IN VITRO STUDY OF THE EFFECT OF ALCOHOL ON DRUG RELEASE FROM MATRIX TABLETS

Nasrin Mahmoudi, Kevin McIntyre, Joseph Lee, Brandon Rowe
– Pharma Solutions, IFF

Where science & creativity meet

The Background

Extended-release, or long-acting tablets, are often formulated and marketed to improve patients' therapeutic outcomes. These tablets are modified to slowly, rather than rapidly, release the drug for absorption into the blood – to reduce the number of times the patient must consume the medication throughout the day. While convenient for patients, extended-release tablets can be difficult to formulate. An increased amount of the drug, relative to fast-acting tablets, with the right blend of excipients is necessary to successfully initiate and maintain a slow drug release – even in the presence of alcohol.

Matrix-forming polymers, such as hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO), are both commonly formulated into modified release matrix tablets. These polymers can help control active ingredient release, whether it's immediate, sustained or delayed. For extended-release tablets, the Food and Drug Administration (FDA) recommends in vitro dissolution testing in media containing up to 40% alcohol (ethanol). This testing evaluates for potential alcohol-induced dose dumping – or the rapid unintended release of a drug, due to alcohol consumption by patients.

The Study

In this study, researchers sought to compare the dissolution performance of propranolol hydrochloride (HCl), a beta blocker drug, from tablets formulated with release-controlling polymers in dissolution media – with and without alcohol. Researchers specifically focused on assessing the extended-release behavior of HPMC and PEO polymers, and selected representative products for each polymer type:

- METHOCEL™ K100M DC2 (HPMC)
- POLYOX™ WSR 301 (PEO)

Researchers then formulated matrix tablets, with propranolol HCl as the model drug, using these release-controlling polymers to evaluate their dissolution performance and potential dose dumping risk.

The Method

Researchers prepared matrix tablet formulations, with propranolol HCl as the model drug. Within these formulations, they incorporated the release controlling polymers – either HPMC (METHOCEL™) or PEO (POLYOX™). Once formulated, the team evaluated the matrix tablets for their physical properties, assay, content uniformity and stability.

Additionally, researchers calculated the tablets' tensile strength (TS), or maximum resistance the tablet can endure. The tablets with a TS of 2 megapascals (MPa) were selected for dissolution testing. The testing was performed in an acidic (1.2 pH) and phosphate buffer (6.8 pH) media with and without alcohol (5% and 40% of ethanol) – using a USP Apparatus 2 at 100 revolutions per minute (rpm). Researchers also performed dissolution testing in a biorelevant system – first in 0.1N HCl, followed by a phosphate buffer with pH 6.8. The similarities between the propranolol's release profiles in different media were determined using a F2 similarity factor, while drug release behavior was compared using the Korsmeyer-Peppas model.

The Results

The HPMC tablets' drug release – in 0.05M of phosphate buffer (without ethanol) – was similar to the release profiles in phosphate buffer with 5% and 40% of ethanol. Between these tests, the F2 similarity factor was 80 and 71, respectively. For the PEO matrix tablets, the drug release in the phosphate buffer (without ethanol) was also similar to the results with 5% and 40% of ethanol – with an F2 value of 96 and 72.

In acidic media, the 5% and 40% alcohol levels did not have a significant effect on propranolol release from the HPMC-based tablet. The drug release at pH 1.2 was similar in alcoholic media, with 89 and 53 F2 similarity values.

As shown in Figures 1 and 2, researchers found no dose dumping effects in the bio-relevant dissolution systems media. There was slightly less swelling in the formulation, as alcohol content increased. Overall, as shown by the n-values of 0.662-0.776 from Korsmeyer-Peppas' equation, the tablets' drug release mechanism resulted from both diffusion and erosion.

Figure 1: Release profile of Propranolol HCl- HPMC Matrix in Biorelevant Media

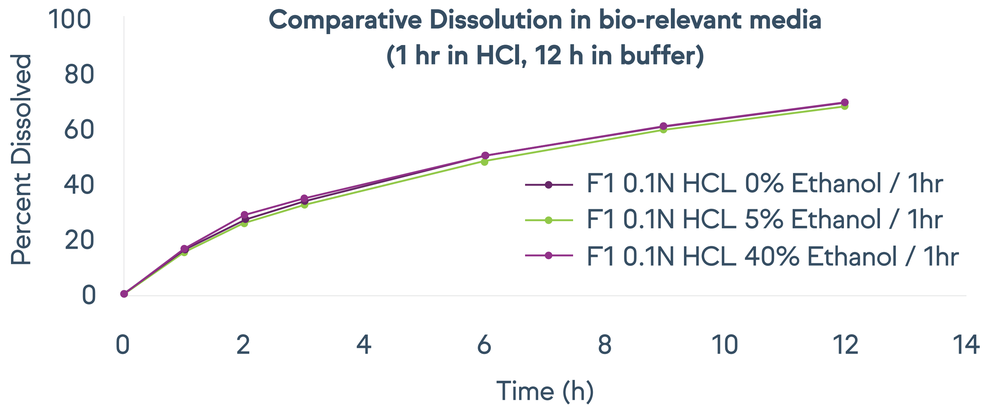
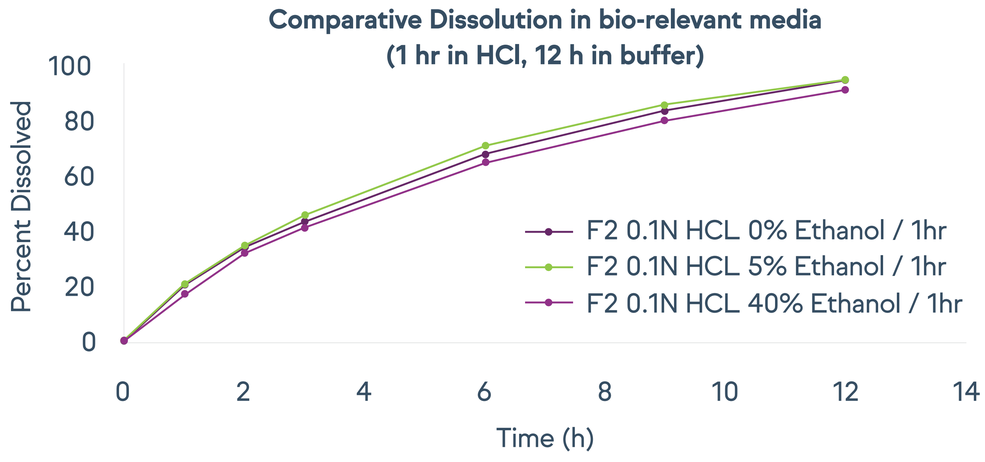


Figure 2: Release profile of Propranolol HCl- PEO Matrix in Biorelevant Media



The Conclusion

As a result of the study, researchers found that both matrix tablets – containing HPMC and PEO – were robust with sufficient TS, low friability and an optimal modified-release profile. No dose dumping was found in either the propranolol HCl matrix tablets in 5% or 40% of ethanol in acidic media (1.2 pH), phosphate buffer (6.8 pH) or bio-relevant media. With the industry's growing interest in ways to mitigate dose dumping, researchers concluded that both HPMC and PEO polymers can be used successfully in modified release tablet formulations – without the risk of alcoholic-induced dose dumping.

To learn more about IFF's broad portfolio of polymers, visit **www.iff.com/portfolio/markets/pharmaceutical**.

References:
1. Mahmoudi Z.N. et al. Influence of Polymer Chemistry in Drug Release of Propranolol HCl Controlled Release Tablets Manufactured via a Direct Compression Method. Contributed poster, AAPS Annual Meeting (USA) 2020.