Development of a sustained-release tablet formulation of novel antihypertensive drug MT-1207

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Introduction

- Hypertension is the most common cardiovascular disease. Many drugs are used to treat hypertension through different mechanisms of action. Combination therapy is necessary for hypertension treatment, and this leads to polypharmacy.
- MT-1207 exhibits highly inhibitory activities simultaneously towards adrenergic a_{1A}, a_{1B} and serotonin 5-HT_{2A} receptors. It can reduce the blood pressure without accelerating the heart rate while improving the auditory brainstem response (ABR) and kidney protection functions. It is considered promising and efficacious in the treatment of hypertension.
- In this poster, the preparation, *in vitro* and *in vivo* assessment of a once-a-day MT-1207 tablet formulation are presented.

Methodology

- The sustained-release tablets were prepared using HPMC K4M and HPMC K15M as release retardants in the different formulations. The tablets were assessed in terms of their hardness, friability and uniformity of weight.
- DSC, FTIR and XRPD analyses were carried out in the tablets to determine any interactions between MT-1207 and the excipients, as well as the polymorphic form of MT-1207. *In vitro* release studies were carried out in 0.1 M phosphate pH 6.8 with 0.2% w/v SDS to acquire the release profile of MT-1207 from the different formulations. The formulation that gave a 24-hour release profile of MT-1207 was forwarded to *in vitro* swelling and erosion studies and pharmacokinetic studies in Beagle dogs.

Results

- DSC, FTIR and XRPD analyses showed that MT-1207 was in the form of the anhydrous crystal in the tablets and that there were no significant physicochemical interactions between the API and the excipients (Figures 1-3).
- HPMC K4M was not able to provide a sustained release of MT-1207 (F1). Therefore, it was substituted with HPMC K15M. F4 (31% w/w HPMC K15M) gave a constant-rate 20-hour release of the drug with more than 90% of the total dose released over 24 hours (Figure 4). The kinetic analysis of drug release, along with the swelling and erosion studies (Figure 5), showed zero-order kinetics and a predominantly erosion-controlled mechanism of drug release.

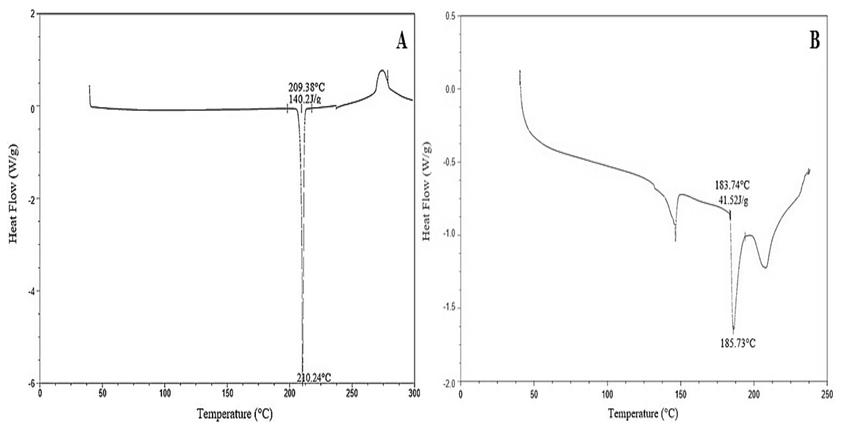

Figure 1: DSC thermograms of (A) MT-1207 and (B) pulverised tablets.

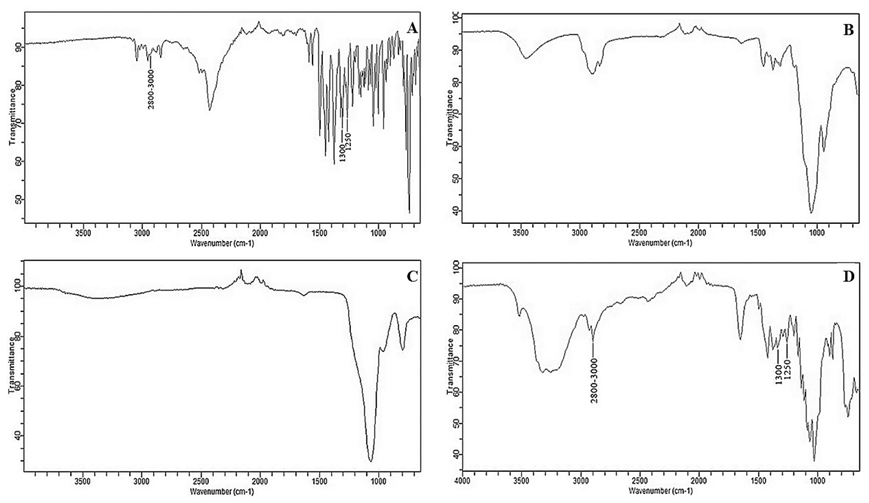

Figure 2: Fourier-Transform Infrared (FTIR) spectra of (A) MT-1207 hydrochloride reference standard, (B) HPMC K15M, (C) colloidal silicon dioxide and (D) pulverised tablets.

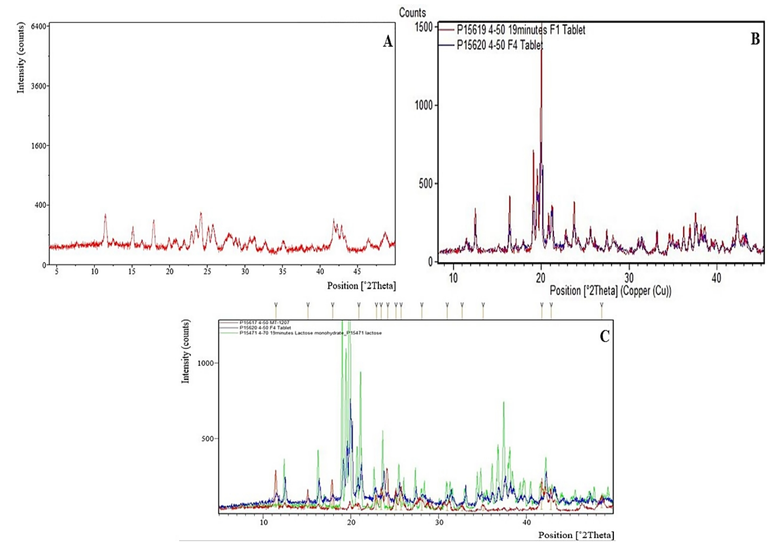

Figure 3: Diffractograms of (A) MT-1207 hydrochloride reference standard, (B) formulations F1 (red) and F4 (blue) and (C) MT-1207 hydrochloride reference standard (red), F4 (blue) and alpha-D-lactose monohydrate (green) combined.

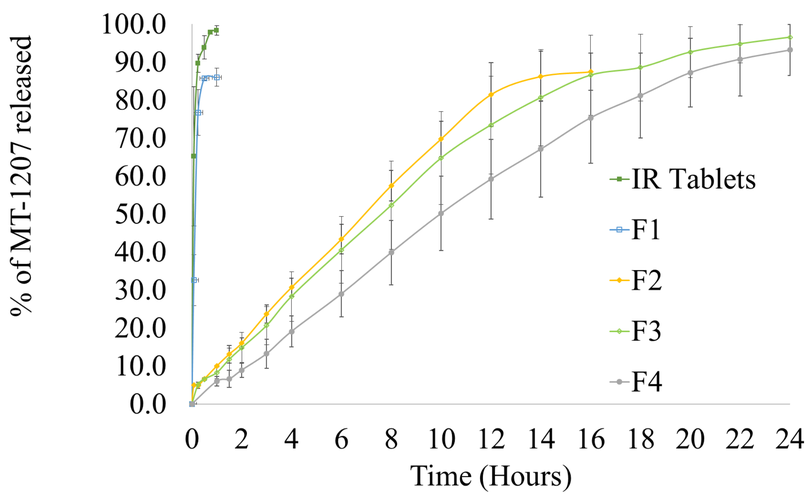

Figure 4: *In vitro* release profiles of MT-1207 from formulations F1, F2, F3 and F4 in 0.1M phosphate pH 6.8 with 0.2% w/v SDS (n=3).

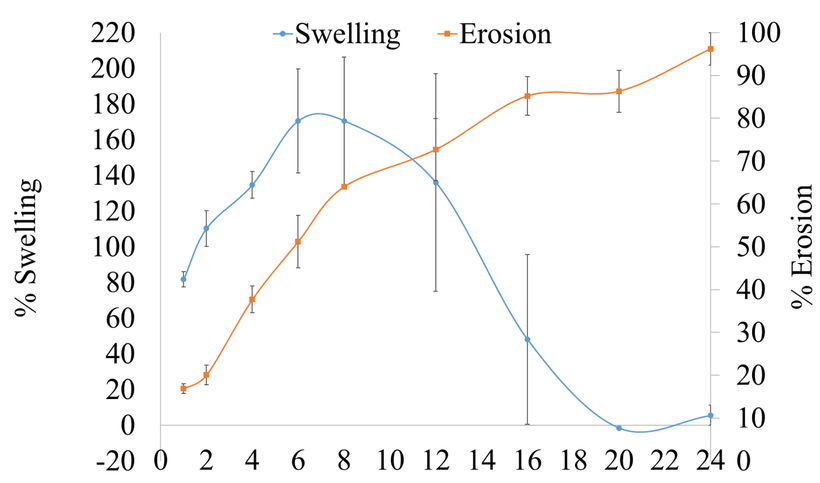

Figure 5: *In vitro* swelling and erosion profiles of formulation F4 in 0.1 M phosphate pH 6.8 with 0.2% w/v SDS (% swelling and % erosion vs time, n=3).

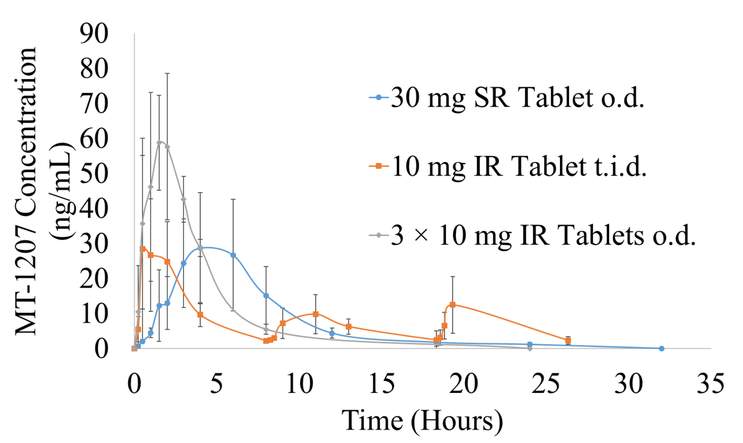

Figure 6: Plasma concentration of MT-1207 in Beagle dog after oral administration of 30 mg SR tablet o.d., 10 mg IR tablet t.i.d. and 3 × 10 mg IR tablet o.d. (n=4).

The *in vivo* study showed that the drug $t_{1/2}$ value was 2.5 times higher than that obtained after administration of the IR tablets and the $AUC_{0-\infty}$ values of both sustained- and immediate-release tablets were identical at the same MT-1207 dose (30 mg). However, the plasma concentration of MT-1207 was not sustained over 24 hours and potentially the drug levels were below the therapeutic window at the 24-hour timepoint (Figure 6).

Conclusions

- A 24-hour sustained release of MT-1207 from the optimised tablet formulation was achieved *in vitro*.
- *In vivo* studies in Beagle dogs showed that the plasma concentration of MT-1207 was not sustained over 24 hours and potentially the drug levels were below the therapeutic window at the 24-hour timepoint.

Future Work

- Hydrophobic polymer(s) will be incorporated into the sustained-release matrix to reduce tablet erosion, thus, potentially, reducing rate of drug release, especially *in vivo*.
- A gastroretentive layer will be included in the formulation to ensure that the whole amount of MT-1207 is released and absorbed from the new sustained-release layer.

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