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Impact of Critical Material Attributes of HPMC on the Release of Gliclazide from Hydrophilic Matrix Tablets

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SUMMARY

The influence of HPMC viscosity and the degree of substitution hydroxypropyl level (DSHP) on the release rate of gliclazide was examined. The increase in the HPMC viscosity led to a significant decrease in the release rate. The second parameter, DSHP, showed a surprisingly high impact on the release rate with higher hydroxypropyl levels leading to a faster drug release. The results demonstrated the need for control on both parameters for formulators of gliclazide tablets in order to ensure a consistent drug release performance.

INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose, HPMC) remains one of the most important and commonly used water-soluble polymers in hydrophilic matrix tablets. Detailed understanding of the release mechanism is still a topic of scientific research (Mašková et al., 2020). This study aimed to determine differences in drug release of a poorly soluble drug, gliclazide when changing two critical material attributes (CMA) of HPMC, namely the substitution level of hydroxypropyl substituents (DSHP) and the molecular chain length, characterized by the viscosity of the polymer.

MATERIALS AND METHODS

HPMC 2208 was manufactured with 3 different levels (high, medium, and low) of hydroxypropyl substitution for viscosities of approximately 4,000 and 100 mPa·s (K4M and K100LV, respectively). The gliclazide hydrophilic matrix tablets were prepared (30 mg gliclazide/tablet) with 30% HPMC of 15 different K4M and K100LV combinations: 3 with neat K4M, 3 with neat K100LV (high, medium, low DSHP for both viscosity grades), and 9 blends of the 6 different HPMC in a 1:1 ratio. The formulation used is shown in Table 1.

Table 1. Formulation of hydrophilic matrix tablets.

Ingredient	wt.-%	mg/tablet
Gliclazide	15	30
HPMC	30	60
Lactose	27	54
MCC (PH-102)	27	54
Aerosil	0.5	1
Na Stearyl Fumarate	0.5	1
Total	100	200

The viscosity of the different HPMC grades and their blends were measured by the Brookfield method in a 2% solution. The direct tablet compression was done in a lab scale 8 station rotary press (Kilian Pressima). The dissolution testing was conducted by hanging baskets using a Type 2 USP method rotating at 100 rpm, in replicates of six tablets in 900 mL of pH 7.4 phosphate buffer, equilibrated to 37±0.5 °C. The gliclazide release was quantified through an in-line ultraviolet (UV) spectrophotometer.

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RESULTS AND DISCUSSION

Altering the HPMC substitution level showed marked differences in drug release from HPMC compacts for both HPMC viscosity grades (Figure 1). From low to mid to high substitution, the polymer becomes more hydrophilic and therefore dissolves more rapidly resulting in a higher drug release rate. Overall the higher viscosity grade (K4M) forms a stronger gel and lower erosion rate leading to a lower release rate.

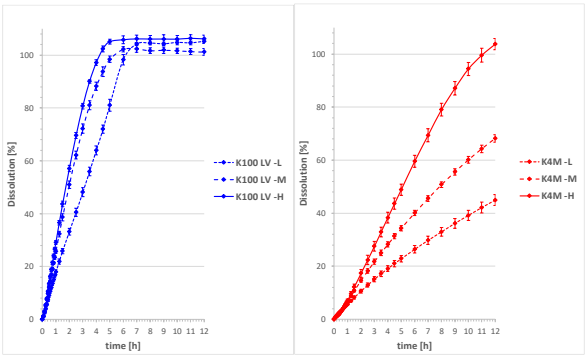

***Figure 1**. Drug release of matrix tablets with K100LV (left) and K4M (right) with different HP levels (L-low, M-medium, H-high).*

The influence of the HPMC viscosity of the neat HPMC or HPMC blends used for tabletting on the release rate is shown in Figure 2 where the drug release after 4 hours is depicted.

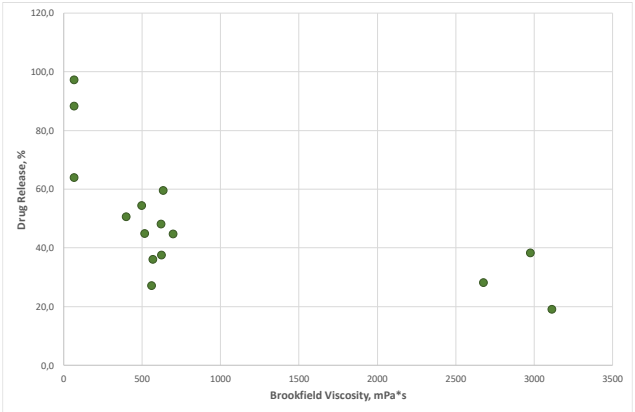

***Figure 2.** Drug release after 4 hours versus Brookfield viscosity of used HPMC (neat polymers and blends)*

An increase of viscosity from formulations with neat K100LV (~100 mPa*s) polymers to the K100LV/K4M blends (~500 mPa*s) resulted in a strong decrease in the release rate. Further increasing the viscosity to ~3,000 mPa*s using the neat K4M polymers leads to a less significant further decrease of the release rate.

A linear correlation between the gliclazide release rate and the hydroxypropyl level can be seen in Figure 3 where the drug release after 1, 2, 4, and 8 hours is shown. Here, only the formulations of the K100LV/K4M blends were used in order to reduce the influence of the polymer viscosity. In particular the broad variation of the release rate e.g. after 4 hours from ~30% to ~60% is surprisingly high.

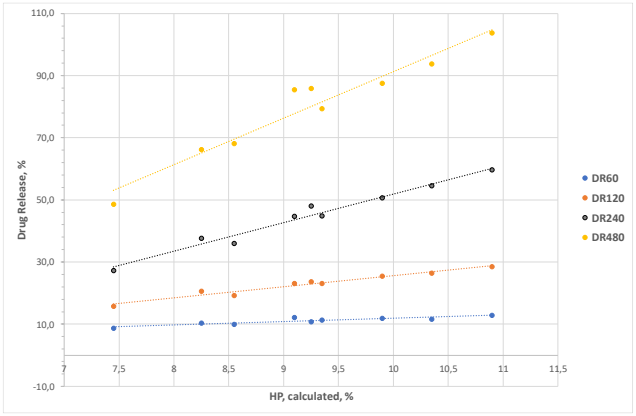

***Figure 3**. Drug release after 1, 2, 4, and 8 hours (DR60, 120, 240, 480) of the K100LV/K4M blend formulations versus hydroxypropyl level (DSHP).*

CONCLUSIONS

The influence of HPMC viscosity and the hydroxypropyl level (DSHP) on the release rate of a poorly soluble API, gliclazide, was examined. The rate can be controlled by both critical material attributes. In particular, the increase of the HPMC viscosity from ~100 mPa*s to ~500 mPa*s led to a significant decrease in the release rate. The second parameter, DSHP, showed a surprisingly high impact on the release rate with higher hydroxypropyl levels leading to a faster drug release. The results demonstrate the needs for formulators of gliclazide tablets to control carefully both parameters, HPMC viscosity and hydroxypropyl levels, in order to ensure a consistent drug release performance.

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