FAST DISSOLVING DRUG DELIVERY SYSTEMS

Gülay YELKEN DEMIREL, MSc
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  - What are Fast Dissolving Dosage Forms?
  - Advantages of Fast Dissolving Drug Delivery Systems (FDDDS)
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  - Intellectual Properties
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Introduction

FDDDS were developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients.*

Regulatory Definitions

**US Definition**
- A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue.
- Tablet weight <500mg. In-vitro USP disintegration test <30 seconds.

*FDA Guidance for Industry - *Orally Disintegrating Tablets*

**EU Definition**
- **Orodispersible tablets** are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.
- Disintegration Test: Orodispersible tablets disintegrate within 3 minutes when examined by the test for disintegration……..

**European Pharmacopoeia (Ph.Eur.)**
What are Fast Dissolving Dosage Forms?

Fast Dissolving Dosage Form

- Oral route of administration
- Solid dosage form
- Rapid disintegration on the tongue

A stable, oral dosage form with the dosing ease of a liquid
Advantages of FDDDS: Onset of drug action

*Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001
Advantages of FDDDS

**FDDDS**

- **Clinical**
  - Enhanced efficacy (quick onset of action, improved effectiveness)
  - Enhanced oral absorption
  - Minimized first-pass effect
  - Faster onset of action

- **Medical**
  - Improved compliance
  - Improved convenience
  - Better taste
  - Administration without water
  - Ease of swallowing

- **Technical**
  - Accurate dosing
  - Common process
  - Conventional equipment
Advantages of FDDDS (cont.)

FDDDS

Business
- Unique product differentiation
- Value-added product line extension
- Provide exclusive marketing
- Extend patent protection
- Reduction of development costs

Formulation
- Rapid disintegration
- Stability
- Improve taste
- Aged-specific formulations (pediatric, geriatric and dysphagic patients)

“Place on your tongue and swallow... then spit out when nobody is looking.”

Gülay YELKEN DEMIREL, MSc

Fast Dissolving Drug Delivery Systems
Limitations of FDDDS

- Limited drug load capacity
- Fragile products, special unit-dose packaging
- Hygroscopicity
- Unpleasant taste of a drug and poor organoleptic properties
- Mucosal irritation of the oral cavity
What are Orally Disintegrating Dosage Forms?

- **Solid single unit dosage forms** for intraoral administration (quick release only)
  - Chewable dosage forms (forced disintegration)
    - Chewable tablets
    - Medicated chewing gums
    - Soft lozenges
  - Orally disintegrating dosage forms (rapid disintegration)
    - Oral disintegrating tablets
    - Oral lyophilized forms
    - Oral films
  - Other dosage forms (slow disintegration)
    - Hard lozenges
    - Buccal tablets
    - Sublingual tablets

*Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001*
Formulation and Technologies
Formulation: Basic Approaches to Develop FDDDS

- Porous structure
- Highly water-soluble excipients
- Appropriate disintegrating agents

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Fast Dissolving Drug Delivery Systems
Technologies for Manufacturing FDDDS

- Oral lyophilized dosage forms
- Orally disintegrating tablets
- Oral films
Technologies for Manufacturing FDDDS

- Oral lyophilized dosage forms
- Orally disintegrating tablets
- Oral films
Oral Lyophilized Dosage Forms

- The most successful fast-dissolving oral dosage forms today

- Resulting solid material is a highly porous matrix network

- Disintegrates in less than 10s, typically less than 5s

- Expensive manufacturing technology

- Freeze dried ODT - Zydis®, RP Scherer in 1986
Oral Lyophilized Dosage Forms: The Zydis® Formulation

<table>
<thead>
<tr>
<th>Formulation Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix former</td>
</tr>
<tr>
<td>Structure former</td>
</tr>
<tr>
<td>Structure promoter</td>
</tr>
<tr>
<td>Sweeteners</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

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Fast Dissolving Drug Delivery Systems

Sanovel
Oral Lyophilized Dosage Forms: The Zydis® Process

Solution or Suspension → filling nozzle → freeze → freeze dry → matrix

blister → pores →

drug in minimum volume of liquid → rapid water permeation and dispersion

Technologies for Manufacturing FDDDS

- Oral lyophilized dosage forms
- Orally disintegrating tablets
- Oral films
Orally Disintegrating Tablets

ODTs are also called as:

✓ Orodispersible tablets

✓ Fast disintegrating tablets, Quick disintegrating tablets

✓ Fast dissolving tablets, Rapid dissolving tablets

✓ Mouth dissolving tablets

✓ Quick melt tablets
Orally Disintegrating Tablets

Main product attributes;

- Easy to manufacture; lower cost
- Less breakable and friable than lyophilized dosage forms
- Sufficient mechanical strength and good package design
- Disintegrate within 20-30 seconds
- May be moisture-sensitive
- Gritty of insoluble excipient residue may remain on the tongue
- Effervescent couples are used
Flavor consideration

- Flavors and sweeteners may be used in formulation
- API taste-masking
  - Microencapsulation
  - Chelation
  - Complexation
  - Cyclodextrins...
Orally Disintegrating Tablets

FORMULATION GOALS

- Taste-masking
- Smooth & creamy mouth feel
- Rapid disintegration
- Low friability
- Packaging
- Ease in manufacture
- Ease in use

Goals:
- Taste masking
- Smooth & creamy mouth feel
- Rapid disintegration
- Low friability
- Ease in manufacture
- Ease in use
Orally Disintegrating Tablets

<table>
<thead>
<tr>
<th>Technology</th>
<th>In-vitro disintegration time(s)</th>
<th>Tablet hardness and robustness</th>
<th>Packaging</th>
<th>Drug-loading dose(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdvaTab (Eurand)</td>
<td>15-30</td>
<td>hard, robust</td>
<td>bottles or blister pack</td>
<td>&lt;700</td>
</tr>
<tr>
<td><strong>DuraSolv (Cima Labs)</strong></td>
<td>&lt;30</td>
<td>hard, robust</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
</tr>
<tr>
<td>FlashDose (Biovail)</td>
<td>5-15</td>
<td>soft, friable</td>
<td>blister pack</td>
<td>&lt;600</td>
</tr>
<tr>
<td>FlashTab (Ethpharm SA)</td>
<td>30-60</td>
<td>relatively durable</td>
<td>blister pack</td>
<td>&lt;650</td>
</tr>
<tr>
<td>Lyoc (Cephalon)</td>
<td>&lt;10</td>
<td>soft, friable</td>
<td>blister pack</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>OraQuick (KV Pharmaceuticals)</td>
<td>&lt;20</td>
<td>relatively durable</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
</tr>
<tr>
<td><strong>OraSolv (Cima Labs)</strong></td>
<td>&lt;30</td>
<td>soft, friable</td>
<td>blister pack</td>
<td>&lt;750</td>
</tr>
<tr>
<td>SATAB (Sato)</td>
<td>&lt;10</td>
<td>relatively durable</td>
<td>blister pack</td>
<td>&lt;600</td>
</tr>
<tr>
<td>WOWTAB (Yamanouchi)</td>
<td>&lt;30</td>
<td>relatively durable</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

Orally Disintegrating Tablets: OraSolv® & DuraSolv™

OraSolv® Technology, Cima Labs Inc.
- Tasted-masked API
- Contains effervescent agents
- Direct compression technique at low compression force
- Soft and fragile nature, packed in specially designed pick and place system (PackSolv™)

DuraSolv™ Technology, Cima Labs Inc.
- Second generation technology
- Used conventional tableting equipment, 15-50 Newton
- Low friability (less than 2 %), packaging in conventional packaging systems
Orally Disintegrating Tablets: OraSolv® & DuraSolv™

<table>
<thead>
<tr>
<th>Formulation Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
</tr>
<tr>
<td>Disintegrant</td>
</tr>
<tr>
<td>Flavor</td>
</tr>
<tr>
<td>Sweetener</td>
</tr>
<tr>
<td>Lubricant</td>
</tr>
<tr>
<td>Colorant, if required</td>
</tr>
<tr>
<td>Effervescent components</td>
</tr>
</tbody>
</table>
Orally Disintegrating Tablets: Excipients

Ideal excipient criteria used in the formulation of ODTs:

- Able to disintegrate quickly
- No interactions with API and other excipients
- No interference in organoleptic properties of the product
Technologies for Manufacturing FDDDS

- Oral lyophilized dosage forms
- Orally disintegrating tablets
- Oral films
Oral Films (Rapid Films)

- Complying with the orodispersible tablet definition of the Ph.Eur.
- Obtained by casting a polymer mass

**Advantages**
- Rapid disintegration
- Elegant presentation
- Improved portability
- Accurate dosing
- Discrete administration

**Limitations**
- Drug loading
- Unpleasant taste of API
- Manufacturing cost
- Stability
- Film integrity
# Oral Films: Formulation

## Formulation Composition

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water soluble polymer</td>
</tr>
<tr>
<td>Plasticizers</td>
</tr>
<tr>
<td>Surfactants</td>
</tr>
<tr>
<td>Sweetening agent</td>
</tr>
<tr>
<td>Saliva stimulating agent</td>
</tr>
<tr>
<td>Fillers, colours, flavors etc.</td>
</tr>
</tbody>
</table>
Oral Films: Methods for Preparation

Manufacturing Methods

- Rolling method
- Solvent casting
- Hot-melt extrusion
- Semi-solid casting
- Solid dispersion

Gülay YELKEN DEMIREL, MSc
Oral Films: Solvent casting method

*Dissolving Films, Particle Sciences Drug Development Services, Technical Brief Volume 3
Evaluating Parameters of FDDDS

- Intellectual Properties
- Evaluation Tests
- Packaging Materials Consideration
- Clinical Considerations: Bioequivalence Studies
Evaluating Parameters of FDDDS

- Intellectual Properties
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## Intellectual Properties for Lyophilized Dosage Forms

<table>
<thead>
<tr>
<th>Documents</th>
<th>Priority date</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 5,046,618</td>
<td>19.11.1990</td>
<td>Rapidly disintegrating tablet</td>
</tr>
<tr>
<td>EP 646 367</td>
<td>01.12.1992</td>
<td>A multilayer laminated blister film</td>
</tr>
</tbody>
</table>

*Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001
# Intellectual Properties for Orally Disintegrating Tablets

**Cima Labs Inc.**
- DuraSolv®, OraSolv®
- At least 14 published international patent applications

<table>
<thead>
<tr>
<th>Documents</th>
<th>Priority date</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 5,503,846, WO 94/21239, EP 0 752 852</td>
<td>17.03.1993</td>
<td>Base coated acid particles and effervescent formulation incorporating same</td>
</tr>
<tr>
<td>US 5,607,697</td>
<td>07.06.1995</td>
<td>Taste masking microparticles for oral dosage forms</td>
</tr>
<tr>
<td>WO 98/14179, EP 1 007 012</td>
<td>01.10.1996</td>
<td>Taste-masked microcapsule compositions and methods of manufacture</td>
</tr>
</tbody>
</table>

*Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001*
Intellectual Properties for Oral films

LTS Lohmann Therapie-Systeme AG

- A larger number of patents covering various processes of oral films

<table>
<thead>
<tr>
<th>Documents</th>
<th>Priority date</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE 40 18 247</td>
<td>07.06.1990</td>
<td>Manufacture process of fast disintegrating film-formed administration forms</td>
</tr>
<tr>
<td>EP 460 588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE 44 19 824</td>
<td>07.06.1994</td>
<td>Volume-expandable, sheet-like application form suitable as an active carrier, in particular for oral application</td>
</tr>
<tr>
<td>WO 95/33452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP 766 556</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US 6,153,222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE 196 52 268</td>
<td>16.12.1996</td>
<td>Active substance carrier for releasing apomorphine into the buccal cavity</td>
</tr>
<tr>
<td>WO 98/26763</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP 959 875</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE 196 52 188</td>
<td>16.12.1996</td>
<td>Flat medicament preparation for the application and release of buprenorphine or a pharmacologically comparable substance in the buccal cavity, and method of producing the same</td>
</tr>
<tr>
<td>WO 98/26780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP 949 925</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE 198 00 682</td>
<td>10.01.1998</td>
<td>Primary package for film- or wafer-like dosage forms</td>
</tr>
<tr>
<td>DE 198 06 966</td>
<td>19.02.1998</td>
<td>Apparatus and process for introducing multiple foil-shaped dosage units into a dispenser and forming a multilayer stack</td>
</tr>
</tbody>
</table>

*Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001*
Evaluating Parameters of FDDDS

- Intellectual Properties
- Evaluation Tests
- Packaging Materials Consideration
- Clinical Considerations: Bioequivalence Studies
Evaluation Tests for FDDDS

- In-process control tests (thickness, hardness, uniformity of weight, friability, disintegration test...)
- Dissolution, assay and impurity analyses
- Wetting time and water absorption ratio

Evaluation Tests for FDDDS

Oral Films

- Thickness
- Dryness test
- Tensile strength
- Percent elongation
- Folding endurance
- Stickiness determination
- Contact angle measurement
Evaluation Tests for FDDDS: Electronic Tongue

- Comparison of formulation with drug and placebo
- Instrumental sensory technique
- Assess the impact on taste of every ingredient
- Measure the bitterness intensity and improve your formulation design/selection
- Taste comparison (brand products and generics, new and original formulations)
Evaluating Parameters of FDDDS

- Intellectual Properties
- Evaluation Tests

- Packaging Materials Consideration
- Clinical Considerations: Bioequivalence Studies
Packaging Materials for FDDDS

- Need special packaging processes and materials

- Patients may need to be specifically instructed on how to open the package and take out a unit

- Child resistant and senior friendly foils, peelable foils
Packaging Materials for FDDDS: PakSolv™

- Packaging technology for OraSolv®
- To protect the friable tablets from breakage during their shipping
- Robotic equipment to handle tablets and transfer them into their packages
Evaluating Parameters of FDDDS

- Intellectual Properties
- Evaluation Tests
- Packaging Materials Consideration

- Clinical Considerations: Bioequivalence Studies
Clinical Considerations: Bioequivalence Studies

- Typically is similar to that of a conventional tablet or capsule containing the same dose of the drug BE studies...

- Using taste-masking polymers may retard the dissolution rate of API and may cause problems.

- If significant degree of buccal or sublingual absorption occurs Clinical studies for product efficacy and safety.
Future of Fast Dissolving Drug Delivery Systems
Future of FDDDS

ODT-Controlled Release Dosage Forms;

- OraSolv®-SR/CR, Cima Lab

- The drug particles would have to be coated to provide the release-controlling effect after the formulation has disintegrated in the mouth.
Future of FDDDS

Orally Disintegrating Mini-Tablets (ODMTs);

- ODMTs may serve as a novel platform technology for pediatrics in future.
Future of FDDDS

OTC Market;

- Pharmaceutical industries have launched several products for the OTC market using OTF technologies.

Multilayer Orally Disintegrating Tablet;

- A good alternative for combine products.
Conclusion

- FDDDS can be used for improving patient compliance, extending patent life, product life cycle and product differentiation.

- Decision criteria:
  - Consider drug pharmaceutical properties
  - Choose suitable technology both manufacturing process and packaging
  - Product patent protection
THANK YOU!

Gülay YELKEN DEMIREL, MSc

Fast Dissolving Drug Delivery Systems