Development of a Multi-Pill Abuse Resistant (MPAR®) Multiparticulate Modified Release Formulation to Prevent Opioid Overdose

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INTRODUCTION

- Prescription opioid abuse and overdose are major society burdens, resulting in significant costs, illnesses and deaths.
- Ensysce Biosciences is developing **Multi-Pill Abuse Resistance (MPAR®)** overdose protection for opioid drugs.
- MPAR® is a combination of **Trypsin Activation Abuse Protection (TAAP™)** prodrug platform (PF614) and a protease inhibitor (nafamostat) that provides overdose protection at a molecular level.[1]
- Short $T_{1/2}$ of nafamostat required an extended-release (ER) product to ensure trypsin inhibition in the intestine. Therefore, nafamostat ER beads with varying release rates were developed for clinical evaluation.

METHOD(S)

Nafamostat Intermediate IR beads (Procept Fluid Bed)

- A coating solution containing nafamostat and Methocel E5 was prepared for drug laying onto Microcrystalline cellulose (MCC) spheres.
- MCC spheres were coated via a bottom spray process to achieve ~8% drug load (700g batch size).

Nafamostat ER beads (Procept Fluid Bed)

- An ER coating suspension was prepared using a combination of two methacrylate copolymers with different permeabilities.
- Polymer coating of the intermediate IR beads was performed via a bottom spray process (200g batch size). The effect of different coating weight gain and polymer ratio on the drug release were assessed.

Capsule filling

- Manual capsule filling.
- Dose range 0.25 – 35mg achieved by adjusting fill weight.

Characterisation

- Yield
- Size distribution (sieve stack)
- Appearance (microscopy)
- Assay and homogeneity
- Related substances
- Release rate (Dissolution)

RESULT(S)

Nafamostat Intermediate IR Beads

The drug laying coating solution was developed to identify the optimum drug and methocel loading and overall solids content. Processing parameters were optimized to reduce coating time as much as possible while ensuring acceptable yields were produced. The beads were characterized by Assay (80.0-100.0% nominal), related substances (NMT 0.5%), PSD <600µm and demonstrated stability up to 3 months under standard conditions. The appearance of the IR beads shown in Figure 1.

Figure 1: Images of the Nafamostat Intermediate IR beads

Nafamostat Intermediate ER Beads

The ER coating suspension was developed to identify the optimum combination of methacrylate copolymers and solids content to achieve a target release of 90% from 4-16 hours. Processing parameters were optimized to reduce coating time as much as possible while ensuring acceptable yields were produced. The beads were characterized by Assay (90.0-110.0% nominal), related substances (NMT 0.1%), PSD 600-1000µm and demonstrated stability up to 3 months under standard conditions.

<u>Varying coating weight gain</u>

Initially a fixed methacrylate polymer ratio (87:13 Polymer 1:Polymer 2) was trialed using different weight gains to achieve the target release rate.

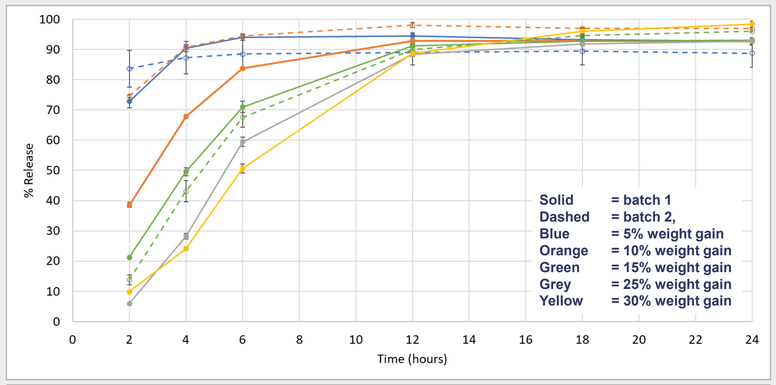

Figure 2: Release profiles at fixed polymer ratio with varying weight gain.

At lower weight gain (<10%), high batch-to-batch variability in release profiles were observed (68-90% at 4 hours) and the slow release target could not be achieved (slowest 90% at 12 hours). Therefore, a fixed weight gain with varied polymer ratio was explored.

<u>Varying polymer ratio with fixed coating weight gain</u>

A range of methacrylate polymer ratios were trialed at various fixed weight gains to achieve the target release rate. At lower weight gains (<10%) high batch to batch variability was observed and the slower target release rate could not be achieved. At too high a weight gain, the beads clumped together within the vessel.

A fixed weight gain (15%) with varied polymer ratio was selected and extremes of the release design space were locked. The fast release formulation (target release 90% at 4 hours) achieved 63-82% at 4 hours, while the slow formulation (target release 90% at 16 hours) achieved 71-79% at 16 hours.

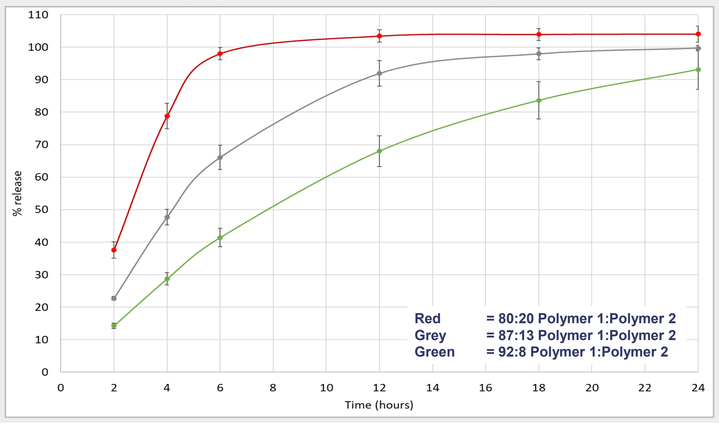

Figure 3: Release profiles at fixed weight gain with varying polymer ratios

These formulations were manufactured 2-4 times through development, regulatory submission, and clinical trial manufacturing with acceptable batch-to-batch reproducibility (Figure 4).

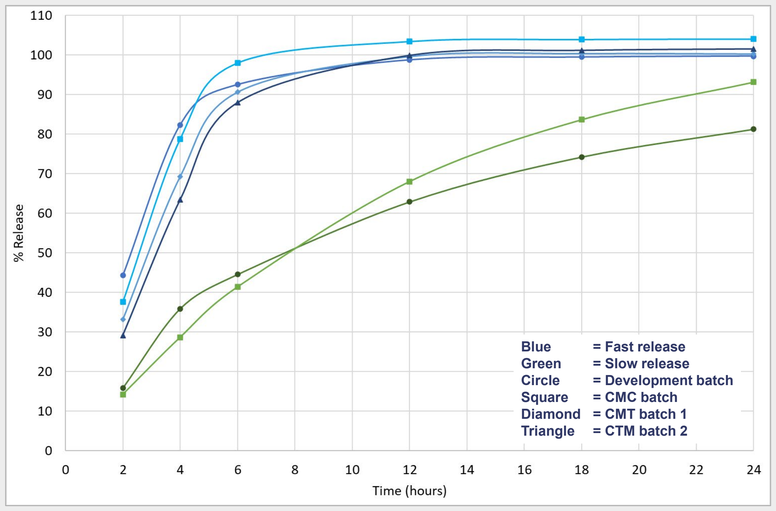

Figure 4: Demonstration of batch-to-batch reproducibility in the release profiles

Nafamostat ER beads were then filled into capsules for clinical dosing, with dose adjusted by fill weight. Thus a 2-dimensional (2D) design space for nafamostat dose range (0.25–35 mg) and release rate (90% cumulative release in 4–16 hours) was developed (Figure 5).

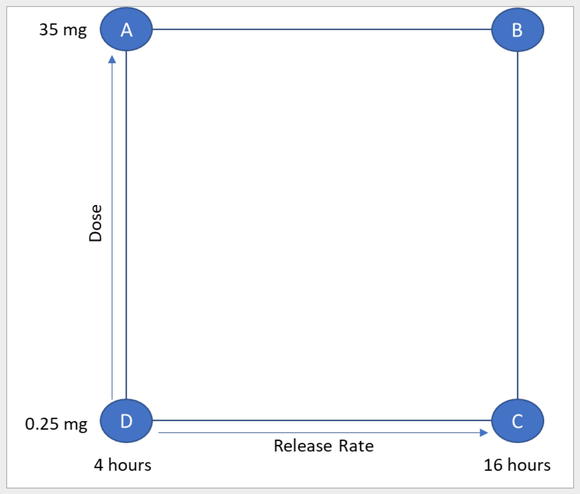

Figure 5: Schematic of the 2D design space applied to the Nafamostat ER Capsules

During the clinical study, the Nafamostat ER capsules were dosed alongside a Nafamostat IR solution. Therefore some *in vitro* dissolution experiments were performed to assess the impact of the addition of the IR solution on the release. The inclusion of the IR solution, resulted in faster apparent release. The ER capsules released at the same rate as without the IR solution; however, as the IR solution was added into the dissolution vessel, it contributed to the overall release as shown in Figure 6.

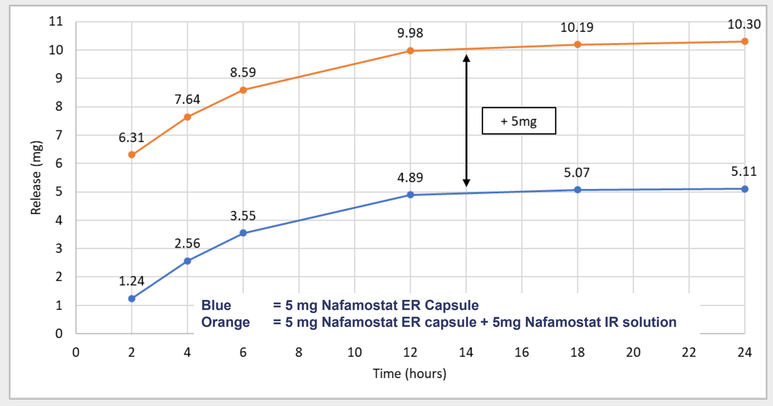

Figure 6: Impact of Nafamostat IR solution on *In vivo* release profiles

CONCLUSION(S) AND LEARNING OBJECTIVE

- Development of a robust nafamostat ER bead formulation design space was achieved, targeting a release rate of 90% in 4–16 hours covering a dose range of 0.25–35 mg, suitable for clinical dosing.
- Reproducibility of release profiles was related to bead batch weight gain and hence this variable was fixed to reduce variability.

REFERENCES

1. Kirkpatrick DL, et al. In vitro and in vivo assessment of the abuse potential of PF614, a novel BIO-MD™ prodrug of oxycodone. J Opioid Manag. 2017;13(1):39-49