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MX-1 Matrix Tablets Show Potential for Zero Order Release While Maintaining Structural Integrity

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Abstract

Purpose: This study was designed to compare the disintegration and drug release behaviour of matrix tablets prepared with a) a new pre-gelatinised starch excipient (MX-1) and b) a conventional matrix-forming excipient, hydroxypropyl methylcellulose (HPMC) using dissolution and scintigraphic methods. The effect of drug solubility on matrix integrity was also investigated by incorporating paracetamol (partially soluble) and ranitidine hydrochloride (highly soluble) separately into each tablet.

Methods: In addition to drug (20% w/w) and matrix-former component (40% w/w), the tablets also contained lactose monohydrate, microcrystalline cellulose and talc. Approximately 6 mg of charcoal, either radiolabelled with ^{99m}Tc-DTPA or 'cold', were added to 500 mg of the mixed powders prior to compression at 1 US short ton to form flat-faced tablets (10.6 mm diameter; approximately 4.5 mm thickness). The tablets underwent USP type I dissolution testing (900 mL, pH 6.8 phosphate buffer, 100 rpm, 37±0.5 °C, n=3). For non-radiolabelled tablets, drug release was quantified using UV-spectrophotometry (257 nm for paracetamol, 314 nm for ranitidine hydrochloride). *In vitro* behaviour of radiolabelled tablets were monitored scintigraphically. The number of radioactive counts within each tablet was quantified using region-of-interest (ROI) analysis for each image.

Results: Paracetamol release was slightly faster from HPMC tablets with mean 50% and 90% drug release ($t_{50\%}$ and $t_{90\%}$) achieved by 4.2 h and 10.2 h, respectively. MX-1 tablets with paracetamol had a mean $t_{50\%}$ value of 5.1 h; $t_{90\%}$ was not achieved within 12 h. Release of ranitidine hydrochloride was quicker than that of paracetamol; mean $t_{50\%}$ values for MX-1 and HPMC tablets were 3.0 h and 2.7 h respectively while the corresponding mean $t_{90\%}$ values were 9.5 and 7.0 h. ROI analysis showed that MX-1 tablets remained generally intact while drug release progressed for both paracetamol and ranitidine variants. Drug release from HPMC tablets was accompanied by gradual tablet erosion. Figures 1 and 2 show the radiolabel release profiles for paracetamol and ranitidine tablets respectively.

Conclusion: The results of this study imply that MX-1 tablets have the potential to maintain structural integrity while displaying a near zero order drug release profile, independent of drug solubility.

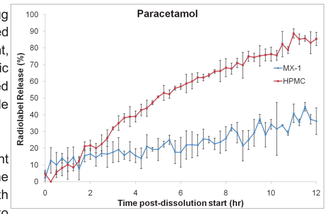

Figure 1: Radiolabel release profiles for paracetamol tablets

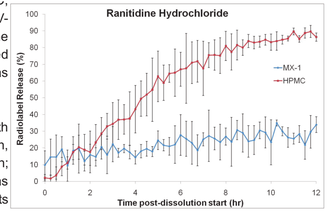

Figure 2: Radiolabel release profiles for ranitidine tablets

PURPOSE

A new pre-gelatinised starch excipient (Swelstar MX-1) has shown potential as a matrix-former which maintains tablet integrity throughout the drug release process. An *in vitro* study was designed to compare the disintegration and drug release behaviour of matrix tablets prepared with a) MX-1 and b) a conventional matrix-forming excipient, hydroxypropyl methylcellulose (HPMC) using dissolution and scintigraphic methods. The effect of drug solubility on matrix integrity was also investigated by incorporating paracetamol (partially soluble) and ranitidine hydrochloride (highly soluble) separately into each tablet.

EXPERIMENTAL METHODS

Four types of tablet were prepared by direct compression:

P1 40%(w/w) MX-1 and 20%(w/w) paracetamol
P2 40%(w/w) HPMC and 20%(w/w) paracetamol
R1 40%(w/w) MX-1 and 20%(w/w) ranitidine HCl
R2 40%(w/w) HPMC and 20%(w/w) ranitidine HCl

All tablets also contained lactose monohydrate, microcrystalline cellulose and talc . Approximately 6 mg of charcoal, either radiolabelled with ^{99m}Tc-DTPA or 'cold', was added to 500 mg of the mixed powders prior to compression at 1 US short ton to form flat faced tablets. **'Cold' *in vitro* dissolution** was performed according to USP I (900 mL, pH 6.8 phosphate buffer, 100 rpm, 37±0.5 °C, n=3). Drug release was quantified using UV-spectrophotometry (257 nm for paracetamol, 314 nm for ranitidine HCl).

Radiolabelled *in vitro* dissolution was performed using a Siemens e-Cam gamma camera fitted with a low energy, high resolution collimator. Images were acquired every 15 min during a 12 hour dissolution period. The number of radioactive counts within each tablet was quantified using region-of-interest (ROI) analysis of each image.

RESULTS AND DISCUSSION

'Cold' *in vitro* dissolution
It was noted that both ranitidine hydrochloride and paracetamol were released more rapidly from HPMC tablets in comparison with MX-1 tablets. MX-1 tablets with paracetamol had a mean $t_{50\%}$ value of 5.1 h; $t_{90\%}$ was not achieved within 12 h. Release of ranitidine hydrochloride was quicker than that of paracetamol; mean $t_{50\%}$ values for MX-1 and HPMC tablets were 3.0 h and 2.7 h respectively while the corresponding mean $t_{90\%}$ values were 9.5 and 7.0 h.

Drug release from HPMC tablets was accompanied by gradual tablet erosion, whilst MX-1 tablets remained relatively intact. This may be a consequence of the tablet integrity remaining relatively stable for the MX-1 tablets in comparison to the gradual erosion of the HPMC tablets .

Radiolabelled *in vitro* dissolution
ROI analysis also showed that MX-1 tablets remained generally intact while drug release progressed for both paracetamol and ranitidine variants (Figure 3). Figures 4 and 5 show drug and radiolabel release for MX-1 and HPMC tablets.

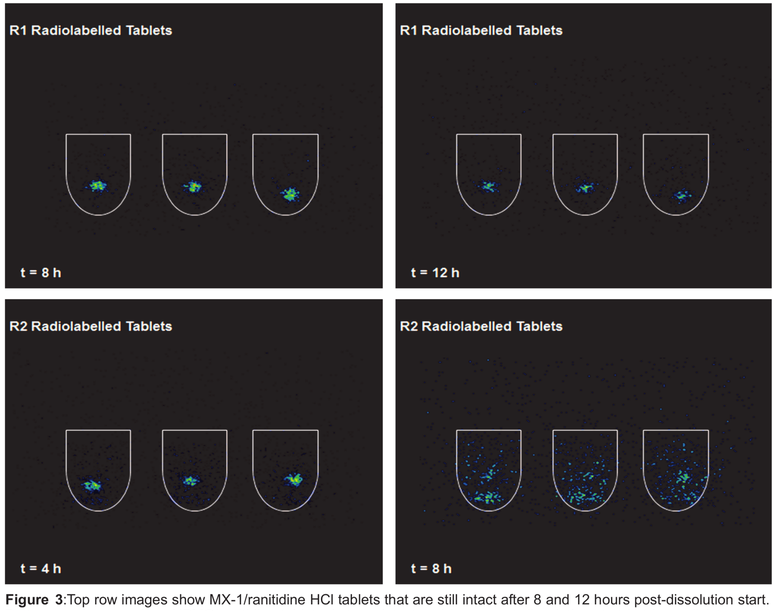

Figure 3:Top row images show MX-1/ranitidine HCl tablets that are still intact after 8 and 12 hours post-dissolution start. Bottom row images show HPMC/ranitidine tablets that are intact at 4 hours post-dissolution start but have disintegrated at 8 hours post-dissolution start.

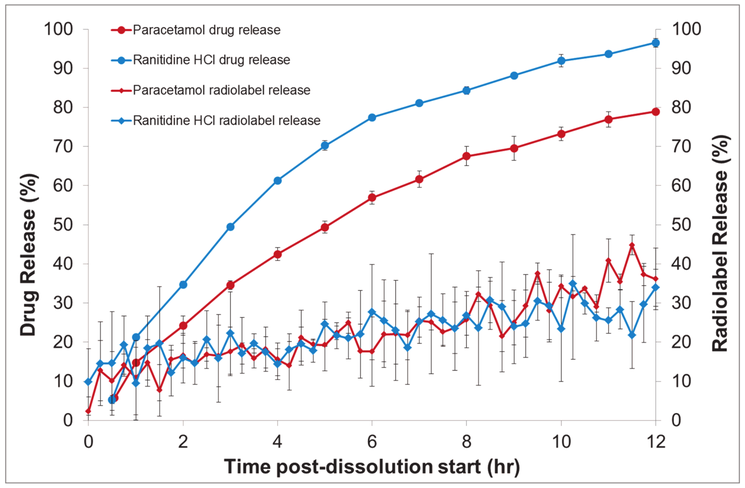

Figure 4: Drug and radiolabel release profiles of MX-1 tablets containing paracetamol or ranitidine HCl

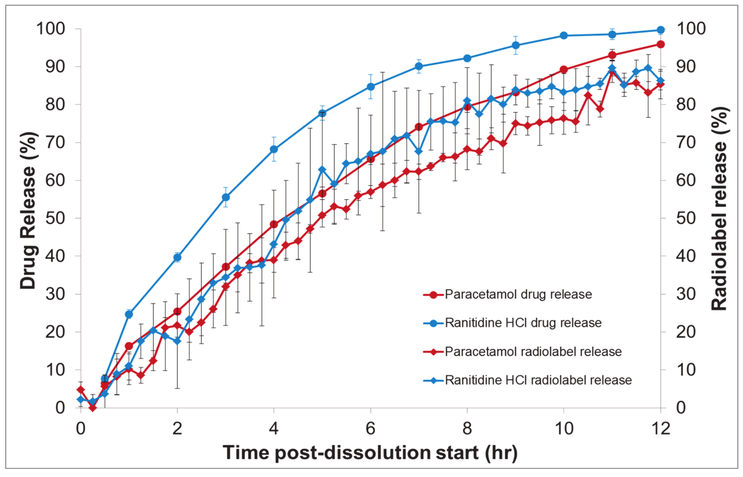

Figure 5: Drug and radiolabel release profiles of HPMC tablets containing paracetamol or ranitidine HCl

CONCLUSION

The results of this study imply that MX-1 tablets have the potential to maintain structural integrity while displaying a near zero order drug release profile, independent of drug solubility.