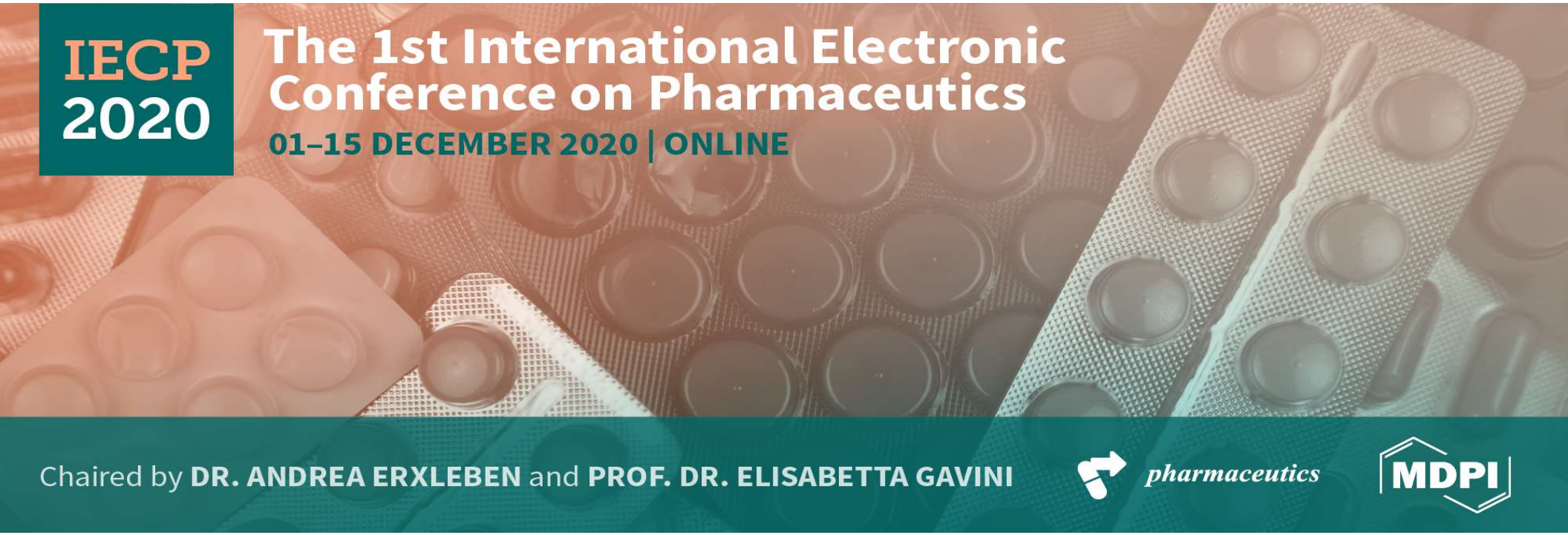

A Novel Intensification Strategy for Wet Media Milling of Drug Suspensions: Bead Mixtures

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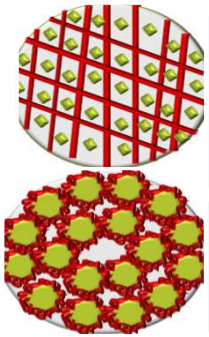
Motivation

- Delivery of poorly water-soluble drugs remains a significant challenge (Kipp, 2004; Lipinski, 2002)
  - Up to 80-90% of drugs in pipeline are poorly water-soluble (Chawla and Bansal, 2007; Shah et al., 2006)
  - Require some form of bioavailability enhancement (Brough and Williams III, 2013)

- Available approaches to enhance the bioavailability:



– Amorphous solid dispersions (Forster et al. 2001; Hancock and Parks, 2000; Knopp et al. 2016)

– Nanocomposites (Singh et al. 2011; Tanaka et al. 2012; Tuomela et al. 2014)

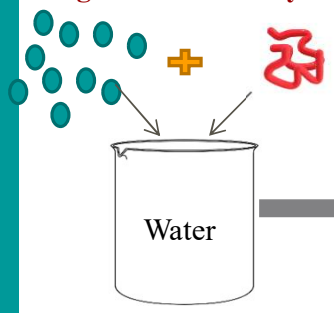
Noyes-Whitney equation

$$\frac{dm}{dt} = k_0 A(C_S - C)$$

Platform Approach: Nanocomposites Containing Drug Nanoparticles

Drug

Polymer



Suspension

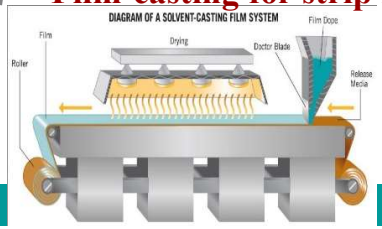
Wet stirred media milling

Fluidized bed coating/drying

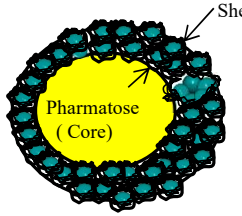
Spray drying

Co-rotating twin-screw extruder

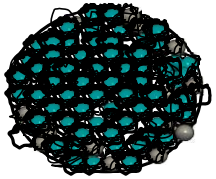
Film-casting for strip film



Core-shell nanocomposite



Matrix type nanocomposite

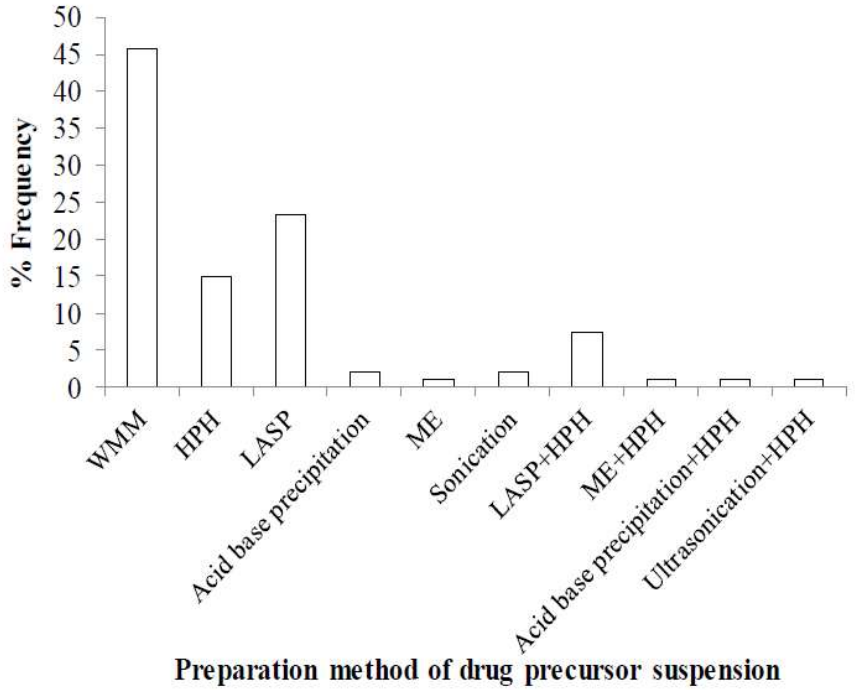


Noodle shape extrudates

Drug strip films

Wet Stirred Media Milling

- Advantages:
  - Production of high drug-loaded, stable suspensions
  - Robust
  - Reproducible
  - Solvent-free
  - Environmentally benign
- Disadvantages:
  - Possible nanoparticle aggregation-growth
  - High energy consumption
  - Long operating hours
  - Contamination by the beads



Bhakay et al., (2018), Pharmaceutics, 10(3), 86.

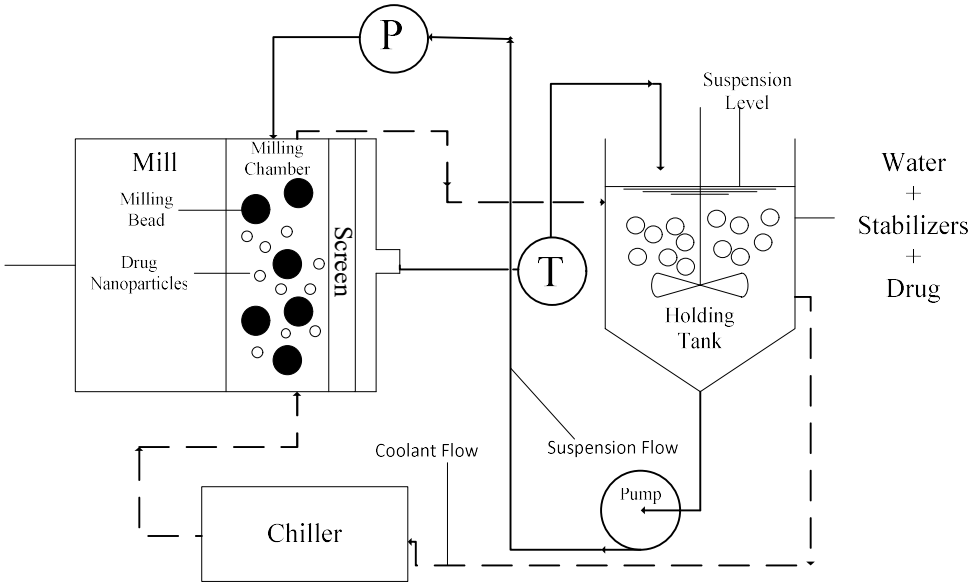
Wet Stirred Media Milling of Drugs

Purpose: Produce stable nanoparticle suspensions of BCS class II drugs

Mode of operation: Suspension is recirculated through the milling chamber

Mechanism of Action: Repetitive compression of drug particles captured between colliding beads (media)

Formulation: BCS class II drug and stabilizers (polymers and surfactants)



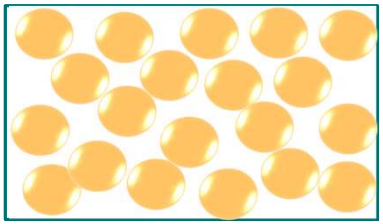
Previous Studies on Wet Stirred Media Milling: Process Optimization

- Afolabi et al. (2014) studied the impact of process parameters
- Li et al. (2017) studied the impact of Zirconia (YSZ) bead sizes and produced sub-100 nm nanoparticles (2015)
- Parker et al. (2020) studied the impact of crosslinked polystyrene (CPS) and YSZ beads
- A possible synergistic effect of CPS-YSZ bead mixture was not studied

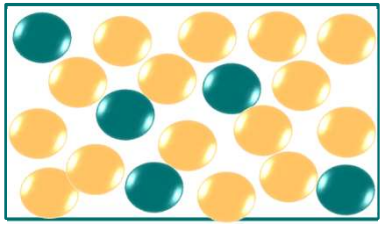
	Polystyrene	Zirconia
ρ_b (kg/m^3)	1040	6000
Y_b (Gpa)	1.5 He et al., 2008	200 Ashby and Cebon, 1993
η_b	0.33 He et al., 2008	0.2 Srikar et al., 2004

Experimental

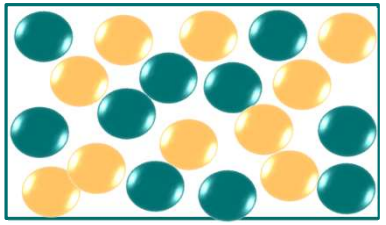
- Materials
  - Fenofibrate (drug): 10%
  - Hydroxypropyl cellulose: 7.5%
  - Sodium dodecyl sulfate: 0.05%
  - 400 µm cross-linked polystyrene **(CPS)** beads and yttrium-stabilized zirconia **(YSZ)** (100:0-0:100)
- Equipment
  - Netzsch MicroCer wet stirred media mill
  - Beckmann Coulter LS 230 for PSD
  - Brookfield Rheometer



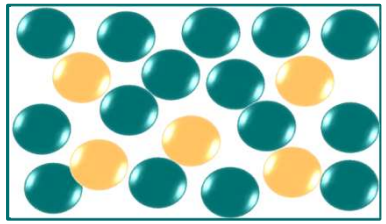
CPS:YSZ=100:0



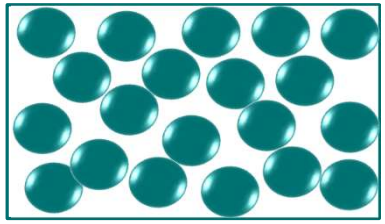
CPS:YSZ=75:25



CPS:YSZ=50:50

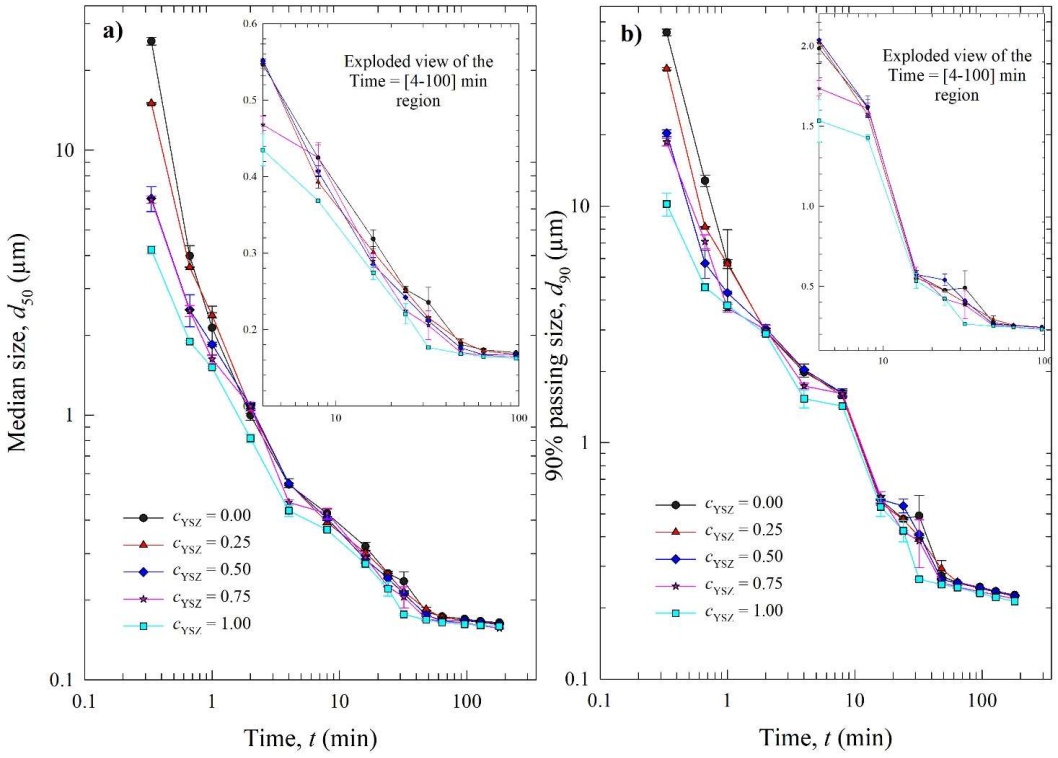


CPS:YSZ=25:75



CPS:YSZ=0:100

Wet Media Milling with Bead Mixtures



Initial drug particle size:

- d_{50} = 25.58 ± 0.06 μm
- d_{90} = 49.32 ± 0.016 μm

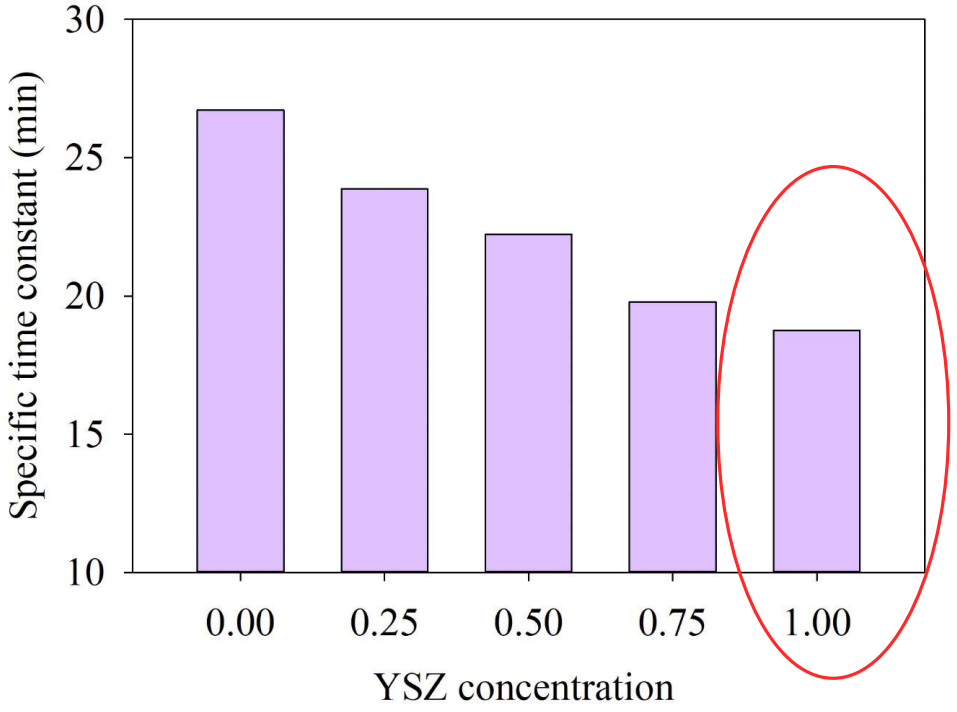
FNB nanosuspensions with d_{50} < 165 nm were produced within 180 min using CPS and YSZ beads and their mixtures

Well-stabilized suspensions: Monotonic decrease of particle size and no particle growth over 7 days (not shown for brevity)

Apparent grinding limit: ~ d_{50} = 160 nm

Specific time constant

- Time required for d50 to reach 0.25 µm
- Faster breakage at higher YSZ concentration in the bead mixture
- The increase in the rate decreases for c_{YSZ}>0.5

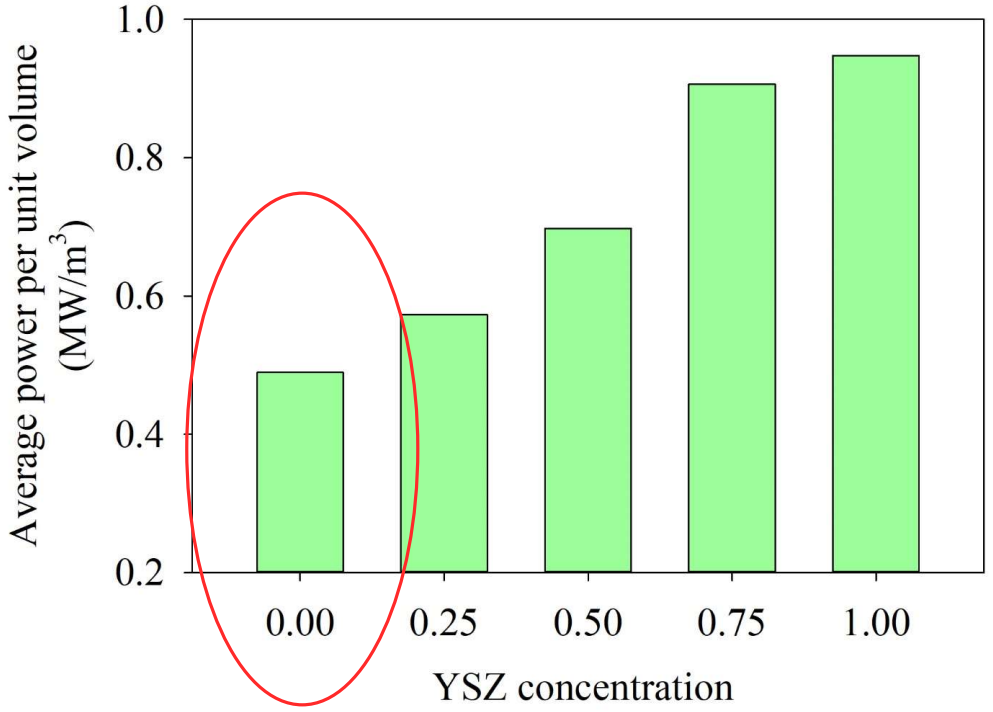


Power

- Power (P) was found by dividing the cumulative energy consumption read from the control panel of the mill by the milling time
- The average stirrer power per unit volume was found

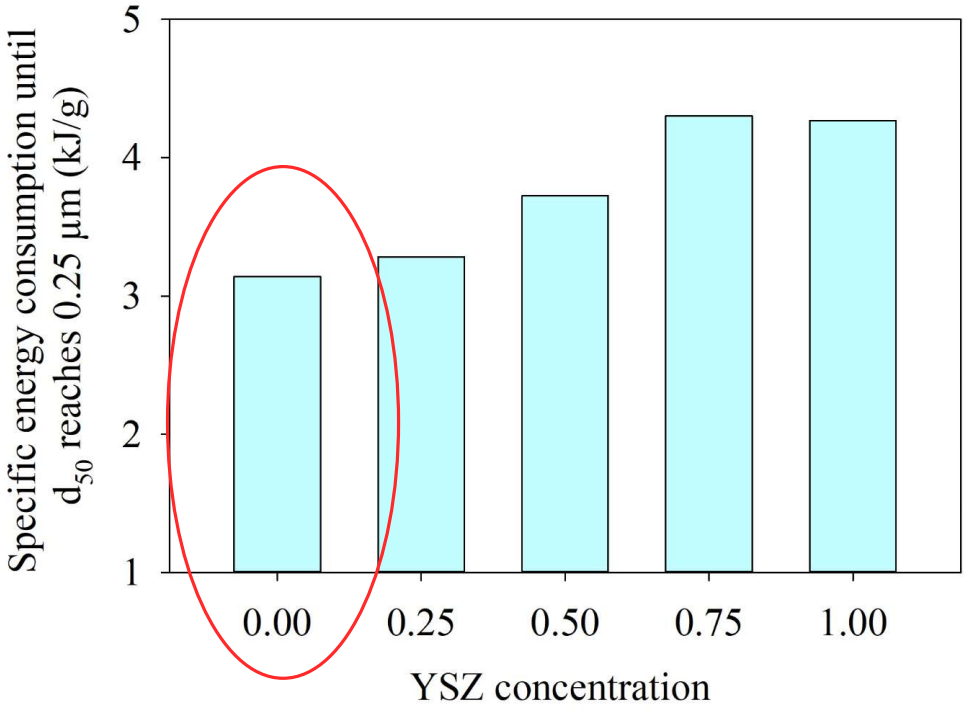
$$P_w = \frac{P}{V}$$

- The more YSZ in the mixture, the more power required



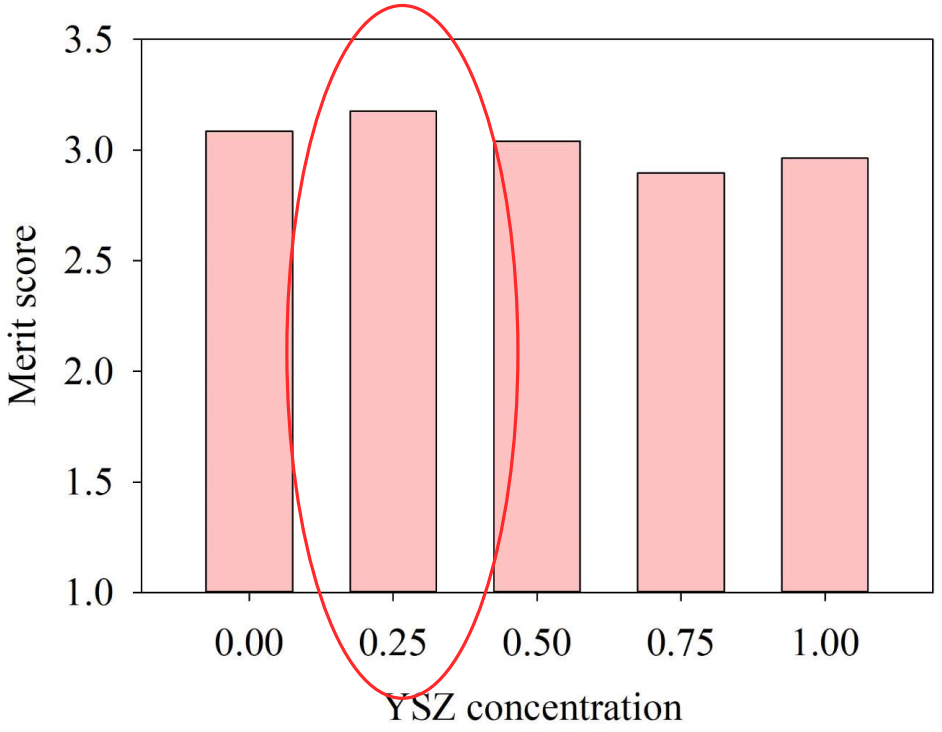
Energy consumption

- Specific energy consumption during d50 reaches 0.25 μm was found
- $E_{td50} = \frac{P_w V_m t_{d50}}{m_D}$
- Higher YSZ concentration caused higher energy consumption
- The increase in energy consumption was less pronounced than that in power.



Merit Score for an Optimum Process

- Both breakage kinetics and energy consumption is considered
- $\overline{t_{d50}} = \frac{t_{d50}}{t_{d50,max} - t_{d50,min}}$
- $\overline{E_{td50}} = \frac{E_{td50}}{E_{td50,max} - E_{td50,min}}$
- $Merit\ score = \frac{2}{\overline{t_{d50}} + \overline{E_{td50}}}$
- Optimum was found in a mixture!



Conclusions

- CPS beads are favorable for energy efficiency (lower utility costs)
- YSZ beads are favorable for fast production (reduced cycle time)
- When the process is designed to reduce both, mixture of beads appears to enable optimization.
- Different operating conditions will be studied in future work.

References

1. Lipinski C. Poor aqueous solubility—an industry wide problem in drug discovery. Am Pharm Rev. 2002;5(3):82-85.

2. Kesisoglou F, Panmai S, Wu Y. Nanosizing — Oral formulation development and biopharmaceutical evaluation. Advanced Drug Delivery Reviews. 2007;59(7):631-644.

3. Bhakay A, Merwade M, Bilgili E, Dave RN. Novel aspects of wet milling for the production of microsuspensions and nanosuspensions of poorly water-soluble drugs. Drug Development and Industrial Pharmacy. 2011;37(8):963-976.

4. Malamatari M, Taylor KMG, Malamataris S, Douroumis D, Kachrimanis K. Pharmaceutical nanocrystals: production by wet milling and applications. Drug Discovery Today. 2018;23(3):534-547.

5. Chen H, Khemtong C, Yang X, Chang X, Gao J. Nanonization strategies for poorly water-soluble drugs. Drug Discovery Today. 2011;16(7):354-360.

6. Mohammad IS, Hu H, Yin L, He W. Drug nanocrystals: Fabrication methods and promising therapeutic applications. International Journal of Pharmaceutics. 2019;562:187-202.

7. Bhakay A, Rahman M, Dave RN, Bilgili E. Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites: Formulation-Processing Aspects and Challenges. Pharmaceutics. 2018;10(3):86.

8. Li M, Azad M, Davé R, Bilgili E. Nanomilling of Drugs for Bioavailability Enhancement: A Holistic Formulation-Process Perspective. In.Pharmaceutics; 2016. p. 17.

9. Peltonen L. Design Space and QbD Approach for Production of Drug Nanocrystals by Wet Media Milling Techniques. Pharmaceutics. 2018;10(3):104.

10. Li M, Yaragudi N, Afolabi A, Dave R, Bilgili E. Sub-100nm drug particle suspensions prepared via wet milling with low bead contamination through novel process intensification. Chemical Engineering Science. 2015;130:207-220.

11. Kawatra SK. Advances in comminution. Littleton, Colorado: Society for Mining, Metallurgy, and Exploration; 2006.

References

12. Afolabi A, Akinlabi O, Bilgili E. Impact of process parameters on the breakage kinetics of poorly water-soluble drugs during wet stirred media milling: A microhydrodynamic view. European Journal of Pharmaceutical Sciences. 2014;51:75-86.

13. Bilgili E, Capece M, Afolabi A. Modeling of milling processes via DEM, PBM, and microhydrodynamics. In: Pandey P, Bharadwaj R, editors. Predictive Modeling of Pharmaceutical Unit Operations: Woodhead Publishing; 2017. p. 159-203.

14. Li M, Alvarez P, Bilgili E. A microhydrodynamic rationale for selection of bead size in preparation of drug nanosuspensions via wet stirred media milling. International Journal of Pharmaceutics. 2017;524(1):178-192.

15. Parker N, Rahman M, Bilgili E. Impact of media material and process parameters on breakage kinetics–energy consumption during wet media milling of drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2020;153:52-67.

16. Rahman M, Arevalo F, Coelho A, Bilgili E. Hybrid nanocrystal–amorphous solid dispersions (HyNASDs) as alternative to ASDs for enhanced release of BCS Class II drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2019;145:12-26.

17. Rahman M, Ahmad S, Tarabokija J, Bilgili E. Roles of surfactant and polymer in drug release from spray-dried hybrid nanocrystal-amorphous solid dispersions (HyNASDs). Powder Technology. 2020;361:663-678.

18. Jamzad S, Fassihi R. Role of surfactant and pH on dissolution properties of fenofibrate and glipizide—A technical note. AAPS PharmSciTech. 2006;7(2):17-22.

19. Azad M, Afolabi A, Bhakay A, Leonardi J, Davé R, Bilgili E. Enhanced physical stabilization of fenofibrate nanosuspensions via wet co-milling with a superdisintegrant and an adsorbing polymer. European Journal of Pharmaceutics and Biopharmaceutics. 2015;94:372-385.

20. Bilgili E, Li M, Afolabi A. Is the combination of cellulosic polymers and anionic surfactants a good strategy for ensuring physical stability of BCS Class II drug nanosuspensions? Pharmaceutical Development and Technology. 2016;21(4):499-510.

21. Knieke C, Azad MA, Davé RN, Bilgili E. A study of the physical stability of wet media-milled fenofibrate suspensions using dynamic equilibrium curves. Chemical Engineering Research and Design. 2013;91(7):1245-1258.

Thank you,
Any Questions?