

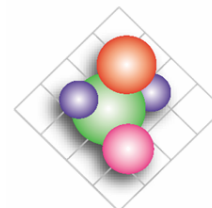
Pharmaceutical Manufacturing for Reduced Environmental Impact

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IIT MMAE Symposium on Sustainability and
Product Development

McCormick Tribune Campus Center
Illinois Institute of Technology
Thursday and Friday, August 7 and 8, 2008



**ENGINEERING RESEARCH CENTER FOR
STRUCTURED ORGANIC PARTICULATE SYSTEMS**

RUTGERS UNIVERSITY
PURDUE UNIVERSITY
NEW JERSEY INSTITUTE OF TECHNOLOGY
UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ

Pharmaceuticals

Benefits

– Health

- *Pharmaceuticals have contributed to a 30 year increase in average life span during the last century*
- *Pharmaceuticals are the main line of defense against new diseases*

– Manufacturing

- *Pharmaceutical Industry is remaining area of US economic strength*

But what about the unused pharmaceutical ...



Sources for Unused Pharmaceuticals

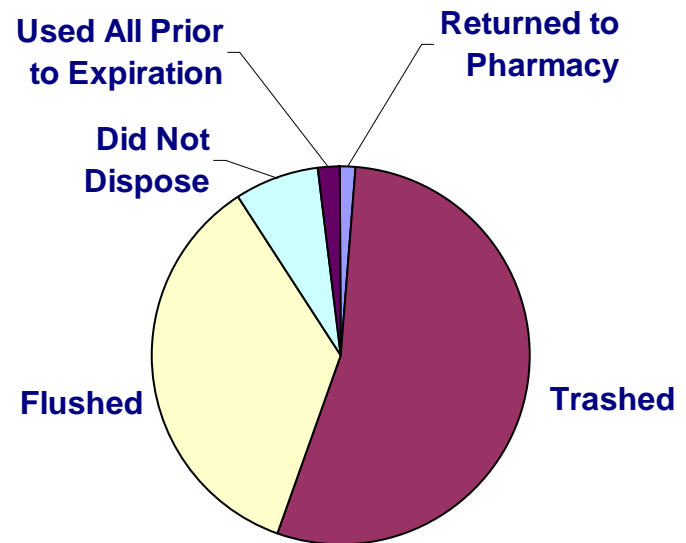
- Before reaching the Market
 - *Batches not in compliance*
- After Reaching the Market, typically pharmaceuticals are not entirely consumed for one of three reasons:
 - *Change in prescription*
 - *Improvement in the patient's health or death*
 - *Daughton and Ruhoy estimate that orphaned medications from the deceased population alone account for as many as 19.7 tons of APIs disposed into U.S. sewage systems annually (Sci. Total. Environ. **2007**, 388, 137).*
 - *Expiration date passed*



Expired Medication Disposal Habits

500 patients surveyed:

- **54%** disposed of medications in the trash
- **35.4%** flushed drugs down the toilet or sink
- **7.2%** did not dispose of medications
- **2%** used all medication prior to expiration
- **1.4%** returned medications to the pharmacy



Main Risks of Improper Disposal Practices

- *Environmental impact*
 - *Accumulation in waterways → potentially harmful effects on wildlife*
- *Accidental ingestion (children & elderly)*
 - *78,000 children/year under 5 treated for unintentional medication poisoning in U.S.*
- *Illegal use or theft*
 - *Appropriation of pharmaceuticals by family and friends, workers in homes, and burglars*
- *Unnecessary accumulation & waste of health care \$\$\$*



If Improperly disposed ... Pharmaceuticals in the Environment

- U.S. Geological Survey monitoring studies National Reconnaissance Study 1999-2000
 - 139 streams analyzed in 30 states
 - Contaminants identified in 80% of these streams
 - 82 contaminants (many were PPCPs) identified
 - Co-occurrence common; average 7 distinct contaminants identified per stream

(Kolpin et al. “Pharmaceuticals, Hormones, & Other Organic Wastewater Contaminants...” *Environmental Science & Technology*. 2002.)
- Flow streams at a drinking water plant 2004
 - Analyzed for 106 contaminants in 24 samples from a drinking water treatment facility
 - 40 contaminants detected; 34 contaminants detected in >10% of samples within the facility.
 - Some medicines also found in finished water

(Stackelberg et al. “Persistence of pharmaceutical compounds...” *Science of the Total*)



How *Manufacturing Strategies* can reduce the impact on *Environment*?

- Improve current manufacturing operations tending to reduce out of spec batches during production
 - *Aligned FDA Quality by Design (QbD) initiative towards a shifting manufacturing paradigm*
- Introduce flexible and dosage personalized forms to reduce the stock unused medications





FDA's view on QbD, Moheb Nasr, 2006

FDA View on Quality by Design (QbD)

- The product is designed to meet performance requirements
- The process is designed to consistently meet product critical quality attributes
- The impact of formulation components and process parameters on product quality is understood
- Critical sources of process variability are identified and controlled
- The process is continually monitored and updated to assure consistent quality over time



Addressing some of the challenges in Pharmaceutical Manufacturing

- **NSF-ERC** (Rutgers, Purdue, NJIT and UPRM)
 - *Recently funded by the National Science Foundation an Engineering Research Center on Structured Organic Particle Systems (C-SOPS), which is focused on advancing the scientific foundation for the optimal design of pharmaceutical products with advanced functionality while developing the methodologies for their active control and manufacturing.*
- **NIPTE**
 - *National Institute for Pharmaceutical Technology and Education. Developing an educational and R&D road map for manufacturing of pharmaceutical products*



ERC-SOPS Research

Levels:

Technology Integration

Enabling Technology

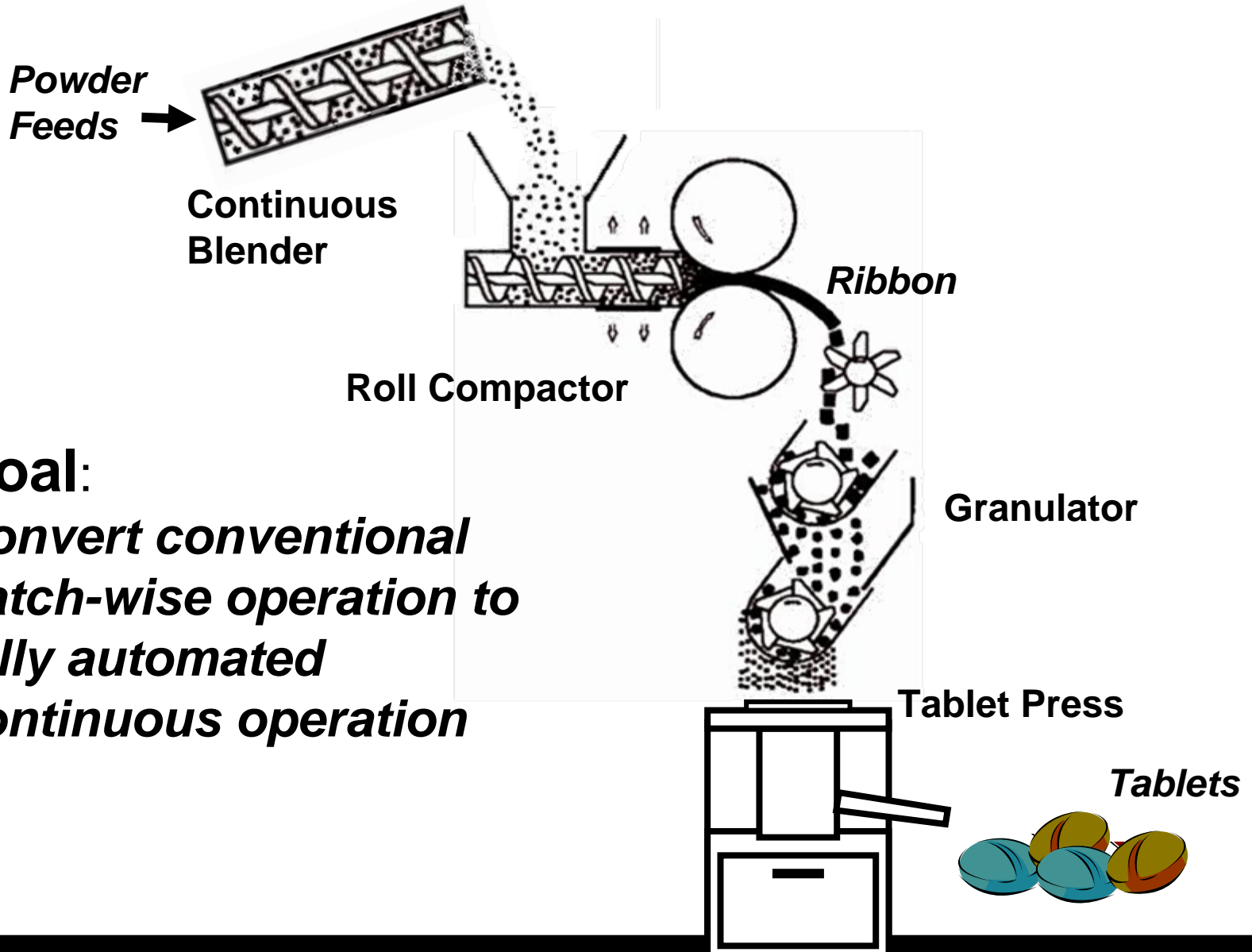
Fundamental Science

<div style="text-align: right;">Test Beds</div> <div style="text-align: left;">Thrusts</div>	Test bed I: Continuous Manufacture of Tablets	Test Bed II: Strip Films	Test Bed III: Multilayer Architectures via Drop-on- Demand
Thrust I: Manufacturing Science	<div style="border: 2px solid black; border-radius: 20px; background-color: #90EE90; padding: 20px; display: inline-block;"> <p style="font-size: 2em; margin: 0;"><u>Projects</u></p> </div>		
Thrust II: Composites Structuring and Characterization			
Thrust III: Particle Formation and Functionalization			

Test Bed themes: Conversion from batch to continuous
Manufacturing of personalized dosage



Test Bed 1: Continuous Manufacturing of Tablets



Goal:
Convert conventional batch-wise operation to fully automated continuous operation



TB1: Continuous Manufacturing of Tablets

Impact

- *Product quality*
 - *Mitigate effects of segregation & agglomeration*
 - *Improved Compact Uniformity*
- *Cost Reduction*
 - *Less material wastage*
 - *Smaller size equipment*
- *Simplified process scale up*
 - *Avoid full dynamic range*
- *Improved manufacturing*
 - *Active process control*
 - *Robust operation*

Technical challenges

- *On-line sensing*
 - *Content uniformity*
 - *Density*
 - *Tablet hardness*
 - *Soft sensors*
- *Predictive models*
 - *Given material properties, predict set points to achieve desired product quality*
- *Process automation*
 - *Models to predict control adjustments given deviations*
 - *Controller design*
 - *Trend monitoring, incipient fault identification & correction*

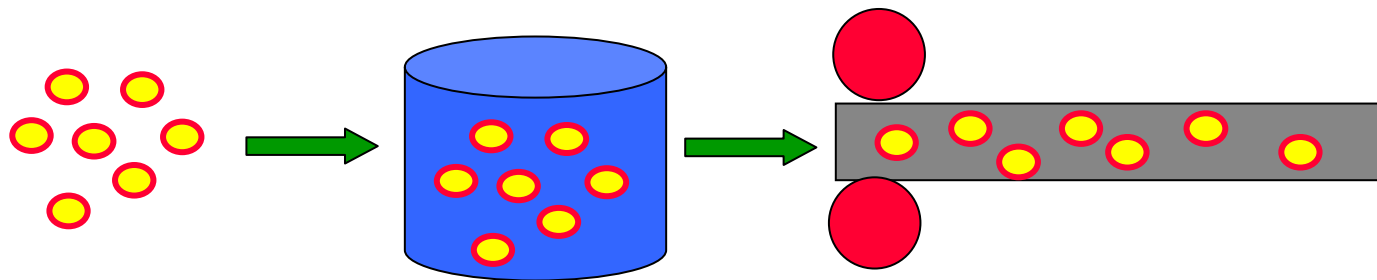


Test Bed 2: Strip Films for Controlled Substance Delivery

Goal: Continuous manufacturing of oral dosage form using engineered particles dispersed in controlled fashion in gel

Impact

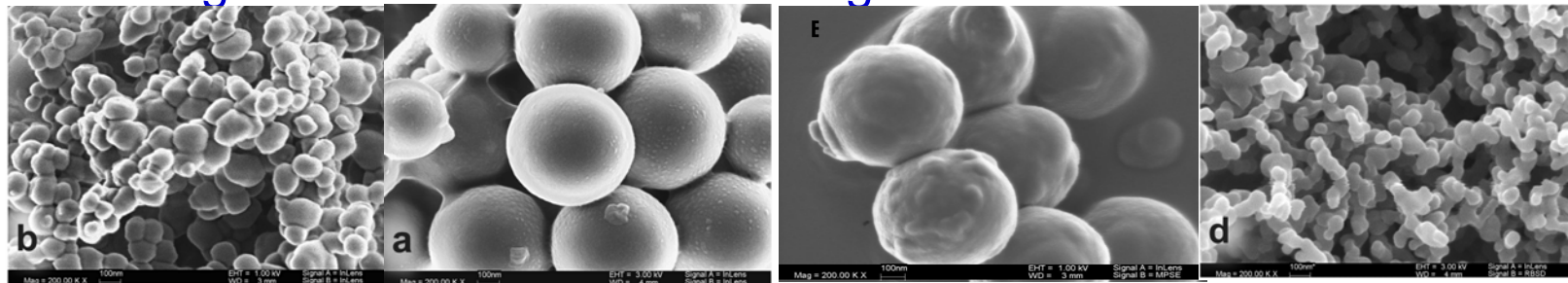
- Engineered particle dispersion into gel allows consistent loading of low dosage and/or low solubility actives
- Drug dissolution controlled by particle size & coating
- Processing of nano particles within suspensions avoids contamination/safety issues of dry powder handling
- Manufacturing is inherently continuous
- Full (100%) automated inspection possible



Test Bed 2: Strip Films for Controlled Substance Delivery

Technical Challenges:

- Understanding of impact of material properties on selection of particle formation method
- Modeling of particle formation processes
- Control of particle size, size distribution & stability
- Suspension stability & homogeneity
- Control of film formation process
- On-line sensing via spectroscopic & vision systems
- Integrated control and monitoring



Test Bed 3: Mini-Manufacturing via Drop-on-Demand

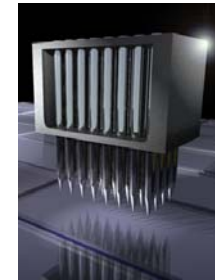
Goal: *Integrated application of drop-on-demand for bottom-up formation of 3-D structured dosage on edible substrate*

Impact

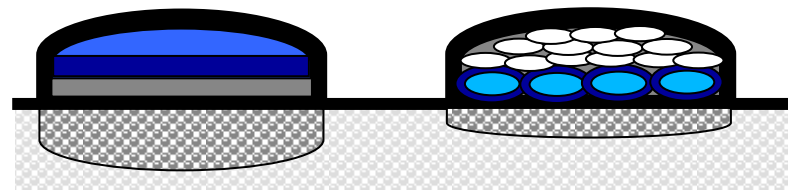
- Compact small scale manufacture for clinical trial quantities, hospital dispensaries, military, 3rd world
- Portable formulary of multiple drugs in cassette form
- Customized, patient specific dosage formulations
- 3-D structures consisting of multiple active components



Ink-jet printing

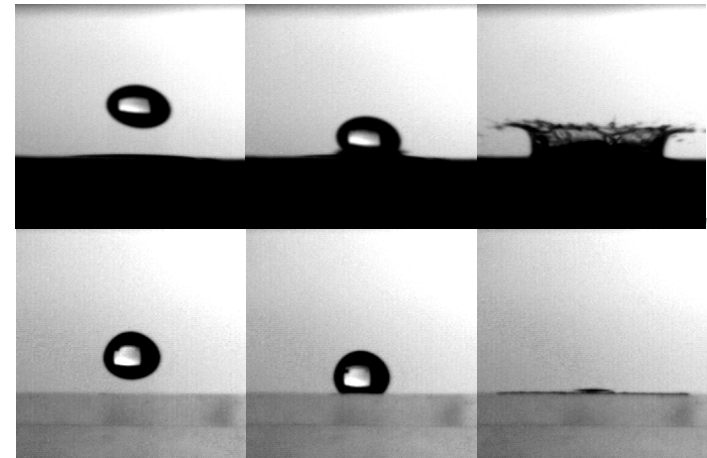
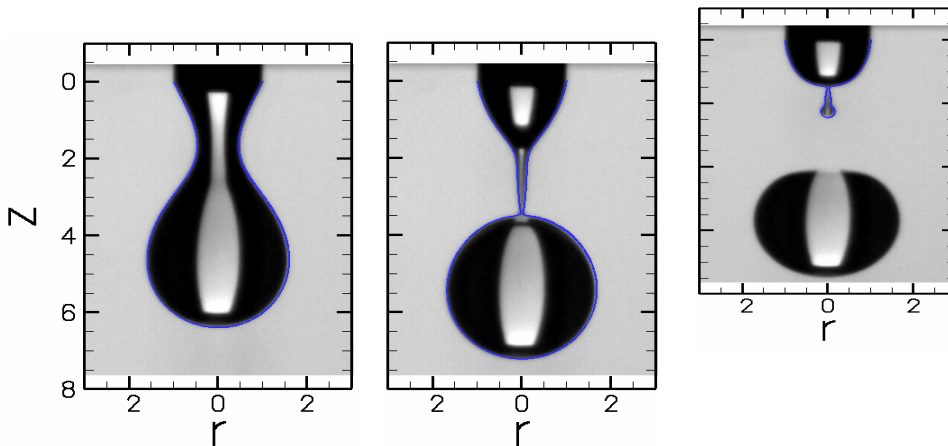


Micro-arraying



Technical Challenges:

- Understand & predict formation of drops of uniform size from complex fluids
- Understand impact & spread of drops of complex fluids on solid substrates
- Modeling of deposition of multilayered structures
- Chemical stability of liquid formulations during processing and on interaction with substrate.
- Crystal form control during processing



Conclusions

- Improving current Pharmaceutical Manufacturing processes and technologies can reduce the environmental impact by diminishing the rejected batches
- Introducing new delivery dosages can reduce the amount of unused dosages which are mostly improperly disposed
- Ample opportunities for technology development and *local* (US) manufacturing

