalline form. These effects could be attributed primarily to the improved solubility and dissolution associated with the amorphization of the drug.[35]

Pitavastatin

The potency of pitavastatin is dose-dependent and appears to be equivalent to that of atorvastatin. Pitavastatin is well absorbed from the gastrointestinal tract (>80%) and achieves C_{max} about 1–2 h after administration. The absolute bioavailability of the drug is relatively high (about 60%).[27] It is available in pharmaceuticals in the form of sodium, calcium and magnesium salts. Several polymorphic forms of pitavastatin (designated as A, B, C, D, E, F and K) are known, as well as amorphous varieties. In the manufacturing process, the final crystalline form of pitavastatin is affected by the conditions of the crystallization process, which can be accelerated by adding the appropriate form of crystals in an amount not exceeding 5%.[36] Form K, compared to the other crystalline varieties, is characterized by better physical and chemical stability, which is extremely important in pre-formulation processes such as drying, grinding or granulation. There was no conversion of this form to another crystalline variety during the manufacturing or storage of the drug.[37] To obtain amorphous pitavastatin, concentrated solutions of the crystalline form in organic solvents, including 1,4-dioxane, tetrahydrofuran and ethyl methyl ketone, are exposed to non-solvents such as heptane or methyl-*t*-butyl ether. Lyophilization of an aqueous solution of pitavastatin calcium is also performed.[36] There is no data available on the differences between crystalline and amorphous forms in in vivo conditions.

Fluvastatin

Fluvastatin has about 33% of the efficacy of atorvastatin in lowering cholesterol in LDL, non-HDL and remnant lipoproteins.[16] Fluvastatin attains C_{max} about 1–2 h after oral administration, and its bioavailability is 20–30%.[25] In pharmaceutical formulations, it occurs as the crystalline sodium salt in the form of a racemic mixture of the (3R, 5S) and (3S, 5R) enantiomers. Numerous crystalline forms (designated as A, B, C, D, E, F, JF, JF1, JF2 and JF3) and amorphous forms are currently distinguished. Individual forms differ from each other in terms of physicochemical properties. Form B is characterized by a lower hygroscopicity than form A and the amorphous form, which improves the handling and storage of the compound.[38,39]

Pravastatin

Pravastatin, similarly to rosuvastatin, is a hydrophilic compound and it is metabolized to a small extent by cytochrome P450 enzymes. It is quickly absorbed from the gastrointestinal tract, obtaining C_{max} after about 1 h, and its bioavailability is about 18%.[27] In pharmaceutical formulations, it is present as the crystalline form of the sodium salt. At present, at least 12 crystalline pravastatin varieties (known as A, B, C, D, E, F, G, H, I, J, K and L) are known to have similar physicochemical properties.[40] Chun et al. described a method for obtaining an amorphous form of the drug: they prepared crystalline pravastatin sodium solid dispersions using various bile salts and observed the complete conversion of the crystalline form into an amorphous form.[41] The permeation flux of amorphous pravastatin from the solid dispersion was much higher than that of the crystalline form from physical mixtures and commercial tablets,[41] which may improve the bioavailability of the compound in pharmaceutical formulations.

Lovastatin

Lovastatin is a crystalline powder that is practically insoluble in water (0.4 mg/mL); it has a partition coefficient (logP) of 4.26. Lovastatin is absorbed from the gastrointestinal tract (30%) and C_{max} is attained after 2–4 h. As a result of the first-pass effect in the liver, the absolute bioavailability of the drug is only 5%.[27] Lovastatin does not show classic polymorphism. However, it is possible to distinguish crystals characterized by identical dimensions of elemental cells but with a different orientation. It has been found that depending on the crystallization conditions, 2 differing morphologically crystalline forms can be obtained, having the form of either plates or needles. This type of polymorphism does not have a significant effect on the physicochemical properties of the drug. Both forms have the same melting point, similar stability, solubility and reactivity. Yoshida et al. reported that

the preservative excipient butylhydroxyanisole causes amorphization of lovastatin crystallites and that the compound is therefore incompatible with lovastatin.[42] Patel and Patel observed a decrease in the crystalline fraction of lovastatin and an increase in the amorphous fraction in solid dispersions of the drug prepared using polyethylene glycol 4000 and polyvinylpyrrolidone K30.[43] Lovastatin prepared in both polymers showed a better dissolution profile than that of the pure crystalline form.

Conclusions

Due to the differences between the crystalline and amorphous forms of drug substances, which affect not only their solubility and dissolution rates but also their storage stability, the choice of the appropriate form is extremely important to ensure effective and safe pharmacotherapy. It is particularly crucial for statins, which are poorly soluble and have low bioavailability. The low total bioavailability of statins creates the need for new polymorphic forms that will increase the therapeutic effect and reduce the dose of the drug taken by the patient. Based on the available scientific reports, it can be concluded that amorphous forms of statins create the possibility of increasing the solubility and bioavailability of this group of drugs, which in turn is an opportunity to increase their effectiveness in the treatment of cardiovascular diseases.

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