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HOT-MELT EXTRUSION BASED SUSTAINED RELEASE IBRUTINIB DELIVERY SYSTEM: AN INHIBITOR OF BRUTON'S TYROSINE KINASE (BTK)

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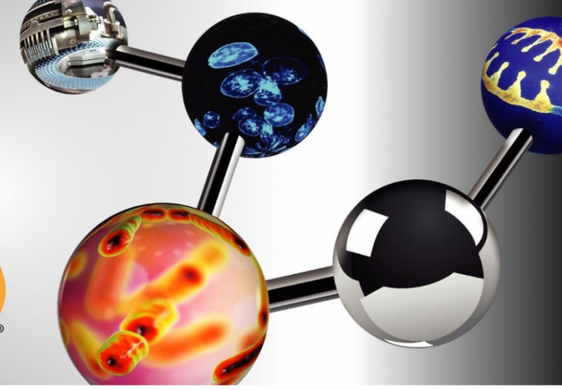


PURPOSE

Ibrutinib is the first Bruton`s tyrosine kinase (BTK) inhibitor for oral administration approved by FDA in 2014 (1). It is the first-line treatment for B-cell malignancies, which are the most common hematologic neoplasia. Ibrutinib is a relatively safe alternative for currently used treatment modalities that are associated with long-term toxicity and resistance (2). However, ibrutinib is considered as Class-II drug according to the Biopharmaceutics classification system (BCS) and has very low solubility in an aqueous medium (13 µg/ml at PH 8.0) and has six different polymorphic forms (3). Furthermore, recommended daily dose of ibrutinib is about 420 mg to 560 mg, which causes severe GI disturbances, with poor patient compliance. This represent a major critical concern because drug is used chronically. Increasing drug solubility and controlling rate of drug release may improve both bioavailability at significantly lower daily administered doses and by implication could minimize GI side effects and improve patient compliance.

OBJECTIVE(S)

The aim of this study is to utilize Hot Melt Extrusion (HME) to develop a stable amorphous solid dispersion (ASD) of ibrutinib using Copovidone (PlasdoneTM S-630 Ultra) as a carrier for inclusion into a hydrating matrix for sustained release delivery. ASD systems based on HME is an efficient technique to overcome poor solubility problems and stabilize the drug`s metastable polymorphic states. It is known that amorphous systems are energetically at a higher thermodynamic state and can dissolve to a much greater extent relative to their crystalline counterpart. A stable sustained-release ASD based system may offer many advantages, including reduction in frequency of administration and GI disturbances with propensity to enhance solubilization while suppressing recrystallization.

METHOD(S)

Series of extrudates at different drug loadings (i.e., 20%, 40% and 60%) were prepared using hot melt extruder, and characterizing solid-state properties, using Advanced rheometer ARES G2, modulated differential scanning calorimetry (mDSC), X-ray powder diffraction (XRPD), and thermogravimetric analysis (TGA). Supersaturated solubility was determined under non-sink condition in 20 mL fasted state simulated intestinal fluid (FaSSIF, pH 6.5) using micro-dissolution system (µDiss Profiler™). The optimized melt extruded ASD was formulated into SR tablet using Manesty BetaPress. Dissolution studies of SR tablet were carried out using standard USP apparatus II at stirring speed of 100 RPM in 900 mL of pH 6.5 FaSSIF at 37 ± 0.5°C.

RESULT(S)

Experimental results shown in Figure-1 A, B, & C and all analytical tests confirmed the formation of stable ASD system with single glass transition temperature in thermogravimetric analysis (Tg) and *modulated differential scanning calorimetry (MDSC) studies* confirming the exitance of single-phase system with no phase separation up to 60% drug loading. *Additionally, X-ray powder diffraction analysis (XRPD)* demonstrated the amorphous state of ibrutinib in all ASD systems (Fig. 1).

Dynamic oscillatory rheological analysis for ASD with 20% API load demonstrated relatively similar rheological response across temperature ranges between 140 °C and 170 °C, this is observed by the parallel and superimposed curves which indicates system`s homogeneity, while deviation or loop formation observed for ASD systems with 40% and 60%, implies inhomogeneity (Fig. 2).

Release rate from ASD powders using micro-dissolution test under non-sink conditions was performed. The percentage of ibrutinib dissolved was determined using integrated fiber-optic UV dip probe at 260 nm. Micro-dissolution testing of ASD systems against crystalline API showed solubility enhancement which was 70% higher for ASD relative to crystalline drug under similar conditions (Figure 3A)

For developed tablets in USP dissolution testing under sink conditions, the ASD-based SR tablets with 20% and 40% API load showed remarkably higher percentage dissolved (87% and 54% respectively) when compared with the crystalline ibrutinib tablets with only 34% drug release (Figure 3B).

❖ ***Figure 1 Thermal and spectroscopic analysis (Thermogravimetric Analysis, modulated differential scanning calorimetry and X-ray powder diffraction XRPD)***

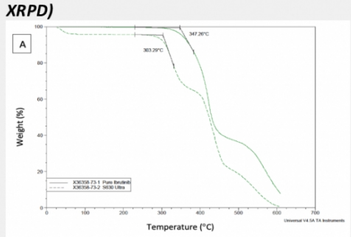


Figure 1-A. TGA Analysis for the pure ibrutinib and Plasdone™ S-630 Ultra.

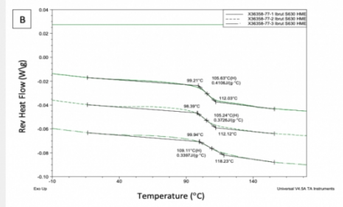


Figure 1-B DSC for 20% drug loading ASD (X36358-77-1), 40% drug loading ASD (X36358-77-2), and 60% drug loading ASD (X36358-77-3).

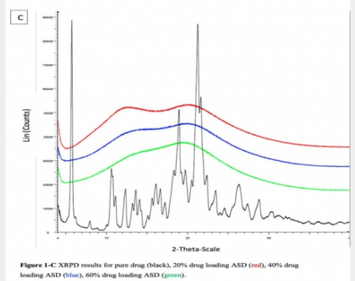


Figure 1-C XRPD results for pure drug (black), 20% drug loading ASD (red), 40% drug loading ASD (blue), 60% drug loading ASD (green).

❖ ***Figure 2* Dynamic oscillatory rheological analysis**

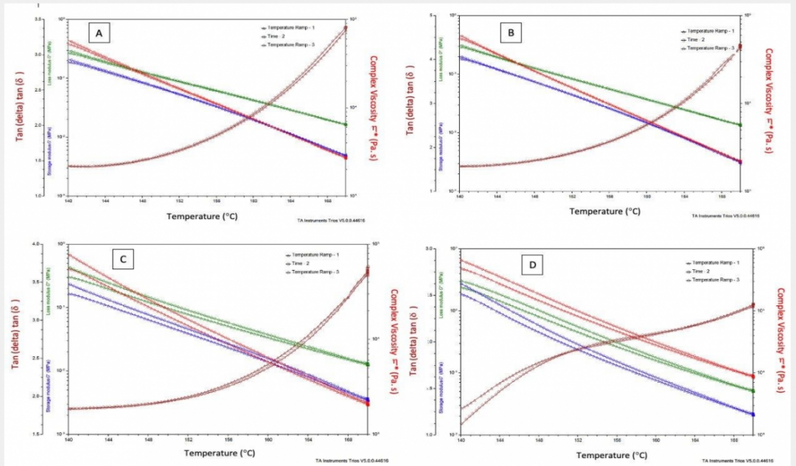
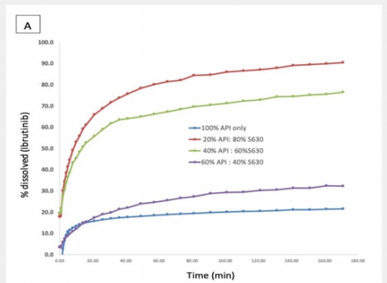
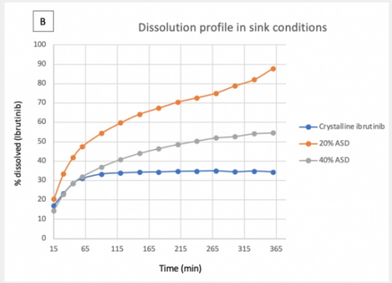


Figure 2 Thermo-rheological behavior of pure copovidone S630 ultra (A), and the three produced ASD systems with 20% (B), 40% (C), and 60% (D) API load.



❖ ***Figure 3 A) Comparison of micro-dissolution profiles for crystalline ibrutinib and three ASDs at 20%, 40%, and 60% drug loadings. Dissolution conditions: 20 mL FaSSIF (pH 6.5, non-sink) at stirrer speed of 300 rpm.***



❖ ***Figure 3 B Dissolution under sink conditions. Sustained release profile of ibrutinib ASD at 20% and 40% drug loadings versus excess amount of crystalline API.***

CONCLUSION:

Based on the results, we have demonstrated that production of a stable ASD system with three different drug loadings (i.e., 20%, 40% and 60%) have amorphous character, showing a single Tg. Furthermore, we achieved enhancement in ibrutinib dissolution rate and attainment of supersaturated state that exceeded saturation solubility of crystalline ibrutinib by 70%. We also successfully developed a sustained-release ASD matrix showing improved dissolution rate and extent, followed by suppression of recrystallization during dissolution of ibrutinib. It is hoped that the developed sustained release ASD ibrutinib tablets with enhanced API solubility and controlled delivery rate may improve patient compliance, reduce daily doses and eliminate unnecessary incidences of gastrointestinal side effects and should be further investigated.

ACKNOWLEDGMENTS & REFERENCES

ACKNOWLEDGMENTS

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