A Novel Delivery-Platform Reduces Cardiac Toxicity of the FDA-approved BTK Inhibitors used in Blood Malignancies

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Purpose

The goal of the current work is to evaluate the use of a novel drug delivery platform primarily based on using the new polymeric materials Soluplus as a promising strategy to combat the current clinical limitations of the FDA-approved BTK inhibitors used in blood malignancies. More specifically, the cardiac toxicities patients encounter while on these medications.

Methods

The new drug delivery platform was developed using a simple solid dispersion methodology. Briefly, ACS-chemical grade APIs of the two recently FDA-approved BTK inhibitors, Acalabrutinib and Zanubrutinib (Figure 1), were mixed with Soluplus in a clinically EMA-approved ratio (illustrated in Figure 2). Acetone was then added to the mixtures and mixed till completely solubilized. Acetone was dried out, and then a warm water was added followed by agitation/ homogenization. Several concentrations of the APIs were prepared in a range of 10 µM-160 µM. APIs without the platform were prepared in DMSO/water mixture. Employing the Invitrogen™ Predictor™ hERG Fluorescence Polarization Assay Kit, these APIs concentrations as well as negative and positive controls as provided by the kit were tested using plate reader. This assay provides an efficient method for determining whether test compounds block the hERG channel or not. Compounds that bind to the hERG channel protein (inhibitors) are identified by their ability to displace the tracer, resulting in a lower signal (Figure 3).

Results

The preliminary data (Figure 4) indicates that formulating the BTK inhibitors using Soluplus-based delivery platform produced significant (*P value* < 0.05) high fluorescence polarization compared to the APIs without the platform in a concentration dependent manner. Reflecting the ability of the platform to reduce the binding potential of these APIs to the hERG channel, and thus causing the unwanted cardiac toxicity.

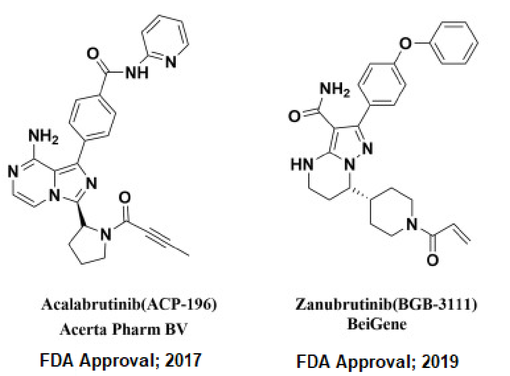

Figure 1: Structures and FDA approval dates of the BTK inhibitors used in the current study

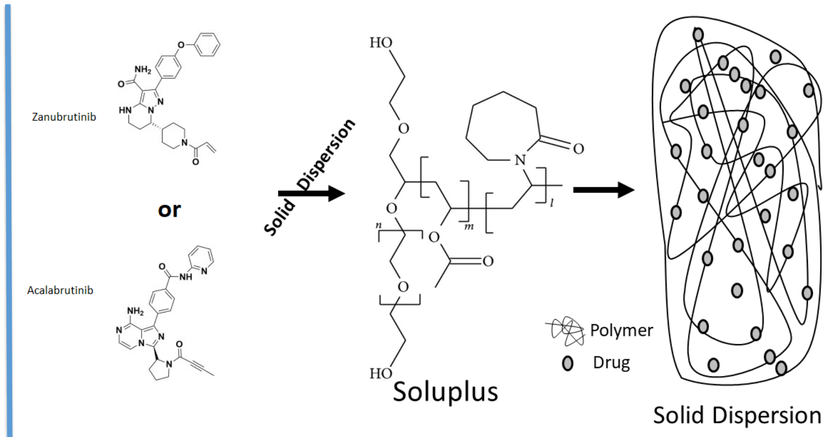

Figure 2: An illustration of the solid dispersion method used to prepare the new delivery platform for the BTK inhibitors.

Predictor™ hERG Polarization Assay Kit

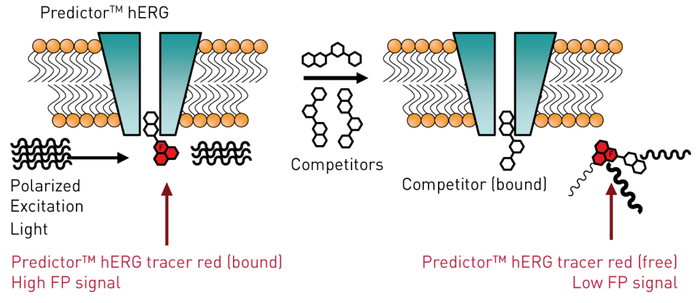

Figure 3: An illustration of the Predictor™ hERG Assay used in the current study.

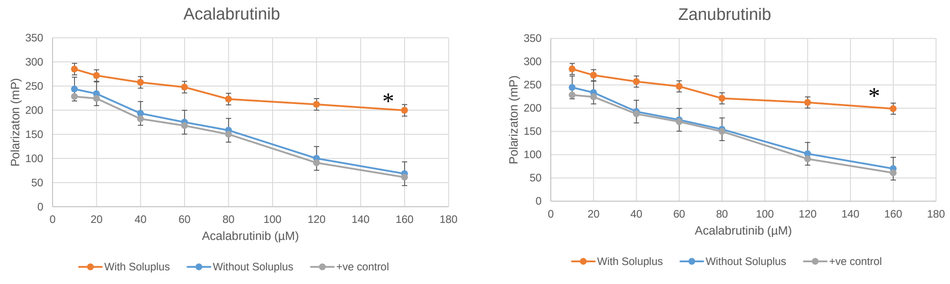

Figure 4: Concentration response curve of the BTK inhibitors used in this study with and without the Soluplus-based drug delivery platform. *Statistically significant reduction in the cardiac hERG channel inhibition upon the use of Soluplus in the delivery platform (*P value* < 0.05).

Conclusion

The data from the current work open the door toward the necessity of keeping exploring the new and emerging excipients as a way to optimize the safety profiles of the recent highly effective targeted cancer therapies such BTK inhibitors.