Mesoporous silica: a solution for amorphous stabilization of poor glass formers

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Introduction

Amorphous formulation technologies to improve oral absorption of poorly soluble active pharmaceutical ingredients (APIs) have become increasingly prevalent[1]. Currently, polymer-based amorphous formulations manufactured by spray drying, hot melt extrusion (HME), or coprecipitation are most common[1]. However, these technologies have challenges in terms of the successful stabilization of poor glass former compounds in the amorphous form[2,3]. An alternative approach is mesoporous silica, which stabilizes APIs in non-crystalline form via molecular adsorption inside nano-scale pores[1].

Aims and Hypothesis

The aim of this work was to first develop amorphous formulations for two poorly soluble poor glass formers using mesoporous silica and hot melt extrusion as model technologies. After successful formulation development, the formulations were assessed from a stabilization perspective, considering both solid state and dissolution performance. It was hypothesized that mesoporous silica would show enhanced amorphous stability for poorly soluble poor glass formers compared to hot melt extrusion.

Methods

Two poor glass formers: Haloperidol and Carbamazepine were formulated in the amorphous form with both HME and Parteck® SLC mesoporous silica. PVA was selected as an optimal polymer for hot-melt extrusion. This was based on three factors: (1) the grade of PVA was specifically designed for optimal HME due to particle size distribution and viscosity, (2) consideration of partial solubility parameters for both drugs and PVA (3) low hygroscopicity of PVA to reduce water uptake in of the extrudates. Mesoporous silica formulations were prepared using the incipient wetness method. An iterative formulation development process was carried out to find the highest % loading that was successful in both formulation technologies for each API. These finalized formulations were then analyzed with non-sink FaSSIF dissolution, SEM, and XRPD. Samples were then stored under ICH Q1 accelerated stability conditions of 40 °C and 75% RH for three months. Samples were periodically taken and analyzed with non-sink FaSSIF dissolution and XRPD.

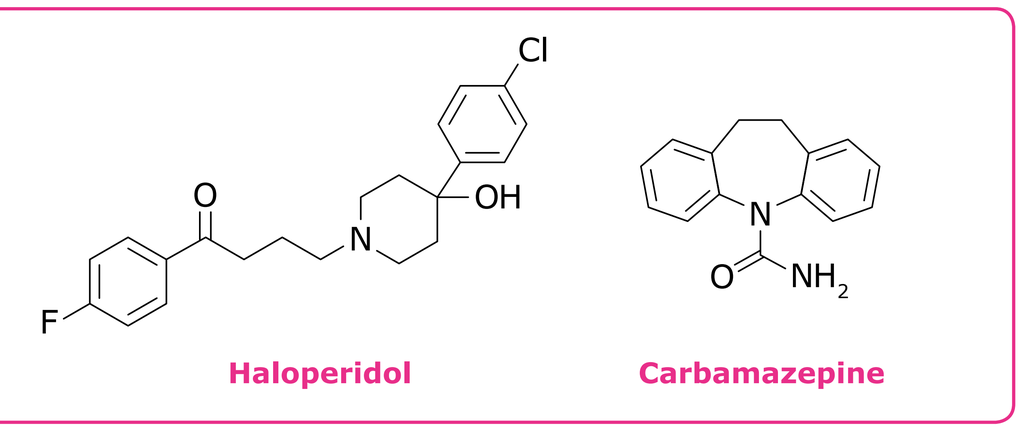

Figure 1: Haloiperidol and Carbamazepine were selected as model poorly soluble poor glass formers.

Results

Formulation Development

Mesoporous silica was successful in stabilizing both APIs in the amorphous form at all drug loadings. HME, on the other hand, was only able to stabilize 20% and 7.5% of carbamazepine and haloperidol, respectively. The stability study was then performed using a 20% and 7.5% API content for carbamazepine and haloperidol, respectively.

Phase Separation

Qualitative macroscopic and microscopic differences were observed between the fresh and one-week stressed samples of the hot-melt extrudates (Figure 2). Extrudates of carbamazepine and haloperidol were transparent immediately after manufacturing. This indicates the presence of molecularly dispersed API throughout the polymer in the amorphous form[1]. However, after only 7 days exposure to 40 and 75% RH, both extrudates became opaque, indicating phase separation in the formulations[1]. This was also confirmed with scanning electron microscopy. This was in contrast to mesoporous silica formulations, in which no macroscopic or microscopic changes were observed between the fresh and one-week stressed samples.

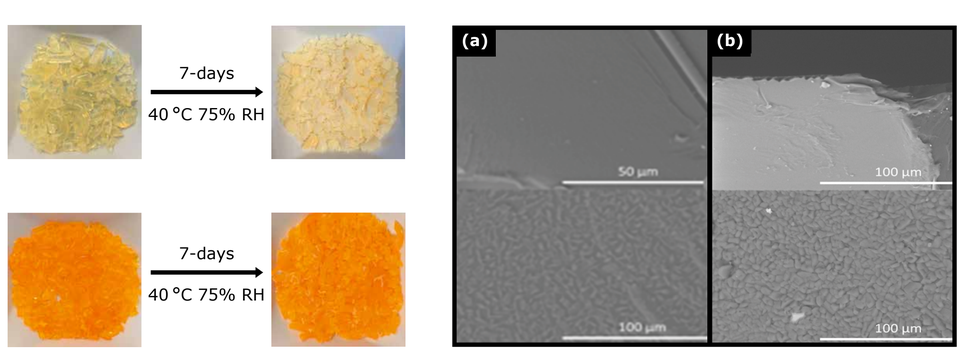

Figure 2: Left: macroscopic changes in HME appearance for haloperidol (top) and carbamazepine (right) was observed after one week under accelerated conditions. Right: phase separation was confirmed microscopically for both haloperidol carbamazepine (a) and haloperidol (b).

Solid State

Carbamazepine and haloperidol loaded silica remained amorphous for the duration of the study. For HME, however, crystallinity was observed after just one week in the stability study (Figure 3), indicating instability of the amorphous API in the formulations. This crystallinity increased in intensity over the duration of the stability study.

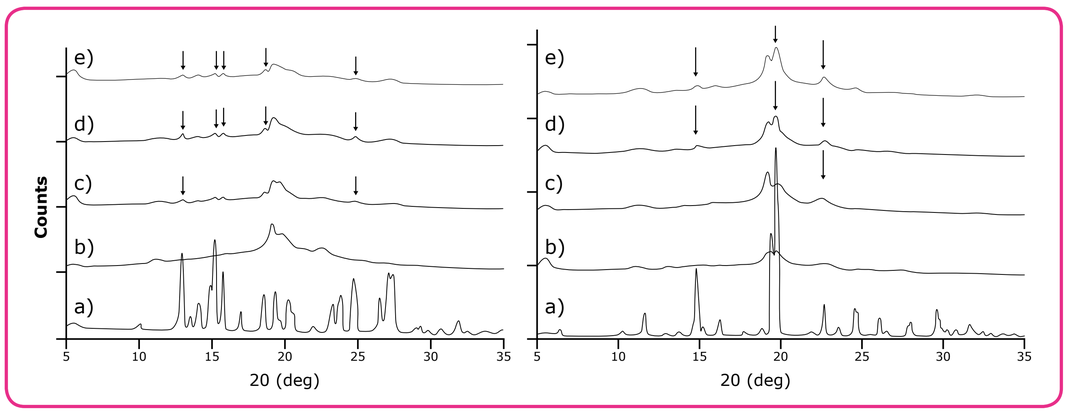

Figure 3: HME formulations for carbamazepine (left) and haloperidol (right) show inconsistent and decreasing dissolution performance for the duration of the stability study.

Dissolution Performance

In line with the phase separation and solid state data, mesoporous silica formulations demonstrated a consistent and unchanged dissolution performance for the duration of the study (Figure 4).

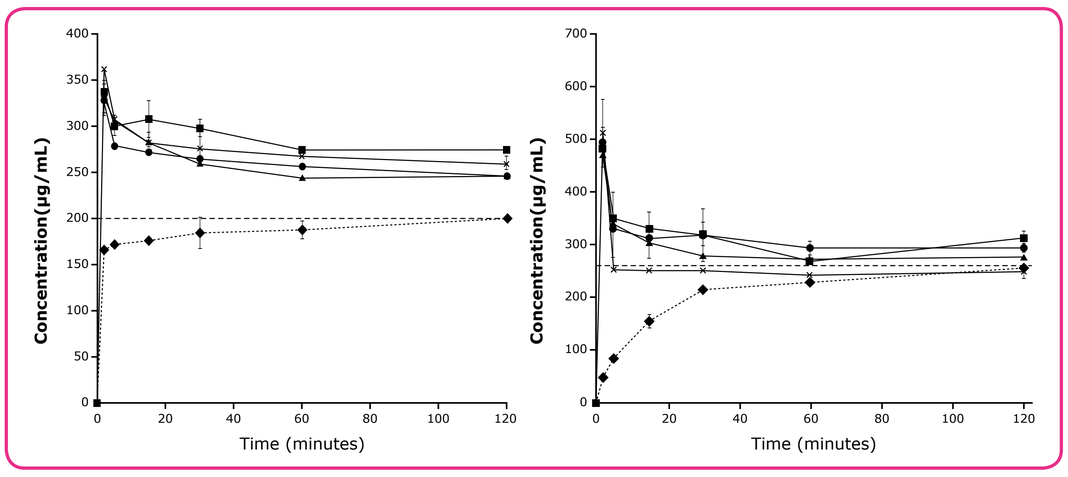

Figure 4: Mesoporous silica formulations for carbamazepine (left) and haloperidol (right) show consistent dissolution performance for the duration of the stability study.

For the HME formulations, dissolution was inconsistent and decreased throughout the study, due to re-crystallization in the extrudates (Figure 5). At the end of the study, dissolution in both HME formulations returned to that of the unmodified, crystalline API.

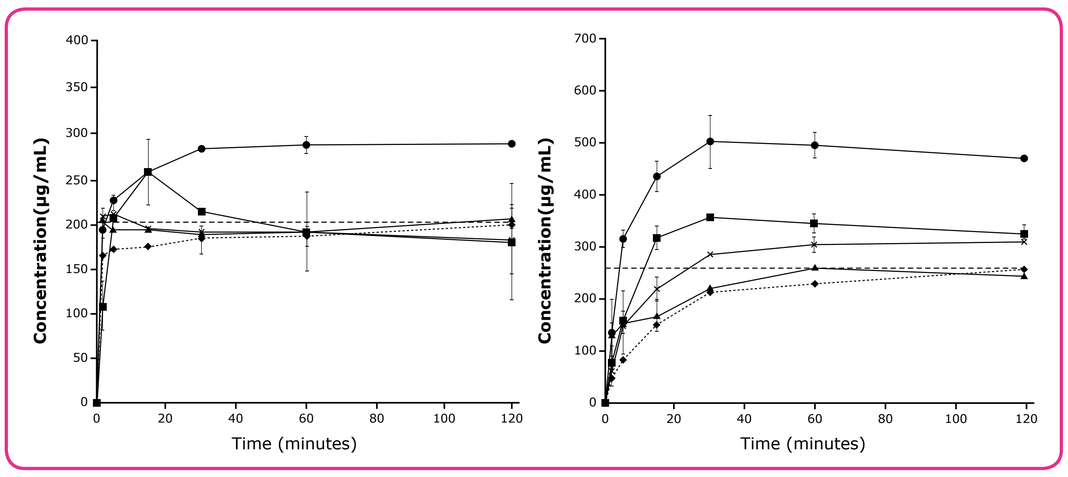

Figure 5: Mesoporous silica formulations for carbamazepine (left) and haloperidol (right) show consistent dissolution performance for the duration of the stability study.

Conclusions

Although polymeric-based amorphous solid dispersions are most prevalent, they may not be suitable for poorly soluble compounds that are also poor glass formers. These compounds, which demonstrate both poor solubility and poor amorphous stability, are challenging for formulation with typical polymer-based technologies due to possible phase separation and recrystallization. Ultimately, these compounds may have an increased risk of failure during pharmaceutical development, as they constitute a risk from both a bioavailability and amorphous stability perspective. In this study, we demonstrated that poor glass forming APIs have increased risk of recrystallization in polymer-based amorphous solid dispersions. By contrast, mesoporous silica was shown to provide optimal stabilization for such APIs. Therefore, mesoporous silica could be an attractive formulation technology to expand the formulation toolbox for APIs that are poor glass formers.

References

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