Recent Advances in Oral Granules and Bi-Layer Tablet Technologies, Solubility Enhancement Solutions, and Oral Disintegrating Tablet Applications

Michael J. Valazza, R.Ph.
Vice President
Global Modified Release Technologies
Email: michael.valazza@catalent.com
Catalyst + Talent.

Our name combines these ideas. From drug and biologic development to delivery technologies and supply solutions, we are the catalyst for your success.
As the #1 drug development and delivery partner in the world, we provide leading development solutions, advanced delivery technologies and innovative supply solutions to the global pharmaceutical, biotech and consumer health industries.

Whether you are looking for a single, tailored solution or multiple answers throughout your product’s lifecycle, we can improve the total value of your treatments—from discovery to market and beyond.

WHY CATALENT? Unrivaled experience, deepest expertise and a track record of market success on a global scale.

We are the #1 industry partner in the development and formulation of drugs, biologics and consumer health products and a world leader in drug delivery technology.

We partner with 90 of the top 100 pharmaceutical and 44 of the top 50 biotech companies, as well as hundreds of smaller innovators.

We operate 20+ global sites serving 1,000+ customers in over 100+ countries.

We support 40% of recent new U.S. drug approvals and are now working on 500+ new development programs.

We use a multi-faceted approach to improve bioavailability, therapeutic profiles and patient adherence.

We are fully dedicated to high standards of quality, cGMP leadership and LEAN operational excellence.

Presentation Overview

1. OSDrC® OptiDose™ Concept – an advancement in tab-in-tab and bi-layer tablet technology
2. Developing Better Treatments for Poorly Soluble Compounds with OptiMelt™ HME
4. Appendix
The OSDrC® OPTIDOSE™ Concept

An advancement in tab-in-tab and bi-layer tablet technology
Single-step manufacturing opens the door to a host of new formulations.

OsDrC® OPTIDOSE™

more products. better treatments. reliably supplied.™

OsDrC® OPTIDOSE™ Technology
One-Step Dry-Coating

Single-step manufacturing opens the door to a host of new formulations

• An innovative first-of-its-kind manufacturing process
• Newly developed rotary punch tableting machine
• Research and technical collaboration between pharmaceutical manufacturer and tableting machine manufacture
OSDrC® OPTIDOSE™ Tablet Press

### PAVG 0554SW7FZ-EDC7F6

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Number of punches</td>
<td>54</td>
</tr>
<tr>
<td>Initial pressure</td>
<td>10 kN</td>
</tr>
<tr>
<td>Secondary pressure</td>
<td>10 kN</td>
</tr>
<tr>
<td>Tertiary pressure</td>
<td>50 kN</td>
</tr>
<tr>
<td>Revolutions</td>
<td>10-35 min⁻¹</td>
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<tr>
<td>Production capacity</td>
<td>32,400-113,400 Tab hr⁻¹</td>
</tr>
<tr>
<td>Dimensions (HxWxD)</td>
<td>2250x1554x1554 mm</td>
</tr>
<tr>
<td>Weight</td>
<td>8.0 t</td>
</tr>
</tbody>
</table>
The Key to OSDrC® OPTIDOSE™ Manufacturing Technology: Variable Double-Punch Configuration
Process Flow for an OSDrC® OPTIDOSE™ Tablet

- Three individual hoppers containing bulk powders
- Excess powder is removed between each layer
- First two layers receive a light compression
- Thieving mechanisms at each stage to continuously monitor process
Basic Structure of an OSDrC® OPTIDOSE™ Tablet

Outer layer forms sides and top

Active pharmaceutical ingredients form core

Outer layer forms base
Representative Punches for OSDrC® OPTIDOSE™

Various tablet configurations can be produced simply by changing punches.
OSDrC® OPTIDOSE™ Technology: Flexibility to Improve Your Treatments

- OSDrC® OPTIDOSE™ technology
  - the broadest range: controlled release, combination products (tablet-within-a-tablet and pellets-within-a-tablet) and dividable tablets
  - optimized dosing, therapeutic, and plasma release profiles to meet patient needs in a high quality, one step manufacturing process.

- Broad Range of Tablet Options:
  - Bi-Layer Tablets
  - Dividable Tablets
  - IR/ER Combination Tablets
  - Combination Products (multiple API in single tablets)
  - Direct Compression Orally Disintegrating Tablets (ODT)
  - Pulsatile Release Tablets
Three Enabling Technologies comprise OSDrC® OPTIDOSETM

One-Step Dry-Coating Technology
Supports single-step manufacturing of pharmaceutical products

Accurate & Flexible Control
Technology allows accurate and flexible positioning of cores

Poor-Compressibility Encasing
Technology allows incorporation of core ingredients with poor compressibility
One-Step Dry-Coating Technology

• Supports single-step manufacturing of pharmaceutical products
  • Ultimate one-step compression system
  • Permits commercial scale production of conventional cored tablets
  • Requires no separate core preparation or supply
  • Permits production of a broad spectrum of high-quality formulations at low cost
  • Potential replacement for sugar- or film-coated tablets
Accurate & Flexible Control Technology

• Allows accurate and flexible positioning of cores
  • Allows positioning of any number of cores
  • Allows positioning in various configurations
  • Permits release control by varying either the positioning of core or thickness of coating
  • Permits commercial-scale production of cored tablets without misaligned cores
Poor-Compressibility Encasing Technology

- Allows incorporation of core ingredients with poor compressibility
  - Allows incorporation of pharmacological agents with poor compressibility (e.g. pure API with a flow aid)
  - Incorporation of pellets in the core permits use as a replacement for capsules
  - Permits development of oral rapid disintegration tablets (ODT) and various other innovative formulations
Delivery Capabilities of OSDrC® OPTIDOSE™

**Controlled Release**
- Positioning technology enables control over the release of the API by the altering thickness of the outer coating.

**Divided Core**
- Since the core remains fully encased in the coating even when the tablet is divided, the intended release profile remains unaffected by dividing the tablet.

**Pellet Core**
- By using pellets in the core instead of powders, drugs that normally must be formulated as capsules can be produced as tablets.

**Thin Coated**
- Able to produce cored tablets with extremely thin coats in a one-step process and can replace sugar and film-coated tablets, substantially reducing manufacturing stages and production costs.

**Variable Core**
- Tablets do not have to be round. The shape of the core, coating thickness, and tablet configuration can be varied simply by changing the punches.
Controlled Release Based on Thickness of Outer Coating Layer

**OSDrC® OPTIDOSETM** makes it possible to control API release by altering the thickness of the outer layer.

Advantages over film-coated tablets include:

- Simplified manufacturing process
- No solvents required
- Low manufacturing cost
- Simplified process control
Developing Better Treatments for Poorly Soluble Compounds with OptiMelt™ HME

A solubility enhancement solution
Bioavailability enhancement represents the biggest challenge in oral drug delivery

What is your biggest challenge in oral drug delivery/formulation development?

N=12

Bioavailability enhancement

“We are seeing more poorly soluble drugs in early phase development. Most of the compounds I have right now are poorly soluble”

– VP, Pharmaceutical Development

“It can be quite resource intensive to develop formulations for poorly-soluble drugs. The problem is most severe when the molecule has both low solubility and high-dose”

– Exe. Director, Pharmaceutical R&D

“Historically, our infrastructure is based on conventional technologies. We don’t have enough capacity and capability in new technologies that address bioavailability issues”

– Director, Formulation Development

SOURCE: Mckinsey & Company Customer interviews
Drug Delivery Technology Platform -
What attributes are needed to capture full value?

An effective solution – delivers drug precisely, reproducibly & safely

Fully integrated solution – equipment, materials, human resource from End-to-End

Compliant solution – equipment, controls, scientific knowledge are current & approvable

Exclusive solution / Freedom to Operate – IP or technical barriers to competition,

Operational solution – acceptable unit dose cost
## Technology Platform Attributes – Hot Melt Extrusion

<table>
<thead>
<tr>
<th>Critical Attributes</th>
<th>OptiMelt™</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An effective solution</td>
<td>• HME dispersions achieve a specific solubility increase in vivo &amp; utilize GRAS excipients</td>
</tr>
<tr>
<td>• Fully integrated solution</td>
<td>• HME is a continuous process suited for scale-up, and finished dosage forms may be made using conventional equipment</td>
</tr>
<tr>
<td>• Compliant solution</td>
<td>• Numerous oral products and devices have been filed with regulatory agencies</td>
</tr>
<tr>
<td>• Exclusive solution</td>
<td>• HME technology requires significant know-how to commercialize. The drug delivery profile may be patentable</td>
</tr>
<tr>
<td>• Operational solution</td>
<td>• Proven in pharma &amp; other industries as a robust process readily integrated into a manufacturing operation</td>
</tr>
</tbody>
</table>
OptiMelt™ HME Technology Platform

- GMP Bench to Pilot to Commercial scale, with global capabilities
  - Schorndorf, Germany and Somerset, New Jersey

- Broadest selection of downstream processing technologies, co-located with OptiMelt™ hot melt extrusion

- Integrated solutions provider, with over 75 years of industry experience
  - Development, formulation, scale-up, manufacturing, packaging

- Formulation acceleration and optimization with open Catalent-BASF bioavailability alliance
  - Broad range of excipients designed specifically to enhance solubility, particularly with hot melt extrusion
  - Non-exclusive arrangement to increase development efficiency and deliver better treatments for your molecules
The Amorphous State & Solid Dispersions
The Amorphous State of a Poorly Soluble API can generate enhanced dissolution and bioavailability due to increased apparent solubility.

The Amorphous State is a thermodynamically unstable relative to the crystalline state, which must be considered when developing a viable drug product.

The Amorphous State is formed by quenching from a melt (e.g. extrusion, granulation, capsule filling) or by controlled precipitation (rotary evaporation, spray drying, freeze drying).
Amorphous State Stabilization

- Amorphous State Stabilization is directed at preventing the initiation and/or reducing the rate of crystal nucleation and growth
- Regulatory Agencies will demand to see good control and understanding of this property
- Available strategies:
  - Avoid Tg reduction (e.g. moisture protection)
  - Elevate Tg significantly above room temperature
  - Chemical interactions (H-bonding, complexation)
  - Anti-nucleation methods (additives, surface modification)
Principles of Solid Dispersions

- **Solid Dispersions** are intimate mixtures of two (or more) components that typically have a high degree of miscibility.
- **Poorly Soluble Drug Dispersions** can achieve enhanced solubility by creating a **physically stable** and **processable non-crystalline form**.

Graphic source: Modified from BASF Pharma Ingredients & Services
OptiMelt™ Hot Melt Extrusion (HME)
Catalent’s OptiMelt™ hot melt extrusion addresses many needs

Approximately 40% of compounds on the market and >80% in development are poorly soluble (BCS class 2/4)

OptiMelt™ hot melt extrusion enhances solubility to bring more products and better treatments to market:

- Achieve desired efficacy, progressing more molecules to approval
- Differentiate product profiles; enhanced solubility
- Enhance patient compliance; reduced pill size/pill burden
- Optimize product performance; controlled release dosage forms
Catalent’s OptiMelt™ hot melt extrusion offers multiple benefits:

- Polymeric formulation matrix eliminates hydrolysis associated with wet agglomeration
- Suitability for sustained/controlled release or enteric coating
- Ability to form capsules, tablets, and multi-particulate dosage forms
- Control dose over a wide range of solubilities or dispersion concentrations
- Film capability for buccal dosage forms
- Very high drug loading up to 90%, decreases tablet size
- Robust, compact, high-throughput manufacturing with little waste
- Solvent-free processing, eliminating need for explosion-proof equipment
- Potential for patient abuse deterance formulations for certain compounds
- Potential for improved safety and side effect profile with lower dosing
- Taste-masking
OptiMelt™ HME Process Advantages

- Twin-screw design delivers excellent co-mixing of components
- Solvent free
- Process is well-controlled and scalable
- Good materials handling/containment
- Extrudate downstream processing is flexible
- Feasibility trials are easy to design and predictive
OptiMelt™ Hot Melt Extrusion – The Basics

- Twin-screw extruders with varying screw design / rotation achieve intimate mixing of drug and excipient
- Shear forces drive co-melting of drug and excipient
- Cooled mixture is a Solid Dispersion preferably containing amorphous (non-crystalline) drug
- Process opportunities
  - *Liquid drugs*
  - *Potent drugs*
  - *Labile drugs (solvent or moisture sensitive)*
Hot Melt Extrusion
Formulation Case Studies
Itraconazole – Kollidon® Solubility Enhancement

Solubility
ITRACONAZOLE + KOLLIDON VA 64

<table>
<thead>
<tr>
<th>Solubility [mg/L]</th>
<th>Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>physical mixture</td>
<td>8.1</td>
</tr>
<tr>
<td>10+90 extrudate</td>
<td>&gt;114</td>
</tr>
<tr>
<td>30+70 extrudate</td>
<td>&gt;124</td>
</tr>
</tbody>
</table>

SOURCE: Catalent Pharma Solutions – Schornforf site
Drug Release from Soluplus® Extrudates

*USP II, 50 rpm, 700 mL 0.1 N HCl, cut extrudates, 100 mg API (n=3)*

Very high drug loads (~50%) are possible without affecting the release profiles in a negative way

SOURCE: BASF Pharma Ingredients & Services
In vivo Performance of Solid Dispersion

*Itraconazole 10 mg / kg bw, beagle dogs (n=5) fasted state*

Massively increased bioavailability of itraconazole from Soluplus® extrudates compared to physical mixture and crystalline API

SOURCE: BASF Pharma Ingredients & Services
Stability of Solid Dispersion (3 month 40°C/75%RH)

USP II, 50 rpm, 700 mL 0.1 N HCl, granulated extrudates with 100 mg itraconazole, (n=3)

Drug release [%]

- after production
- after storage

After accelerated storage conditions dissolution rates are still comparable

SOURCE: BASF Pharma Ingredients & Services
HME: Capturing Value in the future

Relative to crystalline references, Amorphous Solid Dispersions improve bioavailability in 82%

HME provides the platform to realize this potential and capture the full value of your API

## Future of OptiMelt™ Platform Technology

### Critical Attributes

<table>
<thead>
<tr>
<th>Critical Attribute</th>
<th>OptiMelt™</th>
</tr>
</thead>
<tbody>
<tr>
<td>An effective solution</td>
<td>Expertise in selecting formulations that maximize solubility enhancement potential of Solid Dispersions</td>
</tr>
<tr>
<td>Fully integrated solution</td>
<td>Parallel R&amp;D effort on downstream processing (e.g. milling, compression, calendering)</td>
</tr>
<tr>
<td>Compliant solution</td>
<td>Leverages Catalent’s strong audit record. Working with reliable equipment and raw materials suppliers</td>
</tr>
<tr>
<td>Exclusive solution</td>
<td>Optimized HME formulations may yield IP for customers. Opportunities to combine with Catalent proprietary platforms</td>
</tr>
<tr>
<td>Operational solution</td>
<td>Fully integrated with other manufacturing, analytical and packaging services</td>
</tr>
</tbody>
</table>
In Summary – OptiMelt™: A Viable Platform Technology

- **An effective solution** – delivers drug precisely, reproducibly & safely
- **Fully integrated solution** – equipment, materials, human resource from End-to-End
- **Compliant solution** – equipment, controls, scientific knowledge are current & approvable
- **Exclusive solution / Freedom to Operate** – IP or technical barriers to competition,
- **Operational solution** – acceptable unit dose cost
Oral Disintegrating Tablets

Case studies of Zydis® fast-dissolve applications
Selegiline Zydis®
fast dissolve:
anti-parkinsons market
### Zydis Fast Dissolve buccal reformulation of Selegiline: Impact on Product Profile

<table>
<thead>
<tr>
<th><strong>Selegiline vs. Zelapar® fast-dissolve tablets</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet/Capsule Selegiline</strong></td>
</tr>
<tr>
<td>(traditional formulation)</td>
</tr>
<tr>
<td><strong>Zelapar formulated with Zydis fast-dissolve</strong></td>
</tr>
<tr>
<td>(innovative formulation)</td>
</tr>
<tr>
<td><strong>Lower Dose and Less Frequent Dosing</strong></td>
</tr>
<tr>
<td>5-mg doses, taken twice a day (BID). Pill or capsule that must be swallowed.</td>
</tr>
<tr>
<td>1.25-mg or 2.5-mg doses, taken once a day (QD). Tablet that dissolves in mouth within seconds, without water.</td>
</tr>
<tr>
<td><strong>Increased Bioavailability/Faster Onset of Action</strong></td>
</tr>
<tr>
<td>Tmax=1 hour. Digested in the gut, absorbed through the small intestine, processed by the liver.</td>
</tr>
<tr>
<td>Tmax=15 minutes. Innovative transmucosal drug delivery absorbed rapidly through the lining of the mouth directly into the blood.</td>
</tr>
<tr>
<td><strong>Lower Side Effect Potential</strong></td>
</tr>
<tr>
<td>Processed through the liver, producing undesired metabolites.</td>
</tr>
<tr>
<td>Significantly by-passes the liver, producing lower undesired metabolites.</td>
</tr>
</tbody>
</table>

Patients benefited from less frequent dosing, reduced side effects and shorter off-periods.
Zydis re-formulation improved patient compliance

Zelapar has highest Patient Compliance for Medicare patients, based on 12 month longitudinal patient records analysis.

Additional Cohort Compliance Improvements:
- All Ages, Female, All Payers: Zelapar 91.6%, Selegiline 83.7%
- Age 19-65, All genders, All Payers: Zelapar 87.3%, Selegiline 83.8%
Zelapar was launched as a branded generic and experienced substantial sales growth.

**US Sales – Selegiline Class: Anti-Parkinson Market**

- **Zelapar (Zydis)**
- **Eldepryl**
- **Selegiline Generics**

Data Source: IMS Health, 2010

- Zelapar 2010 $ market share: 39.3%
- Zelapar 2010 Unit market share: 10.1%
Allergy Market: Ebastine antihistamine
Zydis formulation of Ebastine for allergic rhinitis has delivered substantial market impact.

- **Launch of a new bioequivalent line extension increased overall sales for the marketer of this product.**

- **Zydis Product has maintained 50% overall unit market share for the entire ebastine class.**

- **83% of patients stated they preferred Zydis fast dissolve tablets vs. standard tablets.**

2011 IMS data
Allergy Market: Grazax® oral immunotherapy
GRAZAX oral immunotherapy: An innovative application of Zydis fast dissolve technology

First once-daily, oral allergy immunotherapy tablet (AIT) approved as a disease altering agent for grass allergy

Efficacy and compliance benefits shown in multiple studies.

Benefits over sub-cutaneous delivery:
- Patient preference for oral treatment (needle phobia)
- Improved patient adherence and compliance, supported by studies
- Prevents accidental needle sticks for patients and providers
- Eliminates needle (sharps) disposal

Value enhancement for patients, physicians and payers in management of this chronic condition

Positive Phase 3 results recently released for US approval
Catalent drug delivery technologies enhance product value by differentiating product profiles

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety / Tolerability</th>
<th>Payer Value</th>
<th>Dosage / Admin.</th>
<th>Indications/Populations</th>
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</thead>
<tbody>
<tr>
<td>• Increased bioavailability</td>
<td>• Targeted drug delivery</td>
<td>• Increased patient compliance</td>
<td>• Less frequent dose regimen (eg. Once daily vs. BID)</td>
<td>• Entire labeled patient population</td>
</tr>
<tr>
<td>• Faster onset of action</td>
<td>• Controlled drug plasma profile (pK)</td>
<td>• Reduction in patient pill burden</td>
<td>• Orally Disintegrating tablets - disperses in mouth without water in usually &lt;3 seconds</td>
<td>• Elderly patient segment</td>
</tr>
<tr>
<td>• Targeted drug delivery</td>
<td>• Reduction in first pass metabolism through the liver</td>
<td>• Extended and flexible dosing - lower cost to treat with increased convenience</td>
<td>• Tablets, Pills, Capsules</td>
<td>• Pediatric patient segment</td>
</tr>
<tr>
<td>• Sustained drug plasma profile (pK)</td>
<td>• Targeted drug delivery</td>
<td>• Poly-therapy with a single dose</td>
<td>• Orally Dissolving Powder - loose free flowing powder granules</td>
<td>• “On the go” lifestyle patient segment</td>
</tr>
<tr>
<td>• Controlled drug plasma profile (pK) to match specific treatment needs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

Catalent delivers Better Treatments:
Brodest range of Drug Delivery Technologies and deep Expertise
Catalent’s full range of value added services:
DELIVERY

SOFTGEL TECHNOLOGIES
- SOFTGEL CAPSULES
- VEGICAPS® CAPSULES

ZYDIS® & LYOPAN® FAST-DISSOLVE TECHNOLOGIES

CONTROLLED RELEASE TECHNOLOGIES
- OSDrC® OPTIDOSE™
- COMPLEX TABLETS
- COATED PELLETS & BEADS
- ADVANCED CAPSULES
- INNOVATIVE API SOLUTIONS
- COMBINATION SOLID PHARMACEUTICALS
- FIXED DOSE COMBINATIONS

INHALATION
- PRESSURIZED METERED-DOSE INHALERS
- DRY POWDER INHALERS
- NASAL SPRAYS
- NEBULIZED SOLUTIONS/SUSPENSIONS

INJECTABLES
- FORMULATION DEVELOPMENT
- PREFILLED SYRINGES
- CLICK-IN SAFETY DEVICE
- PROTECTOR SAFETY SHIELD SYSTEM™
- ASI™ AUTOINJECTOR
- PHASE I/II VIALS

CONSUMER HEALTH
SUPPLY

CLINICAL SUPPLY
GLOBAL COMPARATOR SOURCING
MANUFACTURING & BLINDING
PACKAGING & LABELING
ANALYTICAL SERVICES
DISTRIBUTION & WAREHOUSING

MANUFACTURING
SOFTGEL & VEGICAPS® CAPSULES
CONTROLLED RELEASE TABLETS
ZYDIS® & LYOPAN® FAST-DISSOLVE TABLETS
STERILE: BLOW/FILL/SEAL, IV BAGS, INJECTABLES

COMMERCIAL PACKAGING
BOTTLING
BLISTER PACKAGING
CUSTOMIZED BLISTERS/WALLETING
INJECTABLE PACKAGING & KITTING
SPECIALTY PRODUCT HANDLING

PACKAGING DELIVERY SOLUTIONS
INTEGRATED SUPPLY CHAIN
LATE-STAGE CUSTOMIZATION
PRODUCT LIFECYCLE MANAGEMENT
ANTI-COUNTERFEITING
DESIGN SOLUTIONS
PATIENT ADHERENCE SOLUTIONS
DELPOUCH® UNIT DOSE DELIVERY SYSTEM
MEDIA ENHANCED PACKAGING™ TECHNOLOGY
THANK YOU

To discover more, please continue on to the Appendix slides which follow.

discover more.

CATALENT PHARMA SOLUTIONS
14 SCHOOLHOUSE ROAD
SOMERSET, NJ 08873
+ 1 866 720 3148
www.catalent.com

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APPENDIX
OSDrC®
OPTIDOSE™
Technology
OSDrC® OPTIDOSE™ Tableting Process

Only the lower center punch slides down
Space is filled with powder for the coating, which becomes the base layer of the tablet; at this time, the lower outer punch acts as a die.
OSDrC® OPTIDOSE™ Tableting Process

Pre-compression by the upper and lower center punches
OSDrC® OPTIDOSETM Tableting Process
OSDrC® OPTIDOSE™ Tableting Process

Space is filled with powder for the API layer
OSDrC® OPTIDOSE™ Tableting Process

Pre-compression by the upper and lower center punches
OSDrC® OPTIDOSE™ Tableting Process
Die is filled with remaining powder for the coating
Pre-shaped API layer is pushed up inside the die; the API layer is now completely surrounded by the coating.
OSDrC® OPTIDOSE™ Tableting Process

Compression is completed by the upper and lower punches in flush alignment
OSDrC® OPTIDOSE™ Tableting Process

Finished tablet is released
OSDrC®
OPTIDOSE™
Tablets
Merits of Cored Tablet

- Permits controlled interaction of APIs
- Permits controlled release of API
- Can mask bitter taste of API
- Permits more visually appealing formulations

OSDrC® OPTIDOSE™ permits creation of various value-added tablet formulations
OSDrC® OPTIDOSE™ makes it possible to control API release by altering the thickness of the outer coating.

Advantages over film-coated tablets include:

- Simplified manufacturing process
- No solvents required
- Low manufacturing cost
- Simplified process control
OSDrC® OPTIDOSE™ makes it possible to control API release by altering the thickness of the outer coating.

Advantages over film-coated tablets include:

- Simplified manufacturing process
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Dividable Core Tablets

**Target drug release profiles can be maintained, whether the tablets are divided or not**

- **With conventional technology, enteric tablets could not be divided**
Dividable Core Tablets

Target drug release profiles can be maintained, whether the tablets are divided or not

- With conventional technology, enteric tablets could not be divided

Replacing Capsules with Tablets

Capsule Issues

- Do not facilitate dosage control (cannot be divided)
- Difficult to swallow
- Difficult to prevent tampering
- Relatively high manufacturing cost
Replacing Capsules with Tablets

Possible to encase pellets as a replacement for capsules

• Tests have obtained same release characteristics as capsules
Repeating Capsules with Tablets

Possible to encase pellets as a replacement for capsules

- Tests have obtained same release characteristics as capsules

Yuichi Ozeki
SKK company data (2004)
Accurate placement of multiple cores makes it possible to manufacture pulsatile release formulations.
Pulsatile Release Tablets

Accurate placement of multiple cores makes it possible to manufacture pulsatile release formulations.

Yuichi Ozeki, "The Nakai Award winner’s article" Development of one-step dry-coated tablets (OSDRC® OPTIDOSE™) and the study for its physical characteristics. Journal of Japan Society of Pharmaceutical Machinery and Engineering, Japan, vol 14/4 pp. 12-21 (2005)
Potential for a Host of New Formulations

- Oral rapid disintegration (OD) tablets
  
  Made possible by technology that permits encasement of core pharmaceutical powders in powder form
Potential for a Host of New Formulations

- Various core configurations

Various tablet configurations can be produced simply by changing double punches.
OSDrC® OPTIDOSE™ Data
**Core Misalignment**

**OSDrC® OPTISODE™** rotary tableting machines showed core alignment of less than 0.1mm, a level that is not considered significant to performance.

Yuichi Ozeki
"The Nakai Award winner’s article" Development of one-step dry-coated tablets (OSDrC® OPTIDOSETM) and the study for its physical characteristics, Journal of Japan Society of Pharmaceutical Machinery and Engineering, Japan. vol 14/4 pp. 12-21 (2005)
**Individual Coatings**

**OSDrC® OPTIDOSE™** rotary tableting machines showed the ability to produce individual coatings comparable to film coating.

![Graph showing percent coefficient of variation over tabletting time for different thicknesses of coatings.](image)

Yuichi Ozeki

Cross-contamination was an extremely low 0.03% 
OSDrC® OPTIDOSE™ can effectively control the interaction 
between the API and the coating excipient
The Amorphous State & Solid Dispersions
Amorphous State Structure

Hexagonal Close Packing
fraction of voids = 0.26

Random Close Packing
fraction of voids > 0.36

Amorphous State Thermodynamics

Higher Energy State of Amorphous phase is shown relative to Crystalline phase
Amorphous State Thermal Analysis

Differential Scanning Calorimetry of Amorphous Indomethacin API
The Amorphous State of a Poorly Soluble API can generate enhanced dissolution and bioavailability due to increased apparent solubility.

The Amorphous State is a thermodynamically unstable relative to the crystalline state, which must be considered when developing a viable drug product.

The Amorphous State is formed by quenching from a melt (e.g. extrusion, granulation, capsule filling) or by controlled precipitation (rotary evaporation, spray drying, freeze drying).
# Amorphous State Materials Characterization

<table>
<thead>
<tr>
<th>Critical Properties</th>
<th>Analytical Tools</th>
</tr>
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<tbody>
<tr>
<td>Absence of crystal lattice (no 3D structure)</td>
<td>X-ray Diffraction (XRD)</td>
</tr>
<tr>
<td></td>
<td>Differential Scanning Calorimetry (DSC)</td>
</tr>
<tr>
<td></td>
<td>Polarized Light Microscopy</td>
</tr>
<tr>
<td>Molecular conformation / mobility</td>
<td>Spectroscopy (Raman, SSNMR)</td>
</tr>
<tr>
<td></td>
<td>Relaxation times (SSNMR, rheology)</td>
</tr>
<tr>
<td>Moisture absorption</td>
<td>Dynamic Vapor Sorption (DVS)</td>
</tr>
<tr>
<td>Increased apparent solubility</td>
<td>Kinetic solubility studies (e.g. dissolution, supersaturation)</td>
</tr>
</tbody>
</table>
Amorphous State Stability

Model glass-former: Indomethacin (IMC) $T_g \sim 45^\circ C$

- Critical relationship between Glass Transition Temp ($T_g$) and storage temperature

Crystallization kinetics for different particle sizes of amorphous IMC at 30 °C

Amorphous State Stabilization

- Amorphous State Stabilization is directed at preventing the initiation and/or reducing the rate of crystal nucleation and growth
- Regulatory Agencies will demand to see good control and understanding of this property
- Available strategies:
  - Avoid Tg reduction (e.g. moisture protection)
  - Elevate Tg significantly above room temperature
  - Chemical interactions (H-bonding, complexation)
  - Anti-nucleation methods (additives, surface modification)
Principles of Solid Dispersions

- Solid Dispersions are intimate mixtures of two (or more) components that typically have a high degree of miscibility.
- Poorly Soluble Drug Dispersions can achieve enhanced solubility by creating a physically stable and processable non-crystalline form.
Solid Dispersions – Control of $T_g$

Stabilization of Amorphous IMC using poly(vinylpyrrolidone) by increasing $T_g$ in a molecular dispersion

Solid Dispersions – Drug-Polymer Interactions

Amorphous IMC containing 5% PVP has greatly increased physical stability stored at 30 °C storage for 100 days.

IMC-PVP H-bonding reduces crystal nucleation and growth.

SOURCE: Matsumoto and Zografi, Pharm. Res. 16 (1999) p1722
OptiMelt™ Hot Melt Extrusion (HME)
Catalent’s OptiMelt™ hot melt extrusion addresses many needs

Approximately 40% of compounds on the market and >80% in development are poorly soluble (BCS class 2/4)

OptiMelt™ hot melt extrusion enhances solubility to bring more products and better treatments to market:

• Achieve desired efficacy, progressing more molecules to approval
• Differentiate product profiles; enhanced solubility
• Enhance patient compliance; reduced pill size/pill burden
• Optimize product performance; controlled release dosage forms
Catalent’s OptiMelt™ hot melt extrusion offers multiple benefits

OptiMelt™ hot melt extrusion provides many benefits beyond solubility enhancement:

- polymeric formulation matrix eliminates hydrolysis associated with wet agglomeration
- suitability for sustained/controlled release or enteric coating
- ability to form capsules, tablets, and multi-particulate dosage forms
- control dose over a wide range of solubilities or dispersion concentrations
- film capability for buccal dosage forms
- very high drug loading up to 90%, decreases tablet size
- robust, compact, high-throughput manufacturing with little waste
- solvent-free processing, eliminating need for explosion-proof equipment
- potential for patient abuse deterrence formulations for certain compounds
- potential for improved safety and side effect profile with lower dosing
- taste-masking
OptiMelt™ HME Process Advantages

- Twin-screw design delivers excellent co-mixing of components
- Solvent free
- Process is well-controlled and scalable
- Good materials handling/ containment
- Extrudate downstream processing is flexible
- Feasibility trials are easy to design and predictive
OptiMelt™ Hot Melt Extrusion – The Basics

- Twin-screw extruders with varying screw design / rotation achieve intimate mixing of drug and excipient
- Shear forces drive co-melting of drug and excipient
- Cooled mixture is a Solid Dispersion preferably containing amorphous (non-crystalline) drug
- Process opportunities
  – Liquid drugs
  – Potent drugs
  – Labile drugs (solvent or moisture sensitive)
OptiMelt™ HME Twin Screw Extruder Equipment Variables

Feeder configuration
Processing zone configuration
Die size / number
OptiMelt™ HME - Process Variables and Outputs

- Feed rate input
- Screw speed input
- Barrel temperature inputs

Inputs:
- Main feed
- Feed rate input
- Screw speed input
- Barrel temperature inputs

Outputs:
- Screw speed
- Torque
- Barrel temperature outputs

Materials:
- Polymer
- API

Drive motor and gearbox

Material temp, Pressure, PAT
OptiMelt™ HME – Downstream Extrudate Processing

- A wide range of finished dosage forms can be generated

1. Upstream

2. Compounding → Extrusion

3. Downstream → Pellets, Granules, Calendering, Inj molding

SOURCE: BASF Pharma Ingredients & Services
OptiMelt™ HME – Feasibility Assessments

- Miscibility may be assessed by predictive or small-scale experimental techniques
- DSC of binary mixtures to identify single $T_g$
- Hot stage microscopy to observe phase melting/dissolution at different temperatures
- Film casting of binary mixtures from common solvent – visual examination for crystal formation

A significant benefit of HME is that proof-of-concept evaluations may be performed at small-scale, quickly and with minimal API
OptiMelt™ HME – Feasibility Assessments

The following API information directs formulation strategy:

- API $T_g$ if available or otherwise estimate
  \( \frac{T_g}{T_m} \) [Kelvin] Ratio \( \sim 0.7 \) based on fragility theory.

- API chemical stability at increased temperature

- API availability for H-bonding

- Poorly Soluble Model Drugs:

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Indomethacin</th>
<th>Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g / T_m$ (°C)</td>
<td>-20 / 80</td>
<td>45 / 155</td>
<td>59 / 166</td>
</tr>
<tr>
<td>Solubility at pH7 (µg/mL)</td>
<td>~1</td>
<td>5</td>
<td>~1</td>
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</table>