UNIVERSITY OF LIMERICK
OLLSCOIL LUIMNIGH

Technology Transfer Office

Licensing Opportunity

New Crystalline Forms of Apixaban. Apixaban prevents blood clots and reduces the risk of heart attacks and stroke

Overview

Biologically active molecules, usually as solid forms, are the active ingredients that lie at the heart of most medicines. This means that the material properties of such solid forms (the “active drug substance”) define its stability, solubility, and bioavailability and, ultimately, enable the efficacy of the resulting medicines. The importance of solid forms of drug molecules is particularly important when the drug molecule is hydrophobic and exhibits low water solubility.

Technology

Apixaban (APX) is a drug molecule that is a highly potent, selective, and efficacious inhibitor of blood coagulation factor Xa. APX was developed by Bristol-Myers Squibb and the revenue of the marketed drug product, Eliquis®, was $14.1 billion in 2020. Apixaban sales were $16.7 billion in 2021. The solid form of APX that lies at the heart of Eliquis® exhibits relatively low solubility. This has spawned an investigation into new solid forms of APX including both crystalline forms (e.g., polymorphs, hydrates, cocrystals, and solvates) and amorphous forms. Form N-1 is used Eliquis® as it is considered to be the thermodynamically stable form under ambient conditions, a desirable feature for use in a drug product. Unfortunately, Form N-1 has several problems including poor solubility in water (0.028 mg/mL at 24 °C), relatively low oral bioavailability (about 50% for a single 10 mg dose), and excretion after first-pass metabolism in the gut and liver. Whereas salt formation can address solubility challenges, the molecular structure of APX means that it is not ionizable with most pharmaceutically approved or acceptable acids and bases. Cocrystals are an option in such circumstances, but the existence of cocrystals for any given API is not guaranteed, they can be difficult to manufacture in bulk from solution and their stability in water is generally poor. Nevertheless, at least eight new drug products and three generic drug products are comprised of active drug substances that are cocrystals, most introduced in recent years. Further, cocrystals are accepted as potential drug substances by regulatory bodies such as the US FDA and the EMA. Whereas there are existing cocrystals of APX, their synthesis is challenging, and/or they have stability issues.

Benefits

Researchers at the University of Limerick have invented a novel family of anhydrous APX cocrystals that addresses the problems of previous APX solid forms:

- ✓ They exhibit increased solubility in phosphate-buffered saline (PBS) 6.8 solubility *vs.* Form N-1;
- ✓ They can be readily synthesised at scale in water under ambient conditions;
- ✓ Their compositions are based upon coformers that are generally recognised as safe (GRAS) or pharmaceutically approved);
- ✓ The coformers are low-cost and commercially available;
- ✓ They are kinetically stable under slurry conditions;
- ✓ They are stable to humidity at 40 °C / 75% RH (accelerated stability testing conditions).

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There is a well-established market for Apixaban and the molecule patent is about to expire. There is the potential for interest in generic and novel cocrystal forms. The UL Opportunity is a novel formulation of an existing on-market product. The increasing prevalence of venous thromboembolism-related conditions is expected to aid in the growth of the apixaban market. For instance, the International Society on Thrombosis and Haemostasis 2014 facts, revealed that around 10 million cases of venous thromboembolism occur annually across low, middle, and high-income countries.

Applications

The family of APX solid forms is exemplified by 13 novel APX cocrystals comprised of APX and aliphatic carboxylic acid (fumaric acid) or aromatic carboxylic acids (gallic acid, salicylic acid, vanillic acid, 2,3-dihydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxybenzoic acid, 2,6-dihydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, and 4-aminobenzoic acid) in ratios from 1:0.5 and 1:0.3. Water slurring of APX and carboxylic acids were used to prepare the cocrystals in gram scale. X-ray powder diffraction (XRPD) was used to identify the new APX cocrystals and revealed that they are isostructural.

Single crystal X-ray diffraction (SCXRD) of a representative cocrystal, APX: fumaric acid (APXFUM) showed it to be anhydrous. The stoichiometries of the APX cocrystals were determined by solution proton nuclear magnetic resonance (NMR) spectroscopy. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) confirm that the novel APX cocrystals are stable to at least 190 ˚C and that all members of the family are anhydrous. Powder dissolution profiles revealed that each novel cocrystal exhibits a nearly two-fold increase in solubility vs. the N-1 form of APX. To summarise, a novel family of molecular cocrystals with high APX content offers improved physicochemical properties with respect to solubility, dissolution rate, and/or stability compared to existing crystal forms of APX. Moreover, the novel cocrystals can be readily synthesised by a green method (slurring in water) that is suitable for large-scale manufacturing.

The novel cocrystals invented herein are therefore suitable for use in new drug products, either as new chemical entities with improved efficacy) or as bioequivalent drug substances (generic).

Commercial Opportunity

The University of Limerick is interested in seeking partners to exploit the commercial potential of these technologies by entering into licensing agreements. The University of Limerick has filed a Patent on the novel co-crystals.

Target Market for Innovation: Pharmaceutical sector

☐Development partner

☐Commercial partner

☒Licensing

☐University spin-out

☐Seeking investment

Further IP information

Patent Title: cocrystals

Type: PCT

Country: EPO

Status: Filed

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Figures

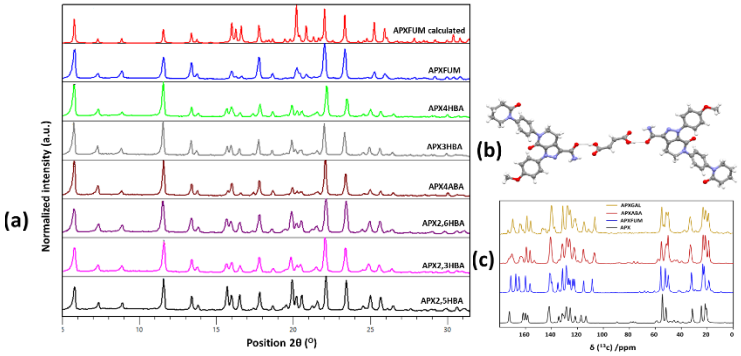

Figure 1: (a) Comparison of calculated and experimental XRPD patterns of the isostructural cocrystals; (b) Crystal structures depicting O−H···O hydrogen bonding in APX:fumaric acid cocrystal; (c) 13C Solid-state NMR spectra of the of APX and selected cocrystals.

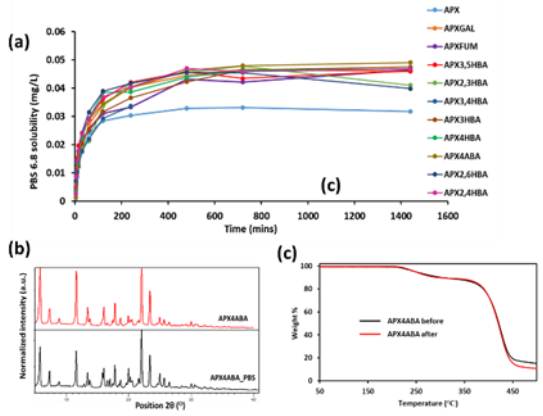

Figure 2. (a) Dissolution profile of APX and respective cocrystals in PBS 6.8 at 37 ˚C; (b) XRPD pattern of the APX:4hydroxy benzoic acid cocrystal before and after the dissolution experiment; (c) Stability study- comparison of TGA of APX:4hydroxy benzoic acid cocrystal before and after exposing to humidity (40 °C / 75% RH).