T3272

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

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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 target validation requiring prolonged plasma levels.

The objective was to develop a "micro-scale" fluid-bed system that met the following criteria to enable these discovery studies:
- ~0.5- to 1-g batches (using ~100 mg of API),
- quick turnaround,
- a platform applicable to a wide range of API,
- tunable release with close to zero-order kinetics, and
- predictable release rate, based on API properties.

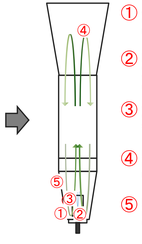
METHODS

A bottom-spray fluid-bed system was developed that features:
- conical-cylindrical chamber with a 12-mm distribution plate,
- custom two-fluid nozzle fed by a syringe pump,
- 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 sphere substrates. The drug-coated beads were then coated with an ethylcellulose/ hydroxypropyl methylcellulose (HPMC) coating.

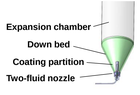
Physical Situation and Design Considerations

Custom Micro-Scale Fluid-Bed Coater

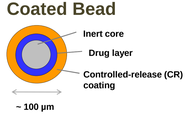


1. **Air Distribution** — Provide and distribute the drying gas for particle circulation and drying.
2. **Particle Entrainment** — Control the number of particles and frequency of passes through the coating region.
3. **Atomization** — Control the droplet size, velocity, and shape of spray inside the partition.
4. **Expansion** — Reduce the particle velocity to allow particles to circulate for additional passes.
5. **Down Bed** — Freely circulate individual particles prior to re-entering the coating region.

Micro-Scale Fluid Bed



Coated Bead



RESULTS

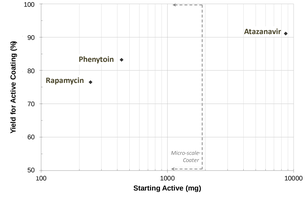
A micro-scale fluid bed coater was successfully developed and used to manufacture small-scale batches of beads with CR coatings using ~100 mg of API and a 1-g bed size. Coating efficiencies exceeded 70%.

Manufacture of Coated Beads

Soda-Lime Glass Microsphere Substrate
Density: 2.5 g/cc
Size Fraction: 53 to 63 µm

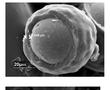
IR Drug-Layered Intermediate
Potency: 100 to 300 mg/g
Size Fraction: < 90 µm

CR-Layered Final Product
Potency: 50 to 150 mg/g
Size Fraction: < 106 µm



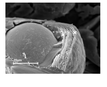
A small bead size (60 µm) was chosen to enable syringe delivery. A dense material (glass) was used to allow adequate fluidization in the micro-scale fluid-bed coater.

CR coated beads were prepared using four model drugs (phenytoin, rapamycin, atazanavir and metoprolol) with drug loadings of ~10% to 20% (by weight) and 70/30 Ethocel 10/HPMC E5 CR coatings of various thicknesses.



Drug-Layered Atazanavir Bead

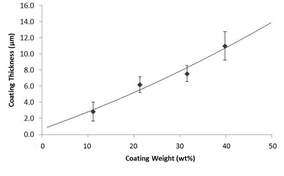
IR drug layer: 75/25 Atazanavir/HPMC E5
Coating weight: 25 wt%
Coating thickness: 5.2 µm ± 1.4 µm
Seed core: 60-µm glass spheres



CR Coated Atazanavir Bead

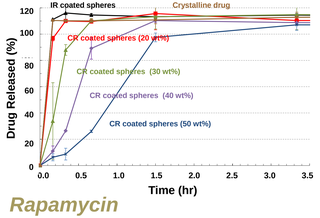
CR coating: 70/30 Ethocel 10/HPMC E5
Coating weight: 35.1 wt%
Coating thickness: 11.0 µm ± 1.8 µm

Average Coating Thickness Versus Coating Weight Of CR Layer

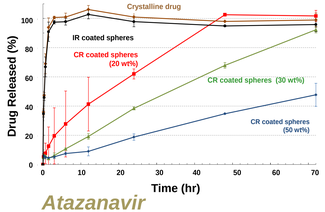


In Vitro Dissolution Profiles for Model Drugs

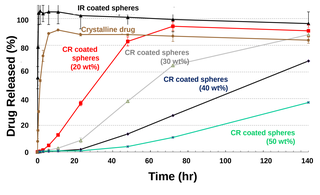
Metoprolol Tartrate



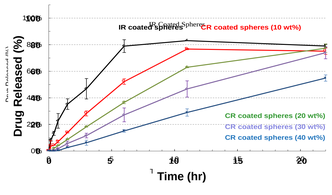
Phenytoin



Rapamycin



Atazanavir

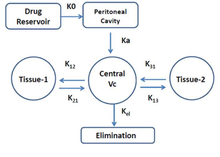


Model Drug Properties and Dissolution Conditions

Drug Property	Rapamycin	Phenytoin	Metoprolol Tartrate	Atazanavir
Water solubility (µg/mL)	26	32	169,000	2
Glass-transition temperature (°C)	93	71	25	104
Melting point (°C)	184	297	124	213
Dissolution medium	0.25% SLS	2% SIF	PBS	PBS

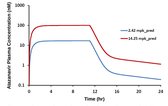
SLS = sodium lauryl sulfate SIF = simulated intestinal fluid, PBS = phosphate buffer solution

Example Model Used for Atazanavir Dose Selection



A model was used to simulate the dose that provides the 100-nM target plasma concentration.
- Atazanavir concentration-time data after intravenous (IV) and intraperitoneal (IP) administration were fitted simultaneously and disposition parameters were estimated.
- Zero-order release rate (K0) was calculated from *in vitro* dissolution profile of spheres with the 40 wt% CR coating.

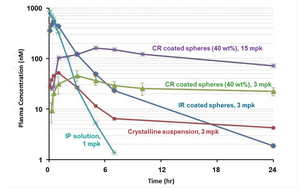
Simulated Plasma Profile



Based on the simulation, 3- and 15-mpk doses were selected for *in vivo* study.

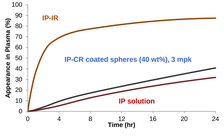
In Vivo Pharmacokinetic (PK) Results

Injection of Atazanavir Beads in Rats



Deconvolution of PK Curves Using IV Data

Form	AUC ng/mL*hr	AUC nM*hr	Dose mpk	% F Deconvolution
IV	397.6	564.1	1	
IP-Xtal	189.4	268.4	3	16.3
IP-IR	1032.2	1460.0	3	87.4
IP-CR	465.6	660.2	3	40.4
IP-CR	1847.5	2620.1	15	31.6
IP Solution	609.2	864	1	



- The modified-release beads provided much more sustained release than the IP solution or IP-IR beads.
- At 3 mpk, approximately 40% of the drug was released in 24 hours from the modified-release beads, compared with ~55% in the *in vitro* test.

CONCLUSIONS

- A miniature fluid-bed coater capable of processing 1-g batches of ~60-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.

Acknowledgments

Radhakrishna Mullapudi, Abhijith Rao, Indanil Rao