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Effect of bicarbonate buffer on the precipitation behavior of drugs

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Purpose

The pH value of human intestinal fluid is maintained by bicarbonate buffer (BCB). On the other hand, phosphate buffer (PB) is often used in in vitro studies. However, little is known about the effect of BCB on the precipitation behavior of drugs. The purpose of the present study was to investigate the effect of BCB on the precipitation behavior of drugs.

Methods

Dantrolene ($pK_a = 6.6$ (A)), flumequine ($pK_a = 6.4$ (A)), glibenclamide ($pK_a = 6.8$ (A)), dipyrindamole ($pK_a = 6.2$ (B)), haloperidol ($pK_a = 8.0$ (B)), naftopidil ($pK_a = 7.3$ (B)), phenazopyridine ($pK_a = 5.2$ (B)), pioglitazone ($pK_a = 5.8$ (B)), prazosin ($pK_a = 6.2$ (B)), triamterene ($pK_a = 6.2$ (B)), and tosufloxacin ($pK_a = 5.8$ (A), 8.7 (B)) were used as model drugs (A: acid, B: base). A model drug was dissolved in pH 3.0 HCl or pH 11.0 NaOH. The drug solution (450 mL) was added to the vessel covered with a floating lid. The pH value was shifted to pH 6.5 by adding 50 mL of 80 mM PB or 100 mM BCB (total 500 mL, buffer capacity = 4.4 mM / Δ pH, ionic strength = 0.14 M, 37°C, 50 rpm). The solid form of the precipitated solid was determined by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC).

Results

There was no significant difference in the precipitation behavior of drugs between PB and BCB except for haloperidol and naftopidil. In the case of haloperidol and naftopidil, the precipitation of drugs occurred faster PB than BCB. The precipitated solid was identified as the free form by PXRD and DSC.

Discussion

The effect of BCB on the precipitation behavior of drugs differed among the drugs. Haloperidol and naftopidil are basic drugs with a tertiary amine and a high pK_a ($pK_a > 7.0$).

Conclusions

The effect of BCB on the precipitation behavior of drugs might be due to the chemical structure and pK_a of the drugs.