Background

Lipid Multicarticulates (LMPs)

- Narrow particle size distribution (PSD)
- Diameter tunable across 50-450 µm
- Easy to swallow with acceptable mouth feel
- Tunable release, amenable to functional coatings

Melt spray congeal (MSC) technology

- Solvent-free, scalable process
  - Suspend API in lipid carrier and pore-former melt
  - Atomize melt to spherical droplets, congeal into solid LMPs
  - PSD controlled by atomization which is scalable
  - CR LMPs require annealing for stabilizing LMP release rate
  - Ideal API properties:
    - Aq. solubility > 0.1 mg/mL to reduce performance risk
    - Lipid solubility < 10% of dose to reduce stability

LMP Characterization

Particle size distribution (PSD), morphology

- Spherical particles with a smooth surface
- Drug particles apparent on LMP surfaces
- PSDs assessed using light microscopy and image analysis
- D50 values 170 µm – 270 µm, span from 0.5-0.7

LMP Potency and Stability

- Observed potency values of 93% – 103% LC
- Uniform potency across LMP sizes for 40% API load
- D50 values tunable across 50 µm

In Vitro Performance

- LMPs annealed for 7 days at 25°C/75% RH
- CR-2 and CR-5 (6% P/(P+C)) selected for stability testing
- < 25% release at 12h for LMPs with less than 6% pore-former
- Performance predicted across formulation space
  - 3-parameter empirical model (RMSE 5.2, p-value 0.01)
  - % release, 12 h = 0.516*(A) + 20.469*(P) – 0.736*(A)*(P), where A = API wt%, P = Pore-former wt%

Performance on Stability

- CR-2: slight decrease in release rate after 1 month at 25°C/60% RH and at 40°C/75% RH
- CR-5: increase in release rate following 1 month at both 25°C/60% RH and 40°C/75% RH
- Annealing incomplete after 7 days

Recommendations:

- CR LMPs require annealing for stabilizing LMP release rate
- Increase P/(P+C) ratio, especially for high drug loads
- Annealing times greater than 7 days required

Predicted In Vivo Performance

- Simulated release in fasted human using GastroPlus software
- Low calculated permeability predicted to limit absorption
- Optimum absorption: majority of release in < 3.5-4 h. After that, almost no absorption predicted in colon.
- Suggest acetazolamide is not well suited for extended release > 4 h
- Consistent with commercial acetazolamide products: 250-mg or 500-mg dose tablets taken 2-4 times daily

Conclusions

- Material sparing, rapid development demonstrated
  - < 50 g of API needed, executed in 12 weeks or less
  - Increased pore-former content and increased annealing time recommended
- LMPs ideal for rapid, early phase clinical trials
  - Market image formulation that can be easily tailored to fit desired product CQAs
  - Development knowledge can be extended beyond selection of clinical trial candidates
  - Complimentary immediate release product can be developed for clinical studies using LMP platform