Small-Scale Manufacture of Modified-Release Coated Beads
For Preclinical Drug Delivery Research

M. Morgen¹, C.K. Tye², E. LaChapelle¹, M. Markovich³, B. Murri¹, M. Shaffer¹, D. Millard¹, Jim Mullin¹, Vinay H.K.², J. Sinha², A. Nigam², J. Italia², S. Mandlekar²,3, S. Konagurthu⁴
¹Bend Research Inc.; ²Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Company R&D Center, Syngene International Ltd.; ³Bristol-Myers Squibb India Pvt. Ltd.; ⁴Agere Pharmaceuticals Inc.

PURPOSE

Modified-release technologies are used early in discovery to
• enable mechanism/target testing of molecules with non-ideal pharmacokinetics,
• reduce dosing frequency,
• reduce stress to animals, and
• enable mechanism/target testing of molecules with non-ideal pharmacokinetics.

RESULTS

A micro-scale fluid bed coater was successfully developed and used to manufacture small-scale batches of beads with CR coatings using ~100 mg of API and a 1-qm bed size. Coating efficiencies exceeded 70%.

METHODS

A bottom-spray fluid bed system was developed that features:
• conical-cylindrical chamber with a 12-mm distribution plate,
• atomization gas control,
• temperature- and humidity-conditioned drying gas,
• process instrumentation, and
• suitability for use with organic solvents.

Model drugs of various solubilities were coated using a cellulose binder (hydroxypropyl cellulose [HPC]) or hypromellose acetate succinate (HPMCAS) onto 60-µm-diameter glass beads. The drug-coated beads were then coated with an ethylcellulose/ hydroxypropyl methylcellulose (HPMC) coating.

Physical Situation and Design Considerations

Custom Micro-Scale Fluid-Bed Coater

1. Feed distribution
2. Atomization gas
3. Air inlet distribution
4. Drug type
5. Coating fluid
6. Coated bed
7. Coating bed
8. Atomization gas
9. Air inlet distribution
10. Feed distribution

Coating Bead

Drug Type

Atazanavir
Metoprolol Tartrate
Phenytoin

Drug Load

Atazanavir
Metoprolol Tartrate
Phenytoin

Soda-Lime Glass Microsphere Substrate

IR drug layer: 75/25 Atazanavir/HPMC E5

SLS = sodium lauryl sulfate  SIF = simulated intestinal fluid, PBS = phosphate buffer solution

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CONCLUSIONS

The modified-release beads provided much more sustained release than the IP solution or IR beads:
• At 3 hrs, approximately 60% of the drug was released in 24 hours from the modified-release beads, compared with ~50% in the in vitro test.

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Radhakrishna Malapudi, Abhiyith Rao, Indanil Rao

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In Vivo Pharmacokinetic (PK) Results
Injection of Atazanavir Beads in Rats

Deconvolution of PK Curves Using IV Data

- A miniature fluid-bed coater capable of processing 1-batch of ~50-µm particles was successfully developed.
- In vitro release profiles were near zero order for several APIs, with release rates strongly dependent on API solubility.
- In vivo release after IP injection was consistent with in vitro profiles.
- This platform enables evaluation of particles with modified-release coatings via oral or injectable routes within the extreme API limitations of the discovery research setting.