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A Newly Discovered Racemic Compound of Pioglitazone Hydrochloride Is More Stable than the Commercial Conglomerate

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Abstract

A novel racemic compound of pioglitazone hydrochloride is discovered 17 years after the FDA approval of the conglomerate. The racemic compound shows a lower dissolution rate than the conglomerate in simulated gastric fluid at room temperature and is more thermodynamically stable as evidenced by solubility measurements. Slurry transformation of a mixture of the two forms converts fully to the racemic compound. This report highlights the necessity to thoroughly explore solid forms to access the most thermodynamically stable form of a pharmaceutical and contrasts the structural features of the two forms.

Graphical Abstract

Active pharmaceutical ingredients (APIs) can exist in various solid forms.¹ The different solid forms will exhibit distinct physical and chemical properties, among which

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ASSOCIATED CONTENT

Supporting Information

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SI 1. Experimental. SI 2. Raman spectroscopy. SI 3. Powder X-ray diffraction (PXRD). SI 4. Single crystal structure determination. SI 5. Differential scanning calorimetry (DSC). SI 6. Intrinsic dissolution rates. SI 7. Solubility measurement (PDF)

Accession Codes

CCDC 1514934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

thermodynamic stability is perhaps the most significant in the pharmaceutical industry.² Administration of a metastable form, although often favorable for improving solubility, may lead to phase transformation to a less soluble (thermodynamically stable) form potentially impacting bioavailability.³ During the development of ritonavir as a protease inhibitor at Abbott Laboratories, only one crystalline form was identified (form I). In 1998, two years after the launch of ritonavir as Norvir to the market, capsules began failing dissolution tests. The issue was traced to the appearance of a thermodynamically more stable and less soluble form, form II. This novel polymorph of ritonavir resulted in the withdrawal of the original capsules. Ritonavir tablets were subsequently remarketed as a solid dispersion using melt-extrusion in 2010.^{4–6} In a similar incident, the existence of less soluble polymorphs of rotigotine^{7,8} caused a batch product recall in 2008. To lower the risk of phase transformation,⁹ selection and development of the most thermodynamically stable form is usually preferred. The case of ritonavir is an exceptional one because there are few substantiated cases of a more thermodynamically stable form of a drug arising after introduction to market. Herein, we report the first racemic compound of pioglitazone hydrochloride. The crystal structure was determined and compared with that of the known conglomerate. The novel racemic compound shows lower dissolution rate in simulated gastric fluid at room temperature and is demonstrated to be more stable than the currently marketed form.

Pioglitazone hydrochloride (PGH, brand name Actos) (Figure 1) is used to treat type 2 diabetes.¹⁰ It belongs to the Biopharmaceutics Classification System (BCS) class II because of its low solubility in water (0.047 mg/mL).¹¹ Two crystal polymorphs of PGH, form I and form II, have been claimed in patents.^{12,13} However, “Form II” was proven by Sawant et al.¹⁴ to be identical to pioglitazone free base. Form I is a conglomerate which is routinely produced by the synthetic process and is used in the manufacture of the product.¹⁵ The two enantiomers of PGH interconvert *in vivo*, and no pharmacokinetic difference between the two enantiomers is detected, thus justifying the use of a racemate.¹⁶

PGH, like most chiral pharmaceuticals on the market, is administered as a racemate.¹⁷ Crystalline racemates can exist as racemic compounds (both enantiomers exist in the unit cell in a 1:1 ratio) or conglomerates (1:1 mixtures of two pure enantiomers).¹⁸ Statistical analysis reveals that 5–10% of crystalline racemates are conglomerates, while 90–95% are racemic compounds. Numerous surveys have established that the tendency is for racemic compounds to be more stable than conglomerates,^{19–21} although salts show a somewhat higher prevalence of conglomerate formation compared to neutral compounds.²²

The novel racemic compound of PGH was discovered using a halogen-containing polymer library to induce heteronucleation. The halogenated polymer library was prepared following the protocol demonstrated by Price et al.²³ Briefly, six halogenated monomers, mixed in various ratios, were photo-polymerized in the 96 wells of a polypropylene plate with the cross-linker divinylbenzene (DVB) and AIBN as the initiator (Supporting Information, S1). The monomers used to build the halogen polymer library are 3-chloro-2-hydroxypropyl methacrylate (CHPMA), 2,2,2-trifluoroethyl methacrylate (TFEMA), 2,2,3,3-tetrafluoropropyl methacrylate (TFPMA), 4-vinylbenzyl chloride (4-VBC), 1,1-dichloroethene (DCE), and 4-chlorostyrene (4-CS) (Supporting Information, Figure S1). A

solution of PGH was prepared by dissolving 200 mg of PGH in 4.0 mL of methanol (50 mg/mL) at 23 °C. After filtration through a 0.45 μm pore size PTFE filter, 40 μL of the solution was dispensed into each well of the 96-well plate containing halogenated polymers. Crystals were collected after the solvent slowly evaporated at room temperature and characterized using Raman spectroscopy and powder X-ray diffraction (PXRD). The PGH racemic compound was most reliably produced on polymers derived from CHPMA, TFEMA, and TFPMA.

Analysis of the PGH racemic compound by Raman spectroscopy shows characteristic peaks in the region from 650 to 1500 cm^{-1} (Supporting Information, Figure S2). The PXRD pattern of the novel racemic compound exhibits distinct peaks at 9.9, 10.5, 16.0, 17.1, 21.9, 24.4 and 27.8°, 2θ , which are easily distinguishable from the peaks of form I at 8.7, 12.8, 19.8, 20.2, 22.3, 28.4, and 31.2°, 2θ (Supporting Information, Figure S3). Differential scanning calorimetry (DSC) was performed to monitor phase transitions of the two solid forms. For both the conglomerate and the racemic compound, no thermal event can be detected before the endothermic event with an onset at 195.3 and 193.7 °C, respectively, although extensive sample decomposition accompanies melting precluding detailed interpretation of the melting temperatures and enthalpies. (Supporting Information, Figure S4). Both solid forms are stable and do not undergo solid-phase transformations under ambient conditions for at least six months.

The crystal structure of PGH racemic compound was determined using single crystal X-ray diffraction and compared with that of the conglomerate. The conglomerate crystallizes in the $P2_1$ space group ($Z=2$), with the pyridinium and thiazolidinedione rings bridged by chloride ions through ionic bonding ($\text{Cl}^- \dots ^+\text{HN}$) and hydrogen bonding ($\text{Cl}^- \dots \text{HN}$) interactions, respectively, at an angle of 91.0° to form side-to-side homochiral tapes.²⁴ The assembly of the homochiral tapes form the typical 2_1 -column structure observed in conglomerate crystals according to Kinbara et al. (Figure 2a,c).²⁵ The racemic compound crystallizes in the $P2_1/n$ space group ($Z=4$), with the pyridinium and thiazolidinedione rings bridged by chloride ions through ionic bonding ($\text{Cl}^- \dots ^+\text{HN}$) and hydrogen bonding ($\text{Cl}^- \dots \text{HN}$) interactions, respectively, at an angle of 104.2° to form end-to-end homochiral chains. The chain pairs, which are related by inversion, interdigitate at an angle of 77.2° to form the racemic compound (Figure 2b,d). The dissolution rate of PGH solid forms in simulated gastric fluid (without pepsin)²⁶ was determined at room temperature (Figure 3). The racemic compound shows an average intrinsic dissolution rate of 0.874 $\text{mg cm}^{-2} \text{min}^{-1}$, which is 1.55 times lower than that of the conglomerate: 1.36 $\text{mg cm}^{-2} \text{min}^{-1}$. In order to assess the relative thermodynamic stability of the two forms, the solubilities in ethanol at different temperatures were determined by turbidity measurements. The free-energy differences between the conglomerate and the racemic compound were calculated using eq 1,

$$\Delta G = G_C - G_R = RT \ln \left(\frac{X_C}{X_R} \right) \quad (1)$$

where G_C is the free energy of the conglomerate, G_R is the free energy of the racemic compound, X_C is the solubility of the conglomerate, and X_R is the solubility of the racemic compound.^{27,28} Figure 4c shows the G - T relationship from 20 to 65 °C, with the novel racemic compound being the thermodynamically stable form of PGH at all temperatures examined. This result was confirmed by slurry conversion experiments at room temperature. An equal mixture of the two forms was equilibrated, in the presence of ethanol, on a shaker at 500 rpm for a week. The remaining solid was examined using Raman spectroscopy and PXRD. Only peaks corresponding to the racemic compound are present in the spectrum and pattern of the solid (Supporting Information, Figures S2 and S3). Therefore, the PGH racemic compound is experimentally proven to be more thermodynamically stable than the conglomerate. The slurry conversion method is suitable for producing any amount of the pure racemic compound.

In conclusion, a novel racemic compound of PGH was discovered that exhibits a lower dissolution rate in simulated gastric fluid at room temperature than the commercial form. The racemic compound is thermodynamically more stable than the conglomerate as judged by solubility and slurry conversion experiments. This report highlights the necessity to thoroughly explore crystal forms in a racemate-forming system because the occurrence of a less soluble form can exert a significant impact on the bioavailability of a pharmaceutical. The fact that such a form could go undiscovered for so long highlights the complex and unpredictable nature of the kinetics of form conversion in pharmaceuticals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Chemical structure of pioglitazone hydrochloride (PGH).

Figure 2.

Crystal structures of PGH conglomerate (a and c) and racemic compound (b and d). R and S enantiomers of PGH are coded as blue and red, respectively. The green spheres represent chloride ions. The teal dashed lines show ionic interactions and hydrogen bonding interactions. The orange dashed lines in (c) show the 2₁ screw axis.

Figure 3.
Intrinsic dissolution rate profile of PGH forms in simulated gastric fluid at room temperature.

Figure 4. Solubility measurements at varying temperature with the calculated free-energy difference (ΔG) of the PGH forms in ethanol for the (a) racemic compound and (b) conglomerate. (c) Calculated ΔG using eq 1.