In-Vitro Simulation of Adinazolam Mesylate Swellable HPMC Matrix Release Using DDDPlus Software

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ABSTRACT

Pharmaceutical systems containing a mixture of drug, excipients, and polymer can be used as effective controlled release formulations. The presence of drug and excipients in the polymer matrix creates a complex mechanism that undergoes swelling, diffusion and erosion. DDDPlus™, an *in vitro* dissolution simulation software program (Simulations Plus, Inc.) was used to simulate the release of Adinazolam Mesylate from an HPMC K4M matrix. Different concentrations of HPMC-Lactose (filler) ratios were used to characterize the swelling and release behavior. The HPMC grade K4M (MWt 95000) was used to characterize the polymer chain disentanglement concentration (Cp) which influenced the polymer erosion. The active drug concentration was held constant at 3% (w/w) and HPMC-Lactose ratio %(w/w) was varied as 80:17, 65:32, 50:47, 35:62 and 20:77. DDDPlus™ simulations for these formulations accurately matched the *in-vitro* data.

DISCUSSION

DDDPlus™ simulations accurately matched the *in-vitro* data. It was observed that the polymer content and its molecular weight highly influenced the swelling kinetics and release of Adinazolam Mesylate. The matrix with 80% HPMC showed the slowest drug release. A decrease in HPMC concentration increased the release rate of Adinazolam Mesylate and Lactose. This can be attributed to the lower presence of gel layer and faster reptation. In terms of absolute mass of HPMC released, the profiles were almost superimposed conforming to the experimental data. This can be explained in terms of Cp, which is dependent on the polymer molecular weight. It was noted an increase in the agitation rate increased the release of polymer which increased the drug release rate. This can be attributed to the faster reptation and erosion of the polymer.

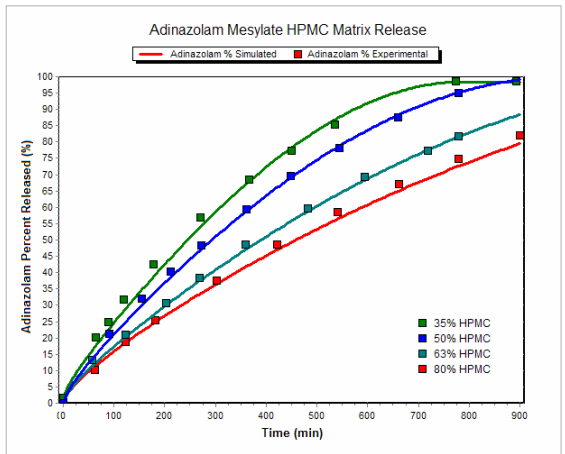
CONCLUSION

The *in-vitro* release simulation of a polymer matrix with varying formulation parameters can be accurately predicted and is highly influenced by the concentration of the polymer present.

REFERENCE

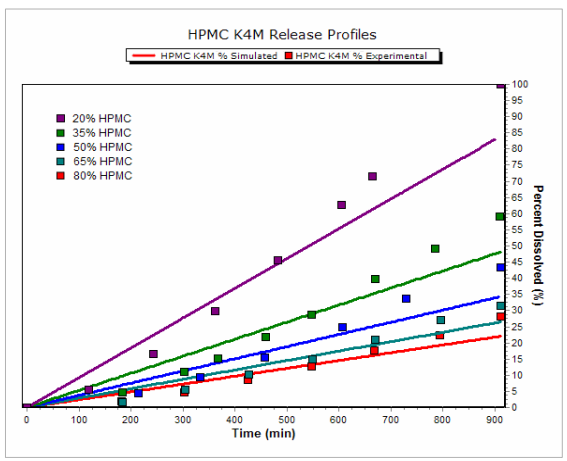
1. Ping Gao, John W.S, Phillip R.N, T. Robert Ju. *Swelling of Hydroxypropyl Methylcellulose Matrix Tablets. 2. Mechanistic Study of the Influence of Formulation Variables on Matrix Performance and Drug Release.* J. Pharm. Sci. 1996; 85: 732
2. Reynolds T.D, Gehrke S.H, Hussain A.S, Shenouda L.S. *Polymer Erosion and Drug Release Characterization of Hydroxypropyl Methylcellulose Matrices.* J. Pharm. Sci. 1998; 87(9): 1115.

ADINAZOLAM RELEASE



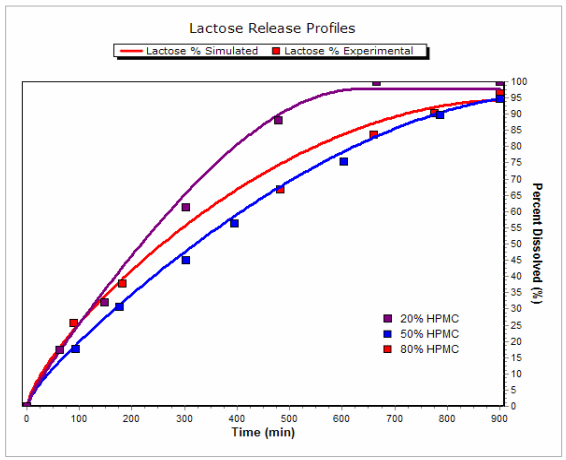
Simulations for Adinazolam Mesylate Release for Different Concentration Ratios of HPMC – Lactose %(w/w). Shows Adinazolam Release Was Faster in Matrix Containing Lower Amount of HPMC.

HPMC K4M RELEASE



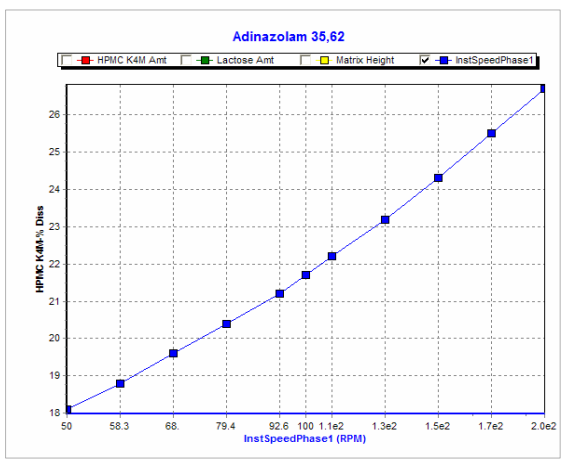
Simulations for HPMC K4M Percent Released for Different Concentrations of HPMC at 200 RPM Stirring Rate. Shows Low Concentration of HPMC Released Faster Because of Lesser Amount of Gel Layer and Faster Reptation.

LACTOSE RELEASE



Simulations for Lactose Release for Different Concentration Ratios of HPMC – Lactose %(w/w). Shows Lactose Released Faster in Matrix Containing Lower Amount of HPMC Subsequently Increasing the Release Rate of Adinazolam.

EFFECT OF STIRRING RATE ON POLYMER



Plot Shows the Sensitivity Analysis for HPMC K4M Release for Varying Paddle Agitation. An Increase in Paddle Speed Causes Faster Reptation and Erosion.