THE EFFECT OF SOLID STATE CHANGES AND PHYSICAL INTERACTIONS WITH EXCIPIENTS ON THE DISSOLUTION BEHAVIOUR OF CARBAMAZEPINE TABLETS

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Introduction

In vitro dissolution tests have been accepted as indispensable quality-control procedures for drugs with low aqueous solubility and whose absorption is dissolution rate limited (class II drugs with respect to Biopharmaceutics Classification System, BCS), since they may provide important information about the *in vivo* absorption of pharmaceuticals[1,2].

Carbamazepine (CBZ), a widely used antiepileptic drug, is one example requiring *in vitro* dissolution testing of tablets to ensure good bioavailability, because CBZ is practically water insoluble, and absorption is dissolution rate limited[3]. However, little information is available about how a possible solid state conversion or crystal habit (morphology) change may affect the dissolution profile of CBZ. It is therefore important to gain a better understanding of solid state transformation phenomena of CBZ during dissolution. For this reason the following objectives were set for the present study:

- To investigate the influence of the existing CBZ form and any solid state conversions on the dissolution behavior of compressed CBZ;
- To study the influence of excipients dissolved in the aqueous phase on the polymorphic changes of CBZ (and thus its dissolution) using different types of excipients with potential to interact with CBZ;
- To observe the morphological changes of compressed CBZ during dissolution using SEM as a direct visualization method.

Materials and Methods

Materials

CBZ form III and DH powder, CBZ form III and DH compacts (400 mg), hydroxypropyl methylcellulose (HPMC) (Mw 26,000 Da), and polyethylene glycol (PEG) (Mw 6,000 Da).

Methods

All dissolution tests were performed using USP apparatus 2 (paddle method) at 50 rpm and 37°C. A six-station dissolution apparatus (D800 dissolution tester, Logan Instrument Corp.) with 200 ml dissolution media (distilled water and each excipient solution (0.1 %)) was used.
The intact, dry CBZ and DH compacts and also compacts recovered at each predetermined time point were measured by scanning electron microscopy (SEM) and x-ray powder diffraction (XRPD). Furthermore, the contact angles between DH compacts and each dissolution medium were also determined.

Results and Discussion

Compacts prepared from CBZ form III

The dissolution profiles of CBZ form III compacts in various dissolution media are shown in Figure 1.

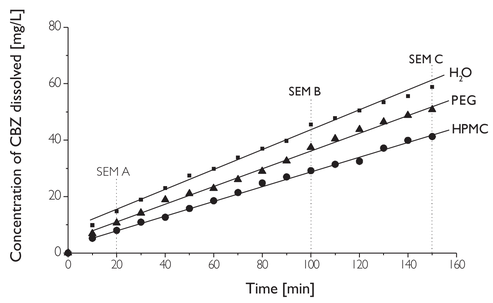

Figure 1. Dissolution profiles of CBZ form III compacts in three different dissolution media: water (■); PEG solution (▲); HPMC solution (●). The dashed lines (SEM A-C) indicate the time points for SEM images shown in Figure 2.

The dissolution profiles were well fitted by a linear function at times between 10 and 150 min. The correlation coefficients (R^2) for all the fitted lines were 0.992, and all the profiles were significantly different at every time point ($P < 0.01$). The dissolution rate of CBZ in water (0.338 mg L^{-1} min^{-1}) was the highest of all the dissolution media used, and also showed the highest dissolution in the initial 10 min. The formation of DH needles can be seen from the SEM micrographs (Figure 2A) and was confirmed by XRPD.

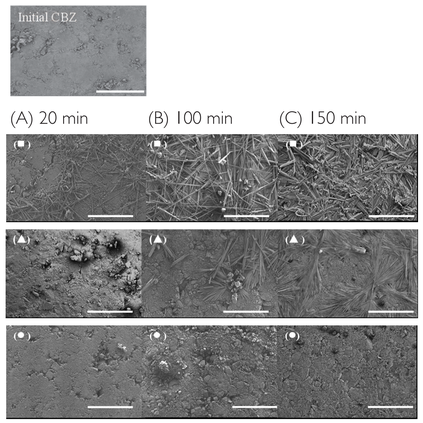

Figure 2. SEM micrographs of initial CBZ compacts and the compacts recovered after dissolution in each medium for 20 (A), 100 (B) and 150 min (C): water (■); PEG solution (▲); and HPMC solution (●). (All photos were taken using the same magnification, bars: 500 μ m).

The SEM images showed an increasing amount of DH over time (Figure 2 ■ A - C), which implies that the dissolved CBZ does not quantitatively stay in solution because (at least partially) it is supplied to continue the DH growth.

The dissolution rate of the CBZ compacts in PEG solution was slightly slower (0.314 mg L^{-1} min^{-1}) than that in water in the first 150 min (Figure 1). The morphology studies of the CBZ compacts in PEG solution showed a clear difference in the DH growing behaviour from those in water. This different morphology and the lower amount of DH needles, both contributed to a lesser increase in the surface area of the compact in PEG solution than that in water, and thus lead to a slower CBZ dissolution rate in the PEG solution than in water.

There was no DH formation during the whole dissolution process in HPMC solution as shown by SEM (Figure 2●), and confirmed by XRPD (Figure 3).

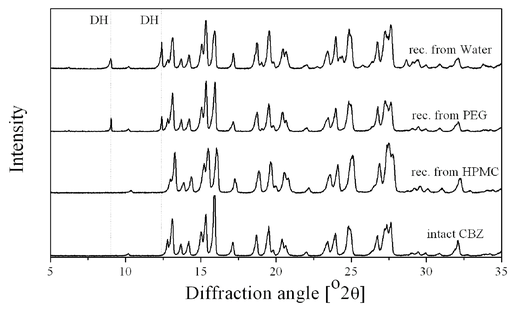

Figure 3. XRPD diffractograms for the intact CBZ compacts and CBZ compacts recovered (rec.) from the three dissolution media after 100 min dissolution. (Dashed lines indicate characteristic peaks of DH).

The dissolution rate of CBZ in water is likely to have been enhanced by the increased surface area from the growth of DH needles, as shown in the previous examples. This however, could not happen in the HPMC solution since there was no DH formation. Also, the strong hydrogen bonding between CBZ and HPMC may have induced a high surface absorption of the HPMC onto the CBZ particles, thus impeding the water contact with CBZ. Both or either of these factors would result in a slower dissolution rate (0.257 mg L^{-1} min^{-1}) in HPMC solution than in both water and PEG solutions.

Compacts prepared from CBZ dihydrate (DH)

The dissolution profiles for the DH compacts in the first 150 min are shown in Figure 4A, and the profiles plotted on a longer time scale (260 min) are shown in Figure 4B.

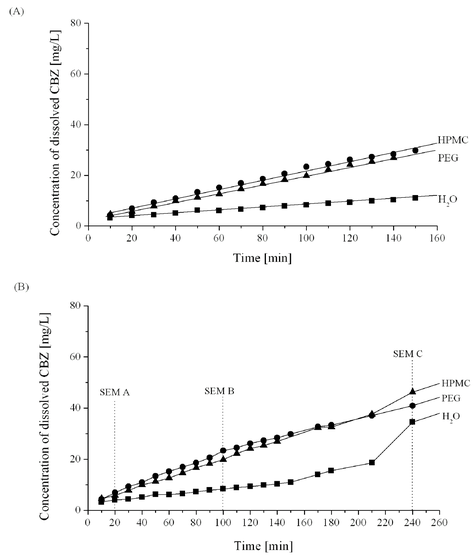

Figure 4. Dissolution profiles of DH compacts in three dissolution media: water (■); PEG solution (▲); HPMC solution (●). The dashed lines (SEM A-C) indicate the time points for SEM images shown in Figure 4B.

The dissolution profiles in Figure 4A were well fitted by a linear function from 10 – 150 min. The correlation coefficients (R^2) for all the fitted lines were ≥ 0.990. The profile obtained from water was significantly different from those of excipient solutions at all the time points ($P < 0.01$). The dissolution profiles in the two excipient solutions were however, not significantly different at any time point including the intercept ($P > 0.05$).

There was no change in solid state (as detected by XRPD shown in Figure 6) in the dissolution of DH compacts.

Without an obvious surface area influence on the initial dissolution profile, the observed dissolution rate of DH compacts in water (0.055 mg L^{-1} min^{-1}) was much lower compared to that from CBZ compacts in the first 150 min (Figure 4A).

The contact angles of DH compacts with the HPMC and PEG solutions (43.1° and 44.8° respectively) were significantly smaller than that of water (61.0°) ($P < 0.01$) confirming that wetting could have played a role in the improved dissolution of DH compacts in the polymer solutions.

References

1. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP 1989. Pharm Res 6(7):612-618.
2. Jamzad S, Fassihi R 2006. AAPS PharmSciTech 7(2):Article 33.
3. Richter K, Terhaag B 1978. Int J Clin Pharmacol and Biopharm 16(8):377-379.

Further reading:
1. Tian F, Zeitler JA, Strachan C J, Saville DJ, Gordon C K, Rades T 2006. J Pharm Biomed Anal 40: 271-280.
2. Tian F, Sandler N, Aaltonen J, Lang C, Saville D J, Gordon KC, Strachan CJ, Rantanen J, Rades T 2006. J Pharm Sci, In press.
3. Tian F, Sandler N, Gordon KC, McGoverin CM, Reay A, Strachan CJ, Saville DJ, Rades T 2006. Eur J Pharm Biopharm In press.
4. Tian F, Saville DJ, Gordon KC, Strachan C J, Zeitler J A, Sandler N, Rades T 2006. J Pharm Pharmacol In press.

The dissolution for the DH compacts dissolved in water showed an abrupt increase between 210 and 240 min (Figure 4B). From the SEM observations, it can be seen that the morphology of the surface of all DH compacts continuously changed during dissolution (Figure 5 ■).

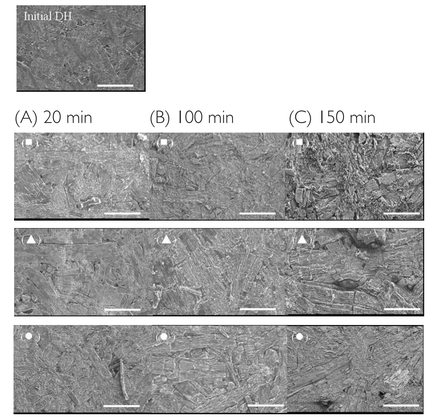

Figure 5. SEM micrographs of initial DH compacts and the compacts recovered after dissolution for 20 (A), 100 (B) and 240 min (C): water (■); PEG solution (▲); and HPMC solution (●). (All photos were taken using the same magnification, bars: 200 μ m).

The initial DH compact had a relatively smooth and densely packed surface (Figure 5). At 260 min, morphology changes of the surfaces of the compacts became very obvious especially for those dissolving in water (Figure 5 ■ C). This suggests that the dissolution of DH crystals from the compact surface may result in a morphology change to a very porous structure of the compact, providing an increased surface area for dissolution with an increase in dissolution rate (as seen in Figure 4B). XRPD confirmed that the porous surface structure shown in Figure 5 ■ C was still DH (Figure 6).

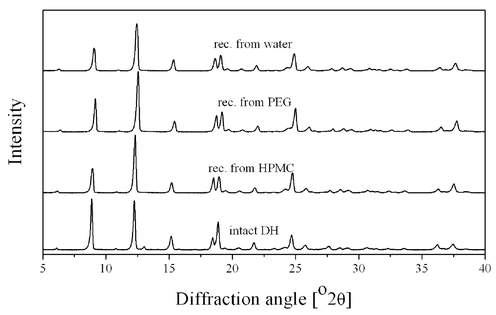

Figure 6. XRPD diffractograms for the intact DH compacts and DH compacts recovered (rec.) from three different dissolution media after 240 min dissolution.

Conclusions

This study has investigated the dissolution of CBZ and DH compacts in water and two excipient solutions: PEG and HPMC solutions (0.1% w/v) using SEM as an important complementary tool to observe morphology changes during the entire dissolution process.

SEM proved to be invaluable for interpretation of the results. Although the dissolution of these compacts in various dissolution media are all complex processes with many contributing factors (type of crystalline form (CBZ or DH), crystal morphology, surface area, and excipient interactions with drug particles), the influence and relative importance of these factors on the resulting dissolution profiles of CBZ and also DH compacts were clarified.

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