

AQUACOAT® ECD: FOOD EFFECT AND PH CONSIDERATIONS

Technical Memorandum

At DuPont, we aim to help our pharma customers with both every day challenges and future solutions. Armed with essential excipients and vital expertise, our broad portfolio is designed to deliver performance and cost advantages in various oral solid dosage forms.

Food effect

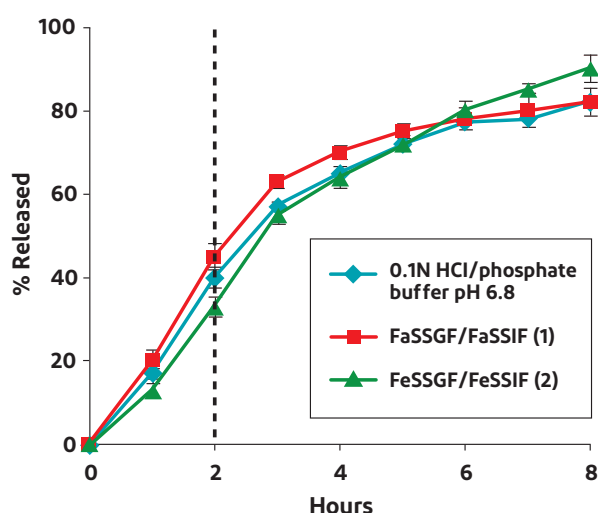
Aquacoat® ECD provides a robust controlled release coating that is unaffected by release media changes in pH or by the presence of fat, carbohydrate, enzymes, surfactants, bile salt and calcium ions.

Although Aquacoat® ECD is generally robust in response to release media changes, it is critical to evaluate the food effect on the controlled release formulation as a whole. This is because the composition and quantity of ingested food can significantly alter the type and amount of bulk fluid surrounding the pellets or tablets during drug release in the gastro-intestinal tract (GIT). Various biorelevant media can be used to support estimation of the effects of the presence of pepsin, sodium taurocholate, lecithin, milk and different types and amounts of ions in the GIT on drug release in fast and fed states.

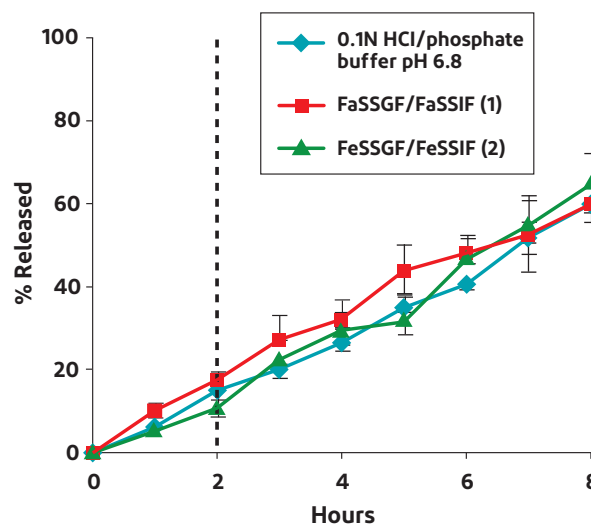
Drug release in media simulating the fast and fed state

The drug release rate of diltiazem and theophylline pellets was measured in a USP 2 paddle apparatus, using a standard medium of 0.1 N HCl for two hours followed by transition to a phosphate buffer of pH 6.8. The resulting release rates were compared with release rates obtained using biorelevant release media that were selected to emulate the fasted and fed states, with a full change of media after two hours. The resulting drug release profiles were similar in all types of bulk fluids, indicating that the presence of pepsin, lecithin, sodium taurocholate as well as milk (3.5% fat) does not affect the release pattern of the different drug types (Figure 1).

Figure 1: Drug release in fed and fasted biorelevant media



(1) Fasted-state simulating gastric fluid/Fasted-state simulating intestine fluid
 (2) Fed-state simulating gastric fluid/Fed-state simulating intestine fluid
 Diltiazem pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 90:10 with a coating level of 30% w/w



(1) Fasted-state simulating gastric fluid/Fasted-state simulating intestine fluid
 (2) Fed-state simulating gastric fluid/Fed-state simulating intestine fluid
 Theophylline pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in a ratio of 85:15 with a coating level of 15% w/w

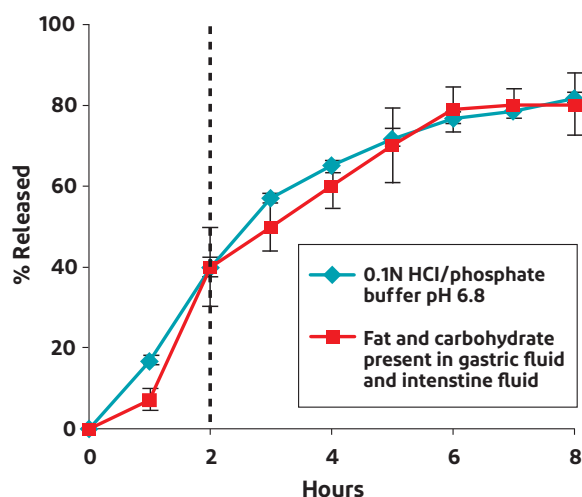
Drug release in media containing fat and carbohydrate

Figure 2 compares the dissolution of Aquacoat® ECD-coated pellets in different media in order to assess the impact of fat and carbohydrates on drug release. One dissolution profile was obtained using a standard medium of 0.1N HCl for two hours followed by transition to a phosphate buffer of pH 6.8. The second profile was obtained using a medium containing fat and carbohydrate to emulate GIT contents. Diltiazem and theophylline release was unaffected by the presence of high amount of fat and carbohydrate.

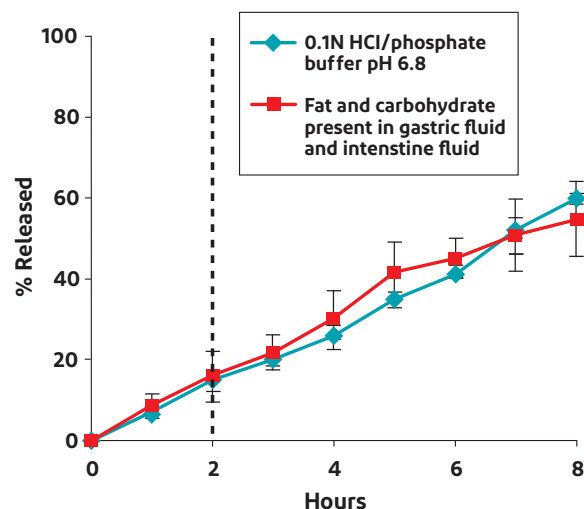
Drug release in media simulating gradual changes in pH levels

USP apparatus 3 was used to understand gradual changes in pH that mimic transition in the GIT. Figure 3 shows that drug release kinetics were not affected by gradual pH changes in the release media. Theophylline and diltiazem pellets coated with Aquacoat® ECD thus showed pH independent drug release.

Figure 2: Drug release in media containing fat and carbohydrate

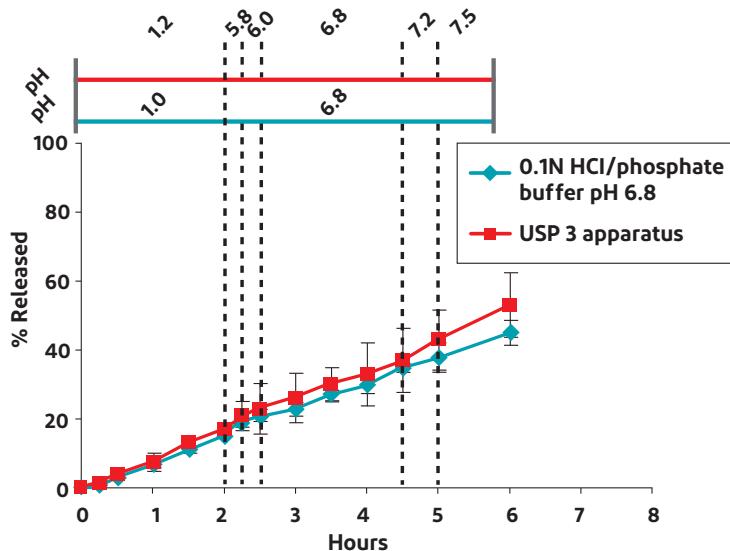


Diltiazem pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 90:10 with a coating level of 30% w/w

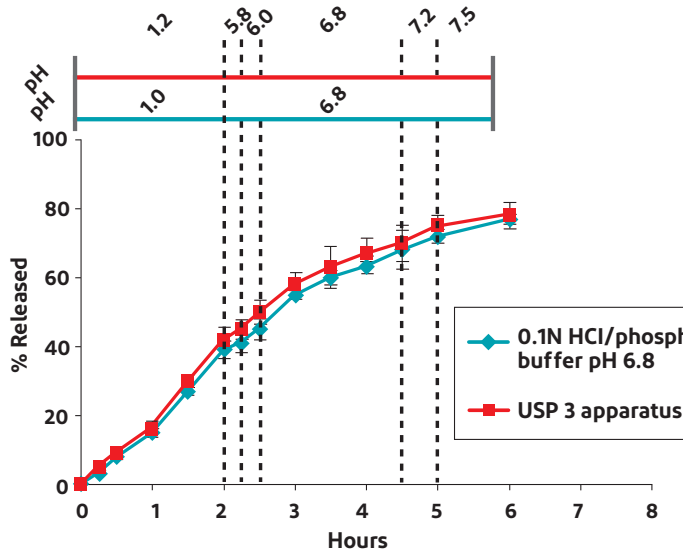


Theophylline pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 85:15 with a coating level of 15% w/w

Figure 3: Drug release in media simulating gradual changes in pH levels



Diltiazem pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 90:10 with a coating level of 30% w/w; vertical markers indicate timing of pH changes according to the USP 3 standard.

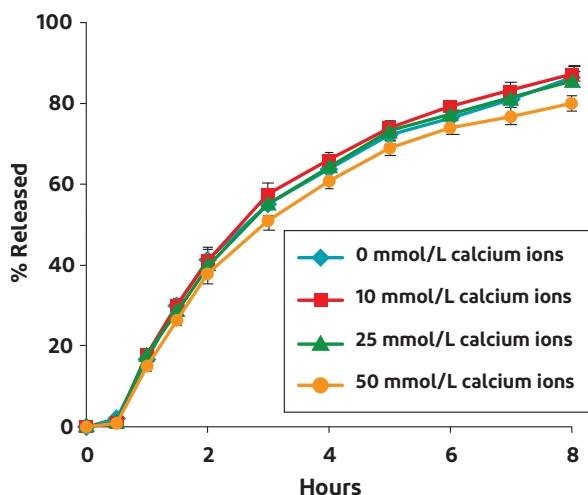


Theophylline pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 85:15 with a coating level of 15% w/w

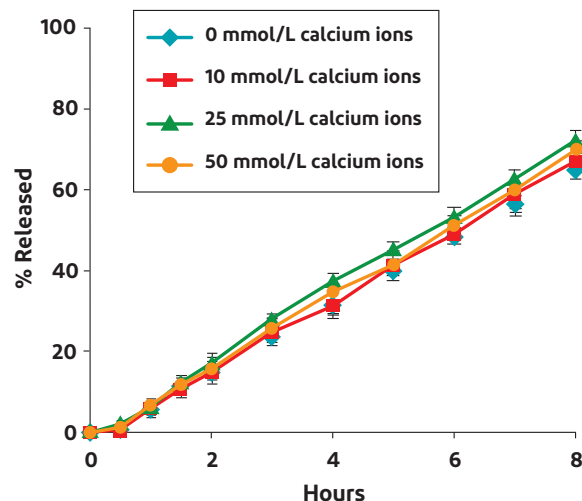
Drug release in media containing various concentrations of calcium ions

Drug release was measured with USP 2 paddle apparatus in release media containing 0, 10, 25, and 50 mmol/L calcium. Figure 4 shows diltiazem and theophylline release in the presence of varying calcium ion levels. Release was unaffected by the presence or absence of calcium ions.

Figure 4: Drug release in media containing various concentrations of calcium ions



Diltiazem pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 90:10 with a coating level of 30% w/w



Theophylline pellets coated with Aquacoat® ECD and PVA-PEG graft copolymer in the ratio of 85:15 with a coating level of 15% w/w

REFERENCES

- Muschert, S., Siepmann, F., Leclercq, B., Carlin, B., Siepmann, J.; Simulated Food Effects on Drug Release from Ethyl Cellulose: PVA-PEG Graft Copolymer-coated Pellets; Drug



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