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FORMULATION DEVELOPMENT OF ENTERICALLY PROTECTED SPRAY DRIED DISPERSIONS OF ADRULIPASE

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PURPOSE

- Oral Delivery of proteins and peptides is challenging due to their poor stability in the GI tract (esp. acidic conditions).
- Deficiency of pancreatic lipase leads to a condition called exocrine pancreatic insufficiency (EPI). Administration of porcine pancreatic enzyme replacement therapy (PERT) remains the primary treatment option for patients with EPI.
- Adrulipase, a recombinant non-porcine lipase is currently in development for the treatment of EPI.
- In the present study, several formulations of Adrulipase combined with an enteric polymer, as a spray dried dispersion (SDD), were evaluated to achieve an optimal delayed release profile while retaining Adrulipase activity. A stability study of the selected lead SDD was also conducted.

OBJECTIVE(S)

- Evaluate spray dried dispersion formulations of Adrulipase to select a lead formulation optimized for acid protection and dissolution profile for further development.
- To evaluate the stability of lead formulation.

METHOD(S)

Spray Drying

Buchi 290 Mini Spray dryer : Adrulipase with HPMCP, HPMCAS, Maltodextrin and Arginine

- Inlet temperature of 90-140°C
- Air flow rate of 400-700 L/h
- Aspirator flow rate of 25-40 m^3/min
- Liquid feed rate of 2-6 mL/min

→ Adrulipase Spray Dried Dispersions — Characterized for moisture content, drug loading and enzyme activity

Dissolution

Transitional Dissolution

- SDD powder ~75 mg Adrulipase (~30 mg for SDD01 and SDD02)
- pH 3 (30 mins) → 6.5 (60 mins) using 1 N NaOH
- Sampling: 15, 30, 35, 45, 60, and 90 min
- Analysis: Adrulipase conc. using Bradford assay and activity using colorimetric assay
- Colorimetric assay : Choi et.al (2003) reported a UV-Vis based colorimetric plate assay to test lipase activity[1]. This procedure was modified and optimized for the current study.

Stability Study

Stability Study of lead formulation (SDD04)

- Stability Conditions: 40°C/75% RH and 25°C/60% RH
- Stability Time points: 0, 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks
- Tests: Appearance, HPLC-SEC , activity

RESULT(S)

➢ Spray Drying and Transitional Dissolution :

- Adrulipase showed similar enzymatic activity before and after spray drying, with and without an enteric polymer.
- SDD02 and SDD03 contained no enteric polymers (>80% release at pH 3, Fig 1).
- SDD containing arginine (SDD07) showed incomplete release at pH 6.5 versus SDD containing maltodextrin (SDD04) at similar drug load.
- A sticky mass was observed on dissolution of SDDs containing arginine as matrix, which might be due to the formation of enzyme-arginine agglomerates. Maltodextrin was thus found to be a better stabilizer for Adrulipase compared to arginine.
- API was spray dried with HPMCP only, in an attempt to maximize drug load, however the drug release from the SDD was slow and incomplete (SDD09).
- HPMCP provided better enteric protection than HPMCAS (SDD04 versus SDD08, 0-10% versus ~40% release at pH 3) at similar concentration and drug loading. This might be due to the difference in the structure of drug-polymer-stabilizer matrix formed upon spray drying.

➢ Lead Formulation :

- **SDD04** was selected as the lead for further development of a capsule dosage form.
- The % spray dried yield was approx. 65-70%, contained approximately 50% drug load, was fully protected at pH 3, and retained activity even after 90 minutes under dissolution conditions. No significant change in HPLC-SEC peak area as well as activity was observed on storage of the material at both stability conditions (Figure 2). No additional impurities/ increase in existing impurities was observed during the testing period.

Figure 1: Transitional Dissolution Studies

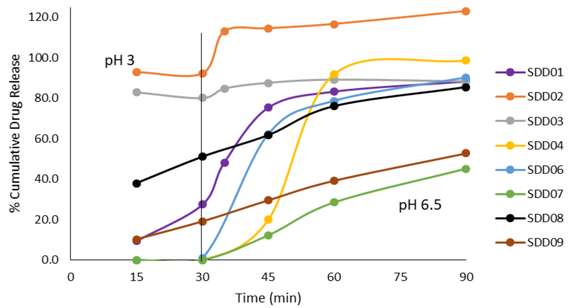

Figure 2: Stability Study of SDD04

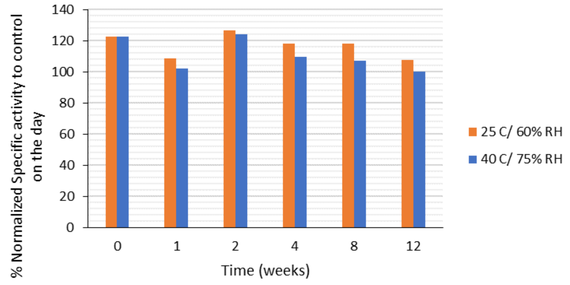

Table 1 : Composition of SDDs

Name	Composition
SDD01	API , Maltodextrin, HPMCP
SDD02	API , Maltodextrin
SDD03	API , Maltodextrin
SDD04	**API , Maltodextrin, HPMCP**
SDD05	Spray dried API (no excipients)
SDD06	API ,Arginine, HPMCP
SDD07	API , Arginine, HPMCP
SDD08	API , Maltodextrin, HPMCAS
SDD09	API, HPMCP

CONCLUSION(S)

- Nine Adrulipase spray-dried dispersions (SDDs) containing various excipients (HPMCP, HPMCAS, maltodextrin and arginine) were prepared and characterized.
- With the goal to generate drug product with a delayed release profile and the highest possible Adrulipase loading, formulation **SDD04** was selected as the lead formulation for further development.
- **SDD04** showed delayed release profile, offering the best protection at acidic pH and rapid release under intestinal conditions, as well as minor loss of activity over 1) 3-month stability assessment (25°C and 40 °C) and 2) formulation processing activities (granulation).
- Granulation to improve flowability and better retention of enzymatic activity during dissolution has been completed and Investigational Medicinal Product (IMP) is being manufactured for clinical study.
- SDD of enzymes with a stabilizing agent and an enteric polymer may provide a novel approach to enable oral delivery of peptides and proteins as therapeutics.

REFERENCE

1. Choi, S. J., Hwang, J. M., & Kim, S. I. (2003). A colorimetric microplate assay method for high throughput analysis of lipase activity. *BMB Reports, 36*(4), 417-420.