Annals of Hematology (2023) 102:219–220
https://doi.org/10.1007/s00277-022-05014-3

LETTER TO THE EDITOR

Impact of tablet crushing on the dissolution of venetoclax

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Received: 30 August 2022 / Accepted: 26 October 2022 / Published online: 4 November 2022

Dear Editor,

Venetoclax is available as 10, 50, and 100 mg film-coated tablets (VENECLEXTA®). Although the 100 mg VENECLEXTA® tablet is the most commonly used, its large size (17.2 mm length and 9.5 mm width) makes it difficult for elderly patients with impaired swallowing ability to ingest. We observed a case in which the patient ingested crushed VENECLEXTA® 100 mg tablets at home due to difficulty in swallowing, resulting in approximately twice the expected venetoclax blood level [1]. We were unable to explain this phenomenon. To the best of our knowledge, there are no previous reports on dissolution of crushed VENECLEXTA® tablets. Therefore, we evaluated the impact of crushing a VENECLEXTA® tablet on its dissolution property.

Dissolution tests were performed on an Erweka model DT light dissolution test system (Langen, Germany) with a paddle. One intact or crushed tablet was added to a 1000-mL vessel containing 900 mL deionized water under shaded conditions. The stirring speed was 50 rpm, and the temperature was controlled at 37 ± 0.5 °C. Five milliliters of the solution were sampled at every measurement time point. After sampling, 5 mL of fresh deionized water were added to the vessel. The test solution was degassed via sonication and vacuum before the dissolution tests. The dissolution tests for crushed and intact VENECLEXTA® tablets were performed using three samples. Test solutions were taken at 1, 2, 3, 4, 5, 10, 15, 20, 30, 60, 90, 120, 180, 240, 300, and 360 min and analyzed by HPLC [2]. Statistical analysis was performed using EZR [3].

In the case of crushed tablets, dissolution began after 1 min and plateaued after 5 min (Fig. 1). The average venetoclax concentration from 5 to 360 min of the dissolution test was 76.2 ± 0.4 μg/mL. Intact tablets began to dissolve 15 min after the start of the test. After 360 min, the average venetoclax concentration reached its highest value of 9.0 μg/mL. A comparison of the concentrations of crushed and intact VENECLEXTA® tablets in the test solutions showed statistically significant differences in concentrations from 1 min after the start of the test ($P < 0.001$; two-sample t-test).

We found that the dissolution behavior of crushed and intact VENECLEXTA® tablets was significantly different during the dissolution tests. These results suggest that accelerated dissolution increases the blood concentration of venetoclax. VENECLEXTA® tablets are an amorphous solid dispersion (ASD) formulation [4]. Like VENECLEXTA® tablets, a significant increase in dissolution rate has been observed following crushing for other ASD formulations such as Noxafil® (posaconazole) and Novir® (ritonavir) [5]. Our results support our previous report [1] and the package insert statement that VENECLEXTA® tablets should not be chewed, crushed, or broken [6]. As ASD is a relatively new formulation technology and the tablets appear to be normal, clinicians and nurses may crush ASD formulations. This can, in turn, significantly impact oral bioavailability and have clinical consequences.

In conclusion, physicians should not recommend crushing VENECLEXTA® for patients who are unable to swallow the tablets.

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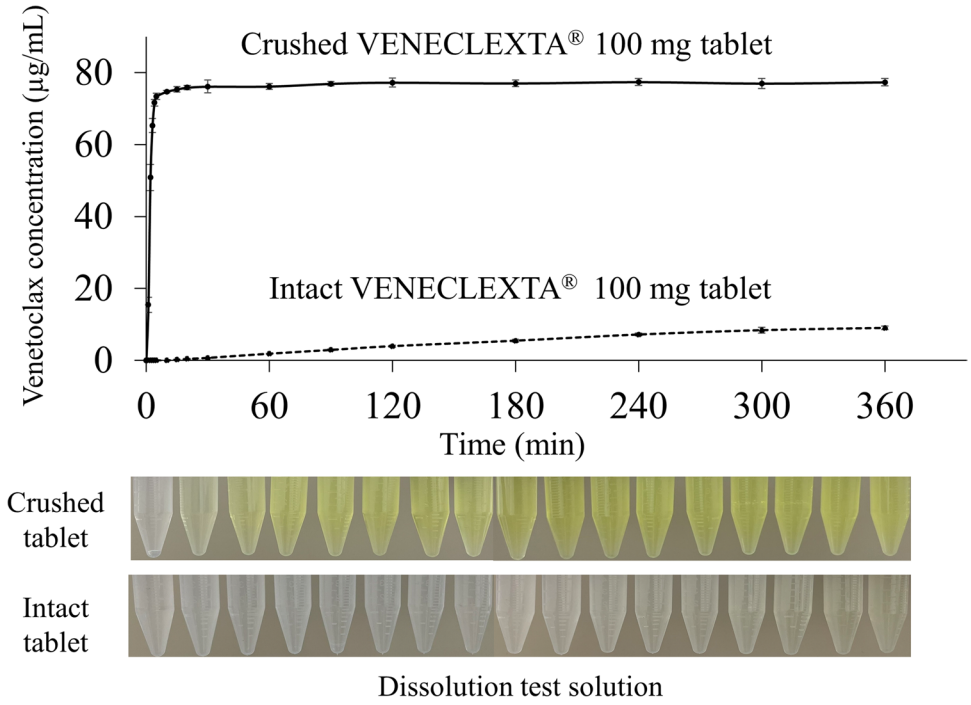

Fig. 1 Dissolution profiles of venetoclax from crushed and intact VENECLEXTA.® tablets ($n = 3$, mean ± SD)

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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