Clinical relevance: Why are enteric coatings failing *in vivo*?

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PURPOSE

Enteric coated (EC) dosage forms are often used to:

- protect acid-labile drugs from degradation by the acidic gastric environment;
- prevent irritation of the gastric mucosa by certain drugs;
- target the drug release to a specific intestinal region.

As the dosage form travels from the stomach to the intestine it is expected that the enteric polymer would dissolve upon reaching a region that has a higher pH than its dissolution pH threshold.

However, there are many reports of unpredictable *in vivo* behaviour of EC dosage forms, which, in many cases, impacted their clinical efficacy. Due to the low *in vivo* buffer capacity, a gap between the bulk and polymer surface pH may exist, which can hinder its dissolution. Thus, EC polymers behaviour in bicarbonate buffer (BCB) may differ greatly from what it's expected in phosphate buffer (PB).

The purpose of this study was to compare the *in vitro* performance of different marketed EC products in both compendial media and BCB at reported *in vivo* molarity and pH values and to elucidate the interaction between BCB and enteric coating polymers.

METHODS

The commercially available drug products tested were of different drug classes, presenting different physicochemical properties, coating material and manufacturers (Table 1).

Table 1. Physicochemical properties and enteric coating composition of the tested products

Drug product	BCS class	pKa	Coating polymer	Dissolution pH threshold
ASPIRIN (Bayer Inc.)	I	Acid (3.41)	Methacrylic acid and ethyl acrylate copolymer	5.5
DICLOFENAC (Sandoz)	II	Acid (4.00)	Hypromellose	5.5
ESOMEPRAZOLE (Apotex)	II	Basic (4.77)	Methacrylic acid copolymer type C	5.5
PANTOPRAZOLE (Teva)	III	Basic (3.55)	Methacrylic acid – ethyl acrylate copolymer	5.5
SULFASALAZINE (PMS)	IV	Acid (3.23)	Acryl resin	6 - 7

All dissolution tests were performed using an USP apparatus 2, 900 mL dissolution media, 75 rpm rotation speed and temperature set at 37.0° C. The tablets were tested in both USP phosphate buffer 50mM and bicarbonate buffer 5mM pH 6.5 after being exposed to HCl 0.1M for two hours.

RESULTS

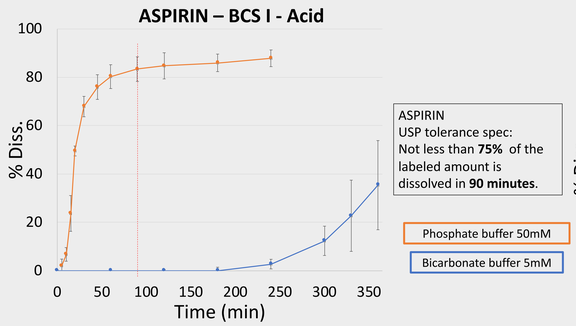


Figure 1. Comparative dissolution profiles of Aspirin EC tablets in phosphate buffer 50mM pH 6.8 (orange line) and bicarbonate buffer 5mM pH 6.5 (blue line), expressed as mean ± SD

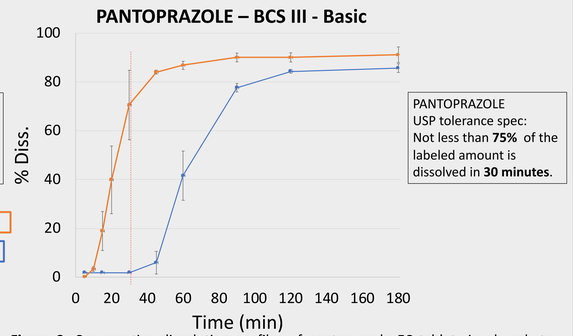


Figure 2. Comparative dissolution profiles of pantoprazole EC tablets in phosphate buffer 50 mM pH 6.8 (orange line) and bicarbonate buffer 5mM pH 6.5 (blue line), expressed as mean ± SD

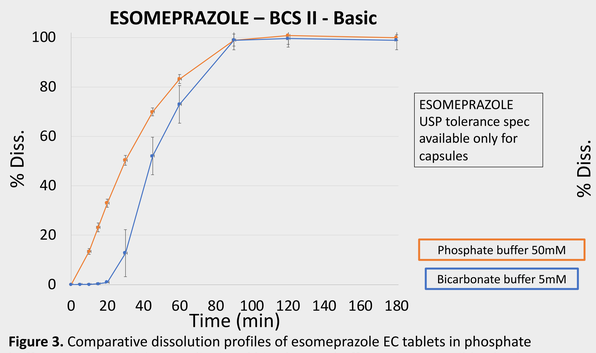


Figure 3. Comparative dissolution profiles of esomeprazole EC tablets in phosphate buffer 50 mM pH 6.8 (orange line) and bicarbonate buffer 5mM pH 6.5 (blue line), expressed as mean ± SD

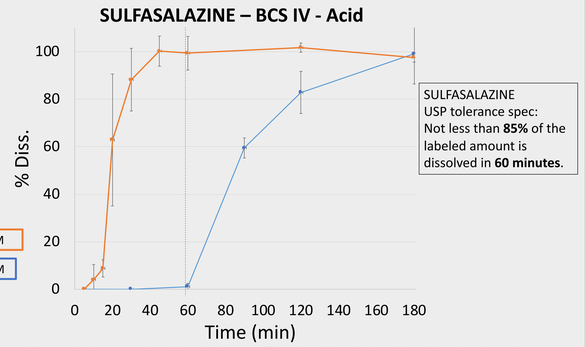


Figure 4. Comparative dissolution profiles of sulfasalazine EC tablets in phosphate buffer 50 mM pH 6.8 (orange line) and bicarbonate buffer 5mM pH 6.5 (blue line), expressed as mean ± SD

QC alternative? - Buffer molarity and pH

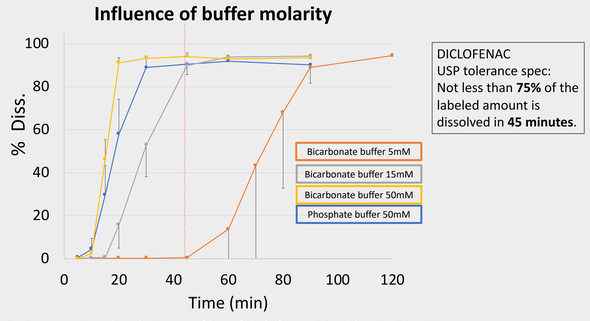


Figure 5. Comparative dissolution profiles of diclofenac EC tablets in 50mM phosphate buffer pH 6.8 (blue line), bicarbonate buffer pH 6.5 at 5mM (orange line), 15mM (grey line) and 50 mM (yellow line), expressed as mean ± SD

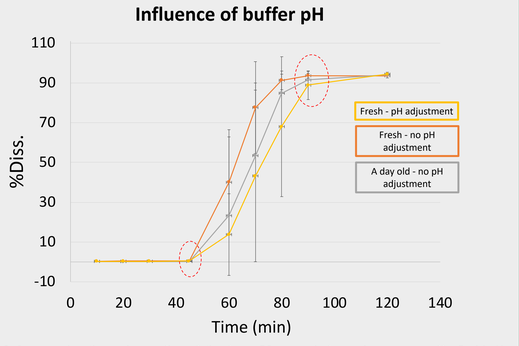
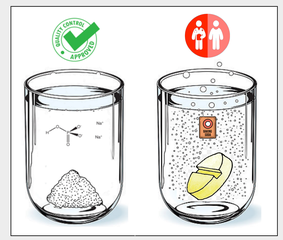


Figure 6. Comparative dissolution profiles of diclofenac EC tablets in fresh bicarbonate buffer 5mM pH 6.5 (yellow line), fresh buffer no pH adjustment (orange line) and a day old with no pH adjustment (grey line) expressed as mean ± SD

CONCLUSIONS

- The lower rate and extent of drug absorption observed *in vivo* was reflected *in vitro* when applying physiologically relevant conditions
- The *in vivo* FAILURE of EC products seems to be due to poor performance in physiologically relevant bicarbonate buffer at low buffer capacity
- The dissolution results in bicarbonate buffer FAIL to meet the current USP criteria
- USP dissolution test for enteric coated tablets is **clinically irrelevant** and can be misleading during the formulation development process
- Population with lower buffer molarity are at risk for therapeutic FAILURE
- Buffer molarity seems to impact the coat opening more than bulk pH
- The assumption of pH threshold for triggering drug release from enteric coated dosage forms is questionable in BCB
- A new QC method for EC products needs to be developed.



REFERENCES AND ACKNOWLEDGEMENTS

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