Development and in vitro testing of a multi-layered enteric coated pellet formulation using fluid bed coating

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Background / Purpose

Hydroxypropyl methycellulose (HPMC) polymer substituted with acetate and succinate or palmitate groups are primarily used for enteric coating of solid oral dosage forms. It dissolves in a pH range of 4.0 to 6.0. The HPMC-based coating shows high performance in drug delivery systems.

Materials / Methods

Sugar sphere pellets (ISO 500 - 560 μm, pharm-a-sphere®), H.G. Werner GmbH, Germany) were coated using a fluid bed 1-MULTIPROCESS® (GDA, Germany). Coating batches were 1 kg. Four different coating layers were applied:

1. Drug layer: HPMC was suspended in HPMC polymer solution (Pharmaco® 603, Shin-Etsu Chemical Co., Japan).
2. Protective isolation layer: Pharmaco® 603, co formulat ed with sucrose (ProFil® & Langen, Germany) and talc (Rio Tinto, UK), was used as a protective layer to physically separate NP2 from the enteric polymer layer.
3. Enteric polymer layer: HPMCAS (AQDOT® LF, Shin-Etsu, Japan), co-formulated with triethyl citrate (TEC, Jangbundae, Switzerland) and talc as plasticiser and glidant respectively, was used as the enteric polymer.

Figure 1. Multi-layered NP2 pellets

Figure 2. Effect of HPMCAS preparation method on drug dissolution rate

Figure 3. Product stability

Results & Discussion

• The USP requirement for enteric drug release (cumulative relative amount of drug released following 120 min exposure to simulated gastric fluid (pH1.2)) was achieved using enteric solutions and aqueous dispersions of HPMCAS (Fig. 2a).

• Enteric protection was not achieved following aqueous polymer dispersion pH a, neutralisation of HPMCAS carbonyl groups. This is due to increased HPMCAS solubility at lower pH (Fig 2a).

• HPMCAS dissolution rate at pH 5.8 was less dependent on polymer preparation method.

• Stable enteric protection was achieved up to 6 months storage at 40°C / 75% RH for all HPMCAS preparation methods investigated.

• Preparation methods producing a polymer solution for application to the NP2 pellet, use organic solvent in an anionic surfactant, NH₄OH-neutralisation for aqueous solution, produced the most stable dissolution profiles at pH 5.8, most likely due to better polymer coalescence in the enteric coating, results lower a, c), and e).

• The most stable HPMCAS formulation was achieved when the HPMCAS was coated using organic solvent. Migration of excess HCl in the aqueous HPMCAS coatings through the protective coating may be a cause of NP2 degradation.

• Further optimisation of aqueous coating / curing parameters are required to produce a stable formulation of NP2 with robust dissolution profile.

Conclusion

• HPMCAS dissolution rate is primarily controlled by diffusion through the film coatings via the microstructural network and the presence of water saturated channels located within the coatings.

• In addition to formulation and process conditions, the coating polymer methods have an effect on the resulting film structural properties and dissolution rate.

• Fluid-bed multilayer processing was successful in the manufacture of NP2 pellets from HPMCAS film coating to produce stable enteric HPMCAS formulation.

References


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