Industrial Encapsulation Processing

Particles 2009 Conference
Micro and Nano Encapsulation

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Overall Objective of this Presentation

- Introduce you to large scale industrial production of controlled release dosage forms.
- Describe current processes, how they arose and why they are commercially and technically successful.
- Suggest means for developing a commercially successful business based on existing and novel processes.
Agenda

- Introduction
- Terminology and Basic Concepts
- Major Processes
- Former Process Development (Idealized)
- Methodology for Process and Product Development
- Conclusion, Meeting the Objective
Agenda

• Introduction

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Introduction

Consumer Products

The Big Picture

- Worldwide Interest
- Difficulties Obtaining Information
- Information Overload
- Idea Overload
- Non-Glamorous Topic
Introduction
Introduction

Worldwide Interest

Microencapsulation
Mikroverkapselung
マイクロカプセル形
Microencapsulados
Introduction
Introduction

Everyone has a great idea that won’t work.
Trails, gravel seek common ground
Recreation tries to keep pace with Ewing Mesa’s changing face
By Missy Votel

Speegle said that a recent geological study concluded there were 160 acres of gravel on the mesa, a veritable mother lode.

“Really, that gravel is a gold mine,” he said, adding that it also is close to the surface, making it even more valuable for its ease of extraction.

“Every time we drive on a road there is gravel underneath it. We’re all using it”.

“...the appetite is only going to get bigger”.
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Anything that can be misunderstood has been misunderstood.
Terminology & Basic Concepts

- Controlled Release
- Basic Structures
- Core/Wall
- Release Profiles
- Science to Technology
- History
Terminology & Basic Concepts

Definition: Controlled Release

- Controlled Delivery
- Sustained Release
- Continuous Release
- Delayed Action
- Extended Action
- Spaced Release
- Long-Play
- Prolonged Action
- Slow Acting
- Gradual Release
- Timed Release
- Targeted Release
Terminology & Basic Concepts

Microcapsule Basic Structures

- Double-walled
- Simple
- Multi-Core
- Irregular
- Trigger
- Matrix

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Terminology & Basic Concepts

Core/Wall

Core
Internal Phase
I.P.
Active, AI
Encapsulate
Payload
Fill

Wall
Coating
Shell
External Phase
Membrane
Terminology & Basic Concepts

Release Profiles

1st order

Zero order

Delay
Terminology & Basic Concepts

Technology

Chemical Processes
- Polycondensation (dispersion, interfacial, Suspension)
- Polymerization (dispersion, emulsion, Suspension)

Physicochemical Processes
- Chelation
- Coacervation
- Solvent Removal
- Suspension Crosslinking
- Vesicle Formation

Physicochemical Interactions & Phase Separation

Mechanical Processes
- Coating
- Extrusion
- Fluidized Bed
- Micronization
- Spraying
- Vapor Deposition

Physics and Chemistry

Polycondensation (dispersion, interfacial, Suspension)
Polymerization (dispersion, emulsion, Suspension)
Polymerisation
Physicochemical Interactions & Phase Separation
Gelation Chelation Crosslinking
Fluid Deposition
History of Controlled Release

1850 - 1950

- Pan coating U.S. Patent 159,899
- Spray drying of emulsions & mixtures Danish patent 36009

Patents and Inventions

- 1890 (estimated) Fillable hard gelatin capsules
- 1934 Opposed soft gelatin sheets, Robert Scherer U.S patent 1,970,396
Terminology & Basic Concepts

History of Controlled Release

1950 - 2000

NCR Coacervation
U.S. Pat. 2,800,457

Sunkist Extrusion
U.S. Pat. 2,809,895

1965

Bottom Spray Fluid Bed
Dale Wurster
U.S. Pat. 3,196,827

Urea/Resorcinol/Formaldehyde
U.S. Pat. 3,755,190

1970

Urea Formaldehyde
In-situ polymerization
U.S. Pat. 3,516,846

1973

Microporous Open Structures
R. Wan
U.S. Pat 4,690,825

1971

Interfacial Polymerization
U.S. Pat. 3,577,515

1980

Microporous Open Structures
R. Chromacek
U.S. Pat. 4,855,127

1987

1990

2000

Patents and Inventions

1950

Liposomes

1951

1960

Organic Phase Separation
U.S. Pat. 3,415,758

1968

1971

Interfacial Polymerization
U.S. Pat. 3,577,515

1980
Terminology & Basic Concepts

Test Parameters

Pharma
- Standard Apparatus
- Standard Media
- Standard Temperatures
- Standard pH’s
- Standard Methods

C & DP
- Methods Differ by Field
- Wildly Variable Media
- Wide Temperature Ranges
- Very High &/or Low pH
- Unique Test Methodology (often no standard available)
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Major Processes

• Selection of Process

• Selected Process
  - Coacervation
  - Fluidized Bed (Wurster)
  - Interfacial Polymerization
  - Melt Extrusion (Injection)
  - Pan Coating
  - Spray Drying
  - Urea/Formaldehyde & Related Processes
  - Seed Coating
Major Processes

**Selection of Process**

- Neglect the value of the core material
- Commercial significance, social significance, consequential value
- Tonnage/Year, not kilograms/batch
- Sustained economic success and marketability
On July 5, 1955, Green received a patent for the process of microencapsulation.

Green first applied his new invention to typing paper. He used microencapsulation to manufacture the first carbon-free carbon paper in the world.

Green and the National Cash Register Company eventually applied microencapsulation to other products. Microencapsulation allowed for the creation of scratch-and-sniff advertisements.

Perhaps the most important contribution of microencapsulation was to the field of pharmacy. Microencapsulation allowed scientists to develop pills that slowly released medication into a patient, allowing the medicine to be dispensed gradually over several hours.

"...it's the quality of the research idea, the soundness with which that problem is analyzed and approached."
### Simple Coacervation

- Characterized by involving one polymer in the coacervate
- Often called “simple” coacervation
- Phase separation governed by repulsive forces
- Can be induced by changes in chemical and physical conditions or a combination of factors: $\Delta$concentration, $\Delta$pH, $\Delta$T°C ionic strength, $\Delta$solvent
Complex Coacervation

- Characterized by involving more than one polymer (+ and – charged)
- Attraction of oppositely charged polyelectrolytes but also involves hydrogen bonding interactions
Major Processes

Diagram of Complex Coacervation

- Make a dispersion of IP in the vehicle phase (Typically Aqueous)
- Coacervation induced and deposition of liquid polymeric wall material
- Solidification of wall material
- Hardening & chemical after treatment
Coacervation

Major Processes
Major Processes

Coacervation
Major Processes

Fluidized Bed Coating
Major Processes

Fluidized Bed

1. Custom Nozzle
2. Screen Retainer
3. Partition Spacer
4. Partition Support Ring
5. Counterbalanced Tilting Cart
6. Redesigned Plenum Chamber
7. Humidity Injection
8. Process Air Dehumidification
9. High Efficiency Filters
10. Continuous Clean Filters
11. Baffled Air Flow
12. Digital Pump Control
13. High Temperature Design
14. HT Blower Cooler
15. Liquid Flow Monitor
17. Load Cell Mounted Tanks
18. Interchangeable Pumps
19. Heated Liquid Lines
20. Heated Nozzle
21. Process Air Chiller
22. High Pressure Blowers
23. HEPA Filtered Process Air
24. Improved Air Flow Control
25. Stainless Steel Frame
26. Improved Expansion Chamber
27. Process Air Flow Monitor
28. Suspended Plumb Deflector
29. GMP Gasketing
Fluidized Bed
Major Processes

Fluidized Bed
Major Processes

Interfacial Polymerization

Water + Surfactant

Hydrocarbon Phase + Monomer

Stirred Mixture (defined shear) o/w

Monomer + Water + Base

Microcapsules

Ploymer Wall

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Major Processes

Interfacial Polymerization

- Diacyl chlorides + Diamines → Polyamides
- Diisocyanates + Diamines → Polyureas
- Diisocyanates + Diols → Polyurathanes
- Diacyl Chlorides + Diols → Polyesters
- Bischloroformates + Diamines → Polycarbonates
Major Processes

Interfacial Polymerization

PENNCAP-M®
MICROENCAPSULATED INSECTICIDE
EPA Registration No. 4581-292
RESTRICTED USE PESTICIDE
GENERAL INFORMATION
AND DIRECTIONS FOR USE
Major Processes

Melt Extrusion

Glass Encapsulation of Flavors

FIG. 3
Major Processes

Melt Extrusion

Glass Encapsulation of Flavors

TWIN SCREW EXTRUDER

Solids Conveying  Melting  Melt Pumping
Major Processes

Melt Extrusion
Major Processes

Pan Coating

PEAR-SHAPED  HEXAGONAL-SHAPED  SPHERICAL-SHAPED
Major Processes

“Pan” Coating
Major Processes

Pan Coating
Major Processes

Spray Drying
Major Processes

Spray Drying
Major Processes

Spray Drying

Temperature

T$_{in}$ Air

T$_{out}$

Droplet

Constant Rate

Top Distance Outlet
Major Processes

Spray Drying
Major Processes

Urea-Formaldehyde

- United States Patent Office
- Patent number 3,516,846
- Filed July 25, 1966
- Patented June 23, 1970
- Title: MICROCAPSULE—CONTAINING PAPER
- Gale E. Matson, Minneapolis, Minnesota, USA
- Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, US
- No international equivalent patents
Major Processes

Urea-Formaldehyde

Basic Process

Pre-Polymer Vessel

Reactor

Dispersion Vessel
Major Processes

Microcapsule surface morphology

The rough outer surface is composed of UF nanoparticles (~150 nm) attached to the microcapsule shell.

Reference: Brown et al., “In Situ Poly(urea-formaldehyde microencapsulation of dicyclopentadiene”
Major Processes

Melamine-Formaldehyde

- United States Patent Office
- Patent number 4,100,103
- Filed December 30, 1976
- Patented July 11, 1978
- Title: CAPSULE MANUFACTURE
- Peter L. Foris et al., Appleton, Wisconsin, USA
- NCR Corporation, Dayton, Ohio, US
- Only one international equivalent patent: DE 2,757,528 Federal Republic of Germany
**Melamine-Formaldehyde**

- Application: production of microcapsules in big concentration, >40%.
- Wall: ~20% of microcapsule volume.
- Microcapsule size: 1 to 15 μm diameter.
- Core: water-insoluble or substantially water-insoluble liquids.
- Wall material: melamine-formaldehyde.
**Major Processes**

**Melamine-Formaldehyde**

- Dissolve a suitable EMA [poly(ethylene-co-maleic anhydride)] into water at 55°C.
- Add the core material and reduce it to the desired droplet size.
- Separately prepare a heated solution of melamine in formaldehyde.
- Mix the two solutions together.
- After two hours, turn off the heat. Wait.
- “The world’s easiest microencapsulation system”
Lasso® MicroTech™, the straight Alachlor formulation with its wide crop use range and its superior micro-encapsulation technology, completes the Alachlor portfolio.
Major Processes

Seed Coating

- Seed Inlet
- Air Plenum
- Rotor
- Drive for Spinning Disk
- Treatment Inlet Into Spinning Disc
- Seed Movement
“Since its establishment 19 years ago, over 50,000,000 lbs of coated seed has been processed by the company with Bailie again recalling the “early years” when less than 3,000,000 lbs were produced in the first six years of operation.”
Outline

• Introduction
• Terminology and Basic Concepts
• Major Processes
• Former Process Development (Idealized)
• Methodology for Process and Product Development
• Conclusion, Meeting the Objective
## Former Process Development

<table>
<thead>
<tr>
<th>BASE TECHNOLOGY</th>
<th>YEAR</th>
<th>ADDITION</th>
<th>CONTROLLED RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Extrusion of Synthetic Fibers into a Bath</td>
<td>1920</td>
<td>Flavor Oils, 1957</td>
<td>Sunkist Process</td>
</tr>
<tr>
<td>4. Emulsion Polymerization</td>
<td></td>
<td>Add Oil to Polymer 1989</td>
<td>APS Polytrap</td>
</tr>
</tbody>
</table>
## Former Process Development

<table>
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<th>ADDITION</th>
<th>CONTROLLED RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Briquetting (Solids Compaction)</td>
<td></td>
<td>Add Ribbons, Liquid Core</td>
<td>RP Scherer</td>
</tr>
<tr>
<td>7. Droplet Stabilization With Surfactants</td>
<td></td>
<td>Form a Massive Wall</td>
<td>Coacervation 1951</td>
</tr>
</tbody>
</table>
## Former Process Development

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<th>YEAR</th>
<th>ADDITION</th>
<th>CONTROLLED RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Polycondensation of Nylon</td>
<td>&gt;1930’s</td>
<td>Water Medium</td>
<td>Interfacial Polymerization</td>
</tr>
<tr>
<td>10. U/F Resins</td>
<td>&lt;1920</td>
<td>Coacervation Formation</td>
<td>U/F, Polymethyleneurea</td>
</tr>
<tr>
<td>11. Pan Coating</td>
<td>19th Century</td>
<td>Specialty Coating, e.g. enteric wall “tunnel coating”</td>
<td>Enhanced Release Continuous Process</td>
</tr>
</tbody>
</table>

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Methodology for Process and Product Development

A Manufacturer of Microcapsules

• How to Begin
• Determining a Process(s)
• Creation of New Processes
How to Begin, Part I

• Start with a problem (opportunity) brought to you by a potential customer

• Qualify the customer’s ability to pay for:
  1. Development if needed
  2. Small production quantities

• Avoid “customers” who propose: “I cannot pay you now, but I’ll buy a whole lot from you in the future if it works.”

• Never use the word “sample”. Use “engineering trial”.

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Process & Product Development

How to Begin, Part II

• Do not go out randomly looking for customers. Avoid proposing solutions looking for a problem.

• Avoid technical successes and commercial failures.

• Here’s how to succeed: Use a systems approach, first starting with a timeline.
Overall Development Principles

- Use a systems concept
- Avoid intuition – use release profile. Be quantitative
- Seek help from experienced professionals in controlled release
- Assign value to applications know-how (formulation experience)
Not only is there but one way of doing things rightly, but there is only one way of seeing them: and that is, seeing the whole of them.
Timeline

- Manufacture (Product & Process Economics)
- Suitable Formulation (Process Selection)
- Packaging
- Distribution (Environmental & Long-Term Product Stability)
- Consumption (Desired Controlled Release)
Process & Product Development

Initial Considerations

- Why control the release?
- Can a controlled release dosage form be avoided?
  Reformulate
  Simple matrix encapsulation
- Process selection is a means to an end
- Avoid water, especially static equilibrium
- Cost analysis
  Process cost
  Materials savings/losses
  Intangible factors
Determine a Release Mechanism

- Diffusion ------never “perfect”
- Fracture ------burst effect, dumping
- Ablation ------abrasion, melting, dissolution
- Remember, you need the active ingredient released at:
  - The time you want
  - The place you want
  - The rate you want
Prior Public Knowledge of Existing Processes

- Patents
- Published Books
- Professional Societies, Journals
- Market Surveys
- Short Courses
- Advertising/Public Relations
- Existing Applications
Conclusion

- Learn from what has been done before
- Use overall development principles
- Lay out a timeline
- Consider the specifics and select a dosage form(s)
- Quantitatively determine a release profile of the dosage form in the product
If no well known process solves the problem (satisfies the customer), what then? Look for adaptable processes. Refer to in-house resources and documentation presumably retained as:

1. Oral tradition, laboratory note books
2. In-house library, comprehensive obscure
3. In-house documentation of applications know-how
4. Compendium of articles: unexpected results, unlikely results, forgotten technology, adaptable processes
**Reactive Spray Technology**

**Simple, robust, reliable process**

Sequential Control:
- Liquid Phase: precursor chemistry in solutions and dispersions
- Aerosol phase: droplet size, dispersion
- Reactor: time / temperature
- Post processing
- Reproducible

**Compositional flexibility**

- Inorganics, metals, metal oxides
- Supported catalysts and supports

**Ability to engineer critical properties**

- Active phase dispersion
- Particle morphology, porosity and size
- Surface area
- Surface chemistries and interfaces
Compendium of Articles


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• Introduce you to large scale industrial production of controlled release dosage forms.

• Describe these processes, how they arose and why they are commercially and technically successful.

• Suggest means for developing a commercially successful business based on these processes.
Thank you for your attention!

Presented by:
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