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Salt disproportionation in bicarbonate buffer

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The intestinal pH is controlled by a bicarbonate buffer (BCB). Therefore, BCB should be used for biorelevant dissolution tests. BCB exhibits unique properties regarding drug dissolution, due to the slow CO_2 to H_2CO_3 hydration reaction. Recently, we developed a simple BCB dissolution test using a floating lid to avoid CO_2 loss and to maintain the pH of BCB [1]. The pH increase is < Δ0.1 pH for several hours. The experimental procedure of the floating lid method is almost the same as phosphate buffer (PB). It is compatible with surfactants because no CO_2 bubbling is used. The floating lid method enabled us to perform various dissolution tests easily and efficiently.

Recently, we reported that pharmaceutical salts and cocrystals show disproportionation to their free form during drug particle dissolution [2]. The purpose of the present study was to investigate the effect of buffer species on the dissolution profiles of poorly soluble drug salts, focusing on bicarbonate buffer (BCB).

Pioglitazone HCl (PIO HCl) and dantrolene sodium (DNT Na) were used as model drugs. Non-sink dissolution tests were performed using PB and BCB (pH 6.5, buffer capacity: 4.4 mM/pH, ionic strength: 0.14 M, with/ without bile micelles). The pH value of BCB was maintained using a floating lid. Because direct *in situ* analysis of suspended particles is difficult, multiple experimental evidences were collected to prove the occurrence of disproportionation at the particle surface during its dissolution. The particles were collected at the early stage of dissolution (< 5 min) and analyzed by powder X-ray diffraction, polarized light microscopy, and scanning electron microscopy. A bulk-phase pH shift precipitation test was also performed.

The dissolution of PIO HCl was slower in BCB than in PB, whereas that of DNT Na was faster in BCB than in PB. The same trend was observed in the presence of bile micelles. Disproportionation to a free form was observed on the surface of salt particles early in their dissolution in both BCB and PB. However, the surface textures in BCB and PB were different. The bulk-phase precipitation of PIO and DNT was little affected by buffer species.

In conclusion, the dissolution profiles of PIO HCl and DNT Na in BCB were markedly different from those in PB. Salt disproportionation at the dissolving particle surface can be affected by buffer species.

[1] Sakamoto A, Izutsu K, Yoshida H, Abe Y, Inoue D, Sugano K. Simple bicarbonate buffer system for dissolution testing: Floating lid method and its application to colonic drug delivery system. *J Drug Deliv Sci Technol.* 2021;63:102447.

[2] Uekusa T, Sugano K. Precipitation behavior of pioglitazone on the particle surface of hydrochloride salt in biorelevant media. *J Pharm Biomed Anal.* 2018;161:45–50.