FAST DISSOLVING DRUG DELIVERY SYSTEMS

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Sanovel

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Introduction

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













** Ashish Garg, M.M. Gupta, Mouth Dissolving Tablets: A Review, Journal of Drug Delivery&Therapeutics; 2013*

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***

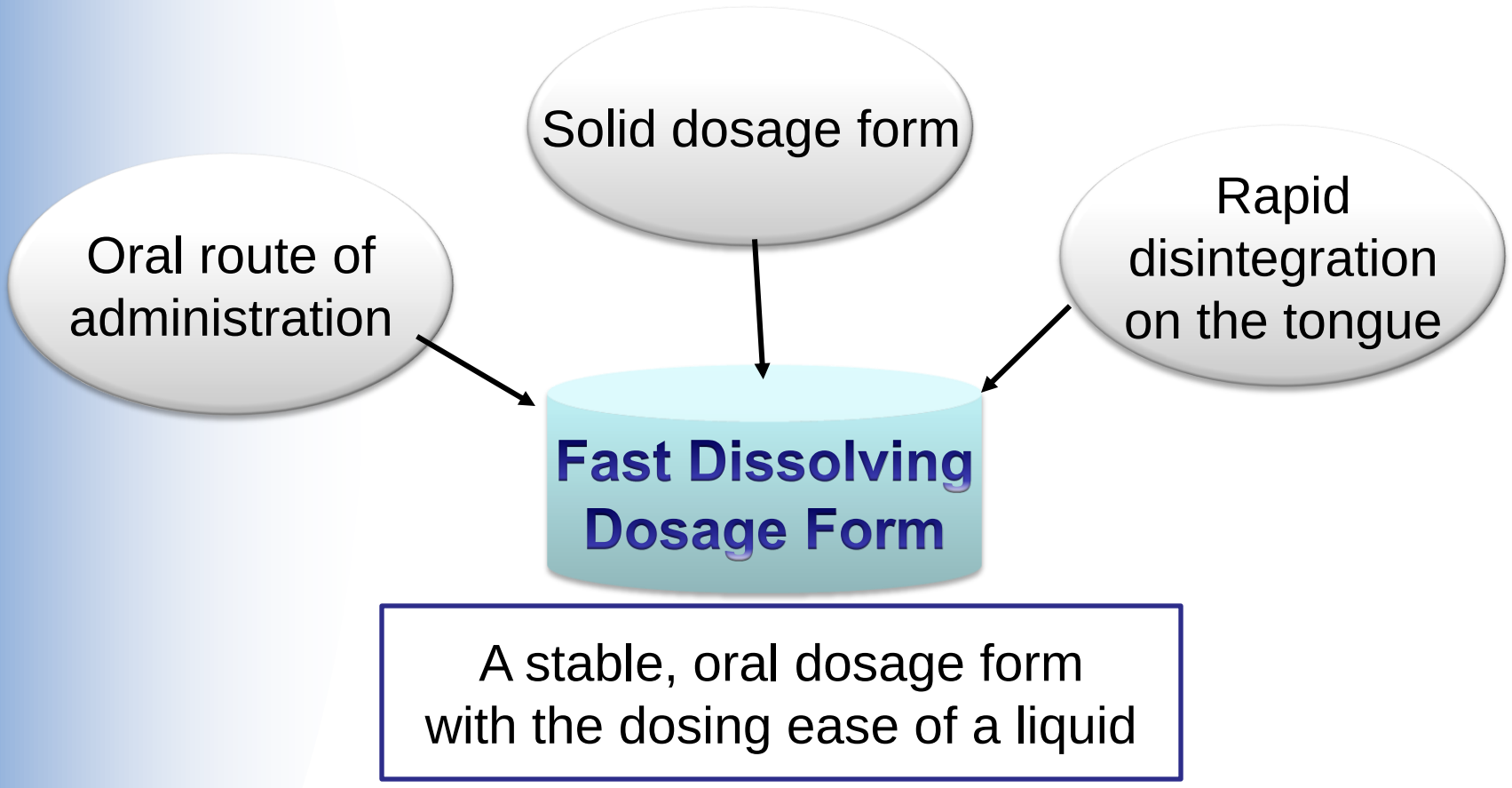


EU Definition**

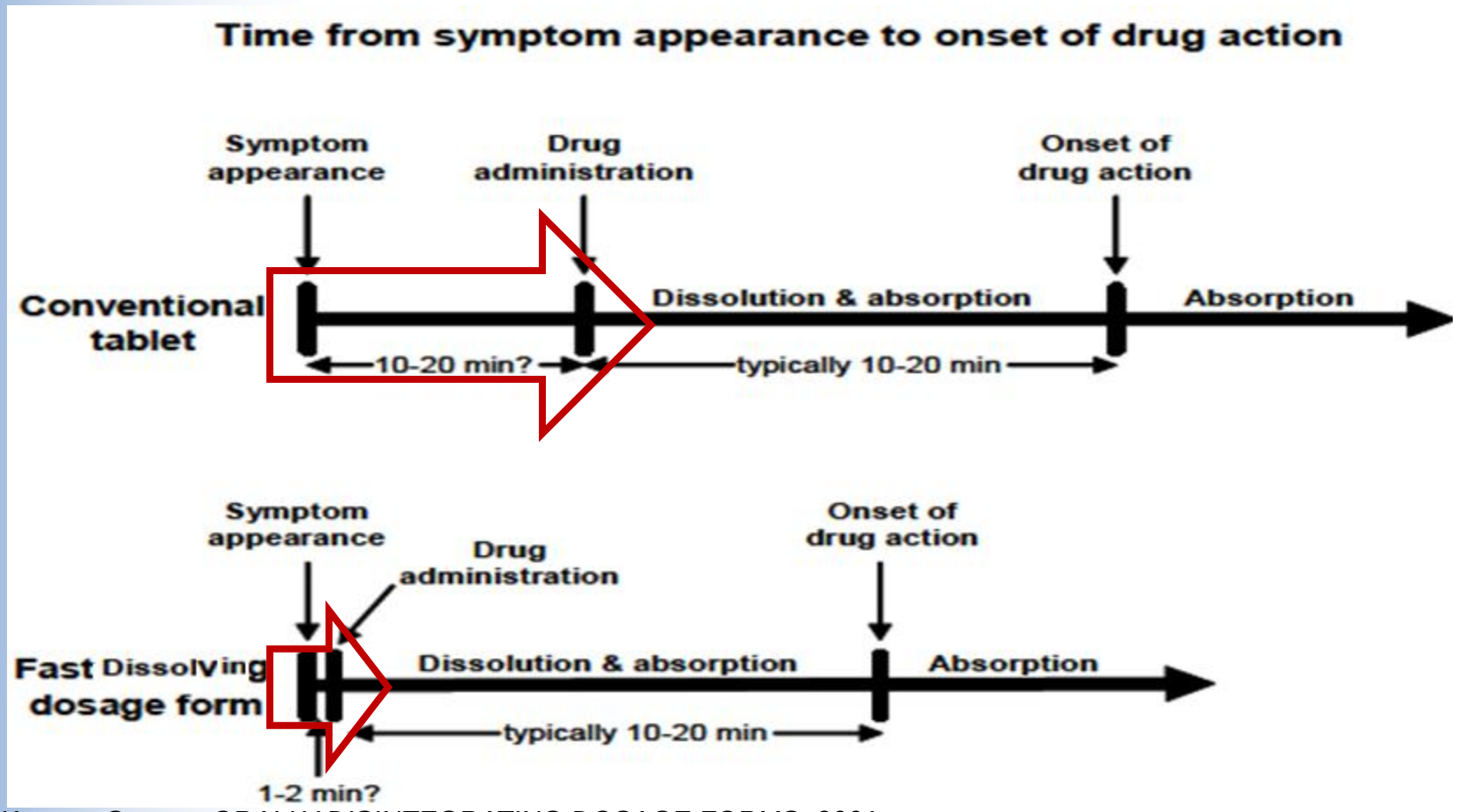
- **Orodispersible tablets** are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.
- Disintegration Test: Orodispersible tablets disintegrate *within 3 minutes* when examined by the test for disintegration…….

***European Pharmacopoeia (Ph.Eur.)*

What are Fast Dissolving Dosage Forms?

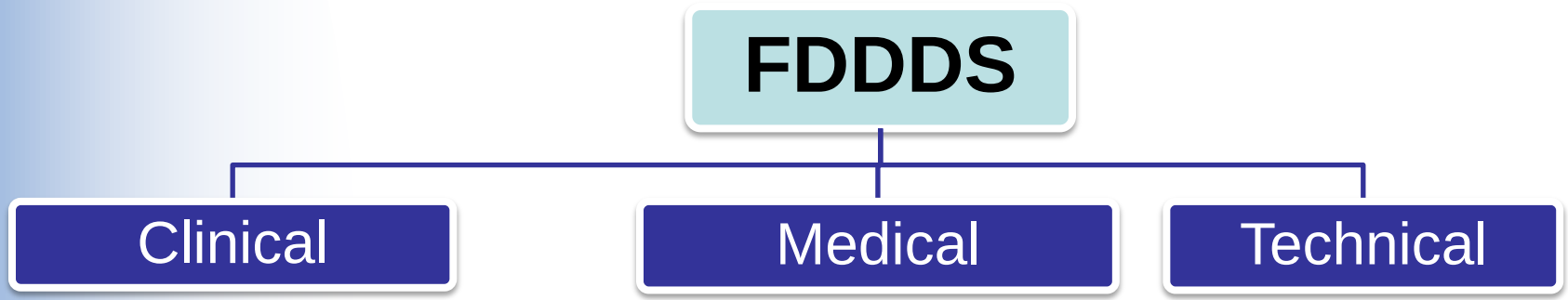


Advantages of FDDDS: Onset of drug action



**Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001*

Advantages of FDDDS



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

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

- ✓ 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

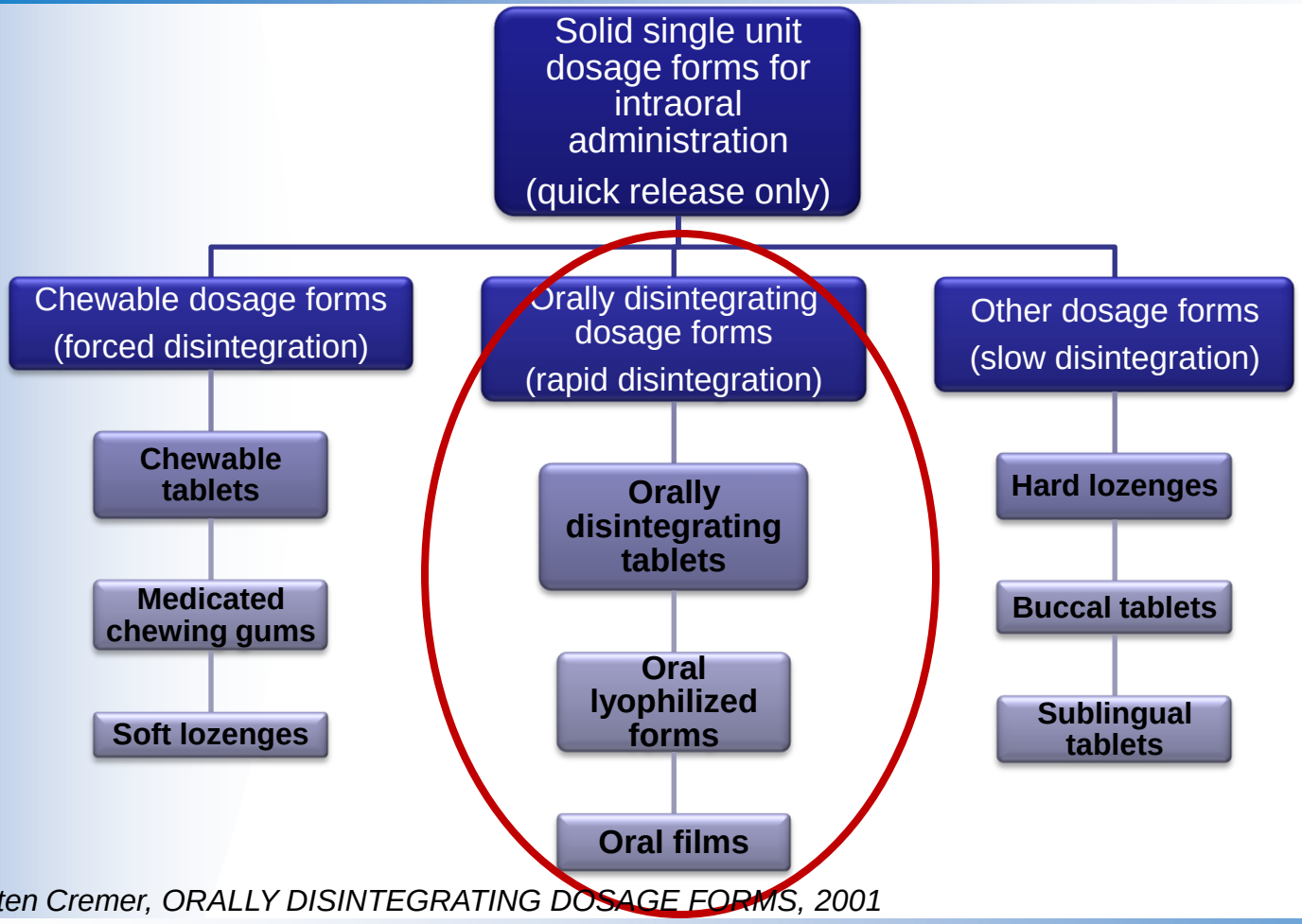
- ✓ Rapid disintegration
- ✓ Stability
- ✓ Improve taste
- ✓ Aged-spesific formulations *(pediatric, geriatric and dysphagic patients)*



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

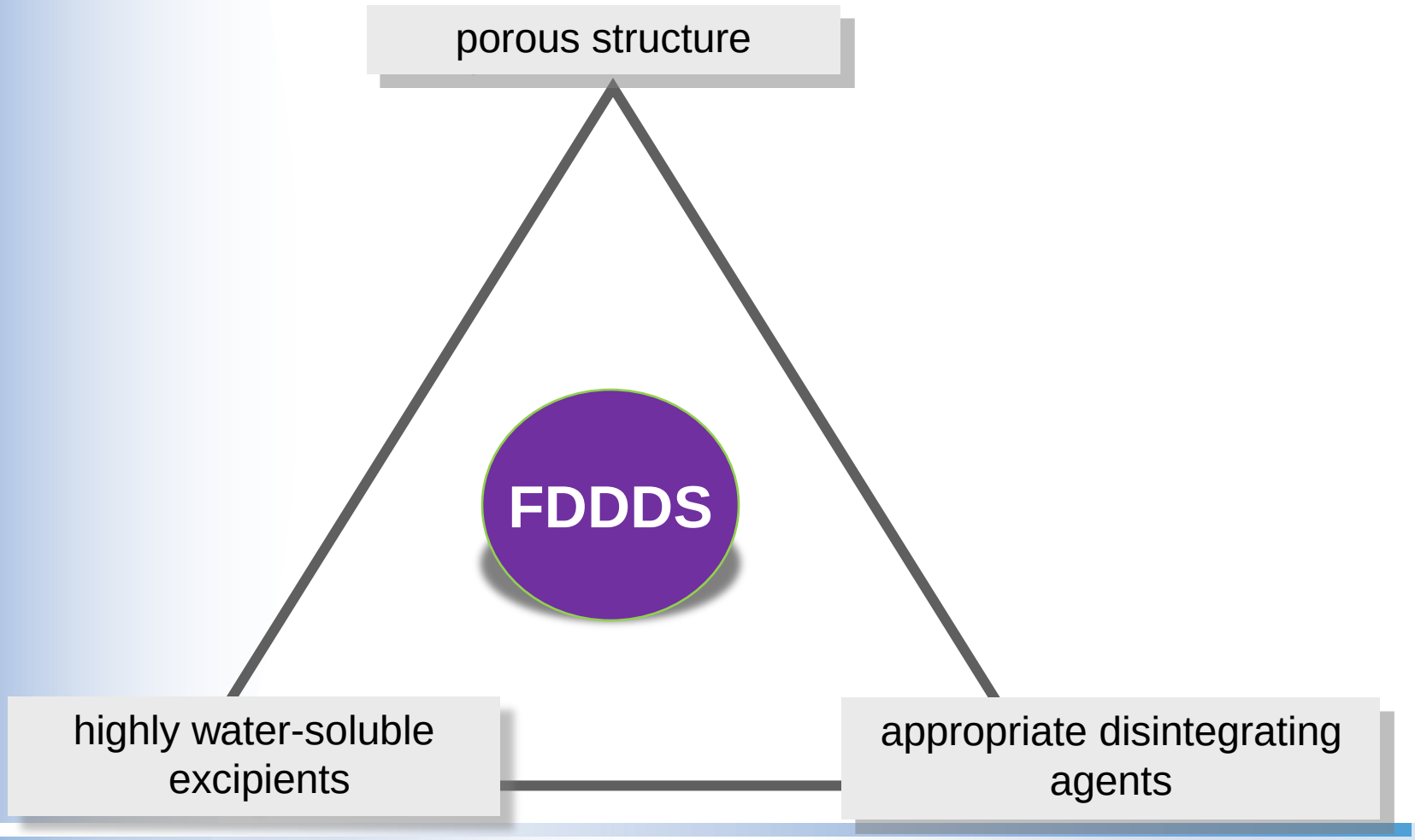
What are Orally Disintegrating Dosage Forms?



Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001

Formulation and Technologies

Formulation:Basic Approaches to Develop FDDDS



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



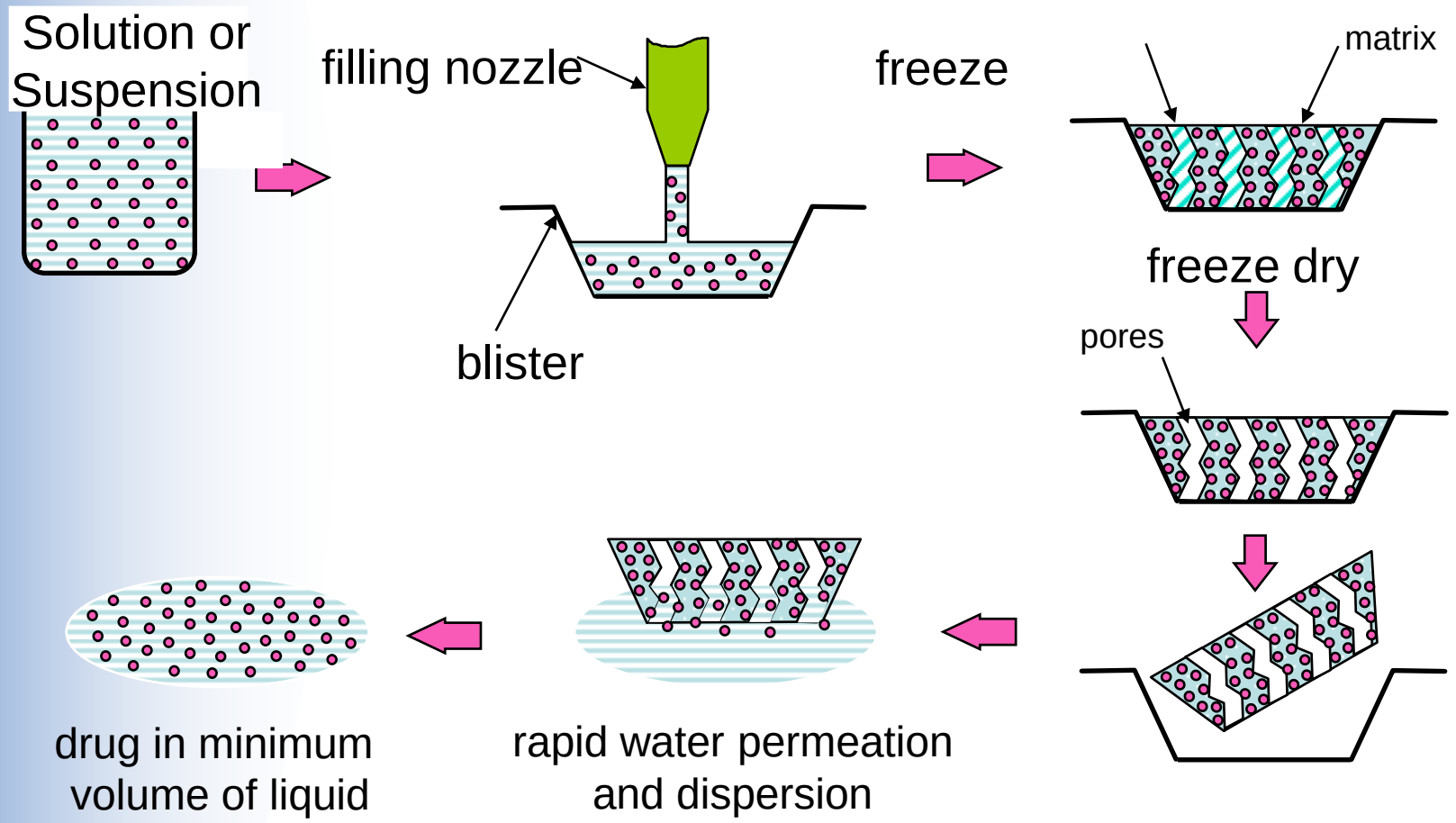
- Freeze dried ODT - Zydis®, RP Scherer in 1986

Oral Lyophilized Dosage Forms: The Zydis® Formulation

Formulation Composition
Matrix former
Structure former
Structure promoter
Sweeteners
Other



Oral Lyophilized Dosage Forms: The Zydis® Process



** Ashish Garg, M.M. Gupta, Mouth Dissolving Tablets: A Review, Journal of Drug Delivery&Therapeutics; 2013*

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

Orally Disintegrating Tablets

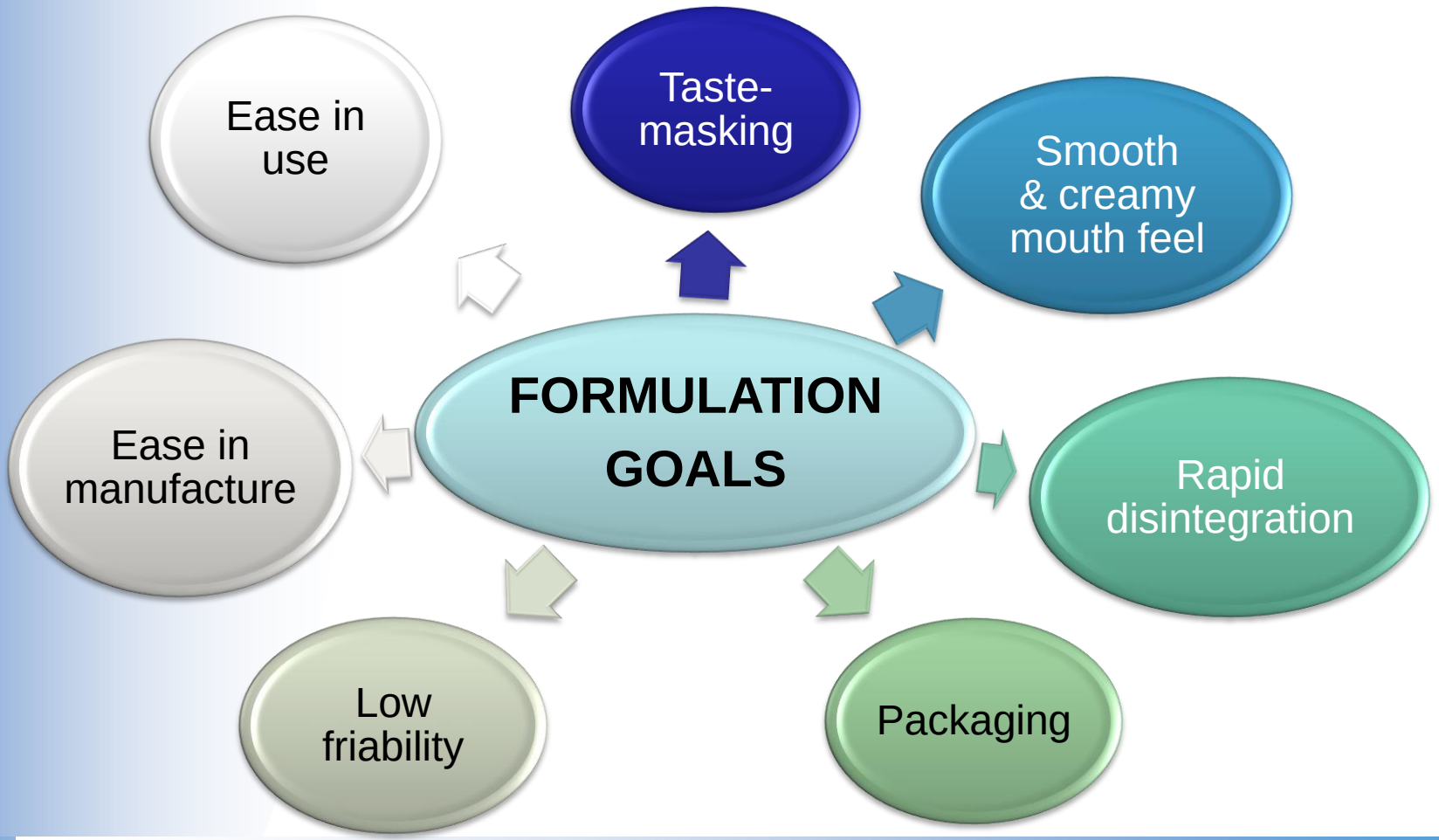
Flavor consideration

- Flavors and sweeteners may be used in formulation

- API taste-masking
  - Microencapsulation
  - Chelation
  - Complexation
  - Cyclodextrins...



Orally Disintegrating Tablets



Orally Disintegrating Tablets

Tablet manufacturers and patented technologies characteristics				
Technology	**In-vitro disintegration time(s)**	**Tablet hardness and robustness**	**Packaging**	**Drug-loading dose(mg)**
AdvaTab(Eurand)	15-30	hard, robust	bottles or blister pack	<700
DuraSolv(Cima Labs)	<30	hard, robust	bottles or blister pack	<500
FlashDose(Biovail)	5-15	soft, friable	blister pack	<600
FlashTab(Ethypharm SA)	30-60	relatively durable	blister pack	<650
Lyoc(Cephalon)	<10	soft, friable	blister pack	<1000
OraQuick(KV Pharmaceuticals)	<20	relatively durable	bottles or blister pack	<500
OraSolv(Cima Labs)	<30	soft, friable	blister pack	<750
SATAB(Sato)	<10	relatively durable	blister pack	<600
WOWTAB(Yamanouchi)	<30	relatively durable	bottles or blister pack	<500

**K. Ostrander, "Advances in Fast Dispersing Technologies-Zydis", Oct. 29, 2003.*

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™

Formulation Composition
Filler
Disintegrant
Flavor
Sweetener
Lubricant
Colorant, if required
Effervescent components



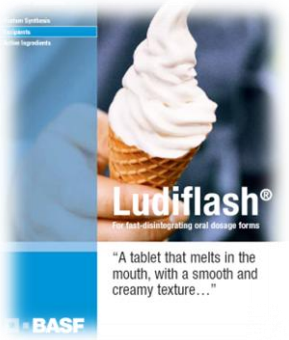


Orally Disintegrating Tablets: Excipients

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









PanExcea™

J.T.Baker

Pharmaburst®

SPI Pharma

Ensure your product line has a bright future.

Pharmaburst is the gold standard ODT system for Rx and OTC, it is fully optimiz for disntegration time, mouthfeel and ease of manufacturing. If you're not using

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

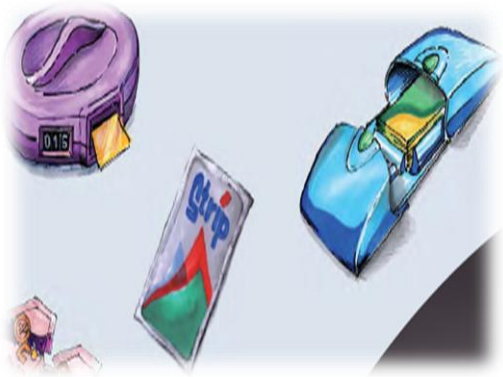
- Drug loading
- Unpleasant taste of API
- Manufacturing cost
- Stability
- Film integrity



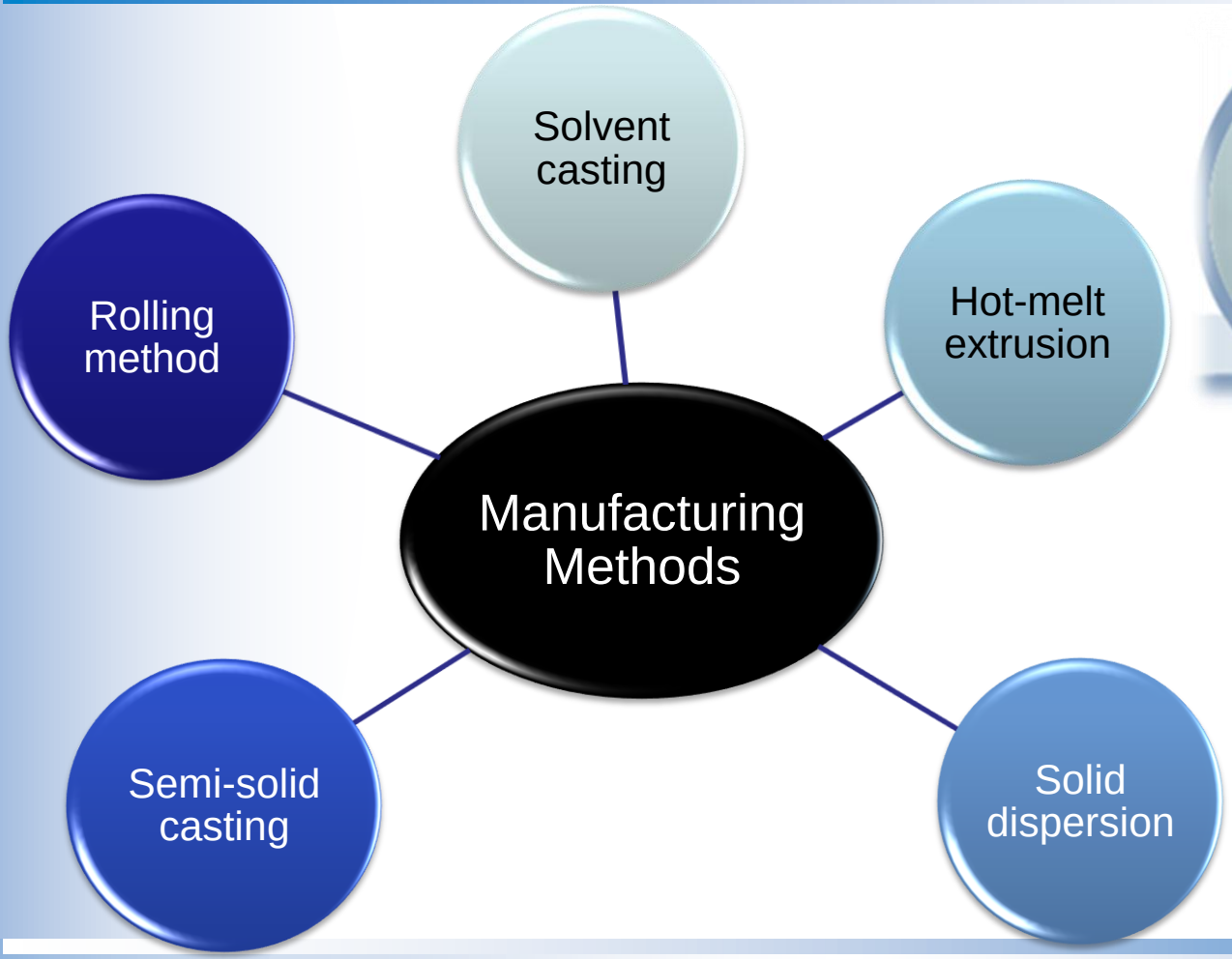
Oral Films: Formulation

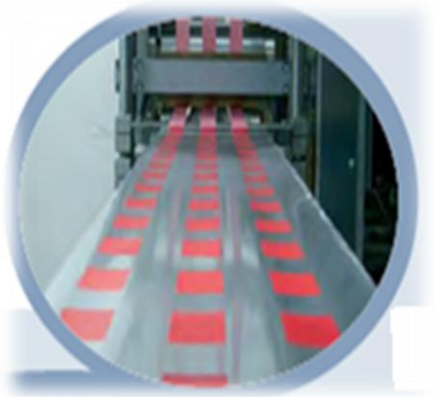
Formulation Composition
Water soluble polymer
Plasticizers
Surfactants
Sweetening agent
Saliva stimulating agent
Fillers, colours, flavors etc.



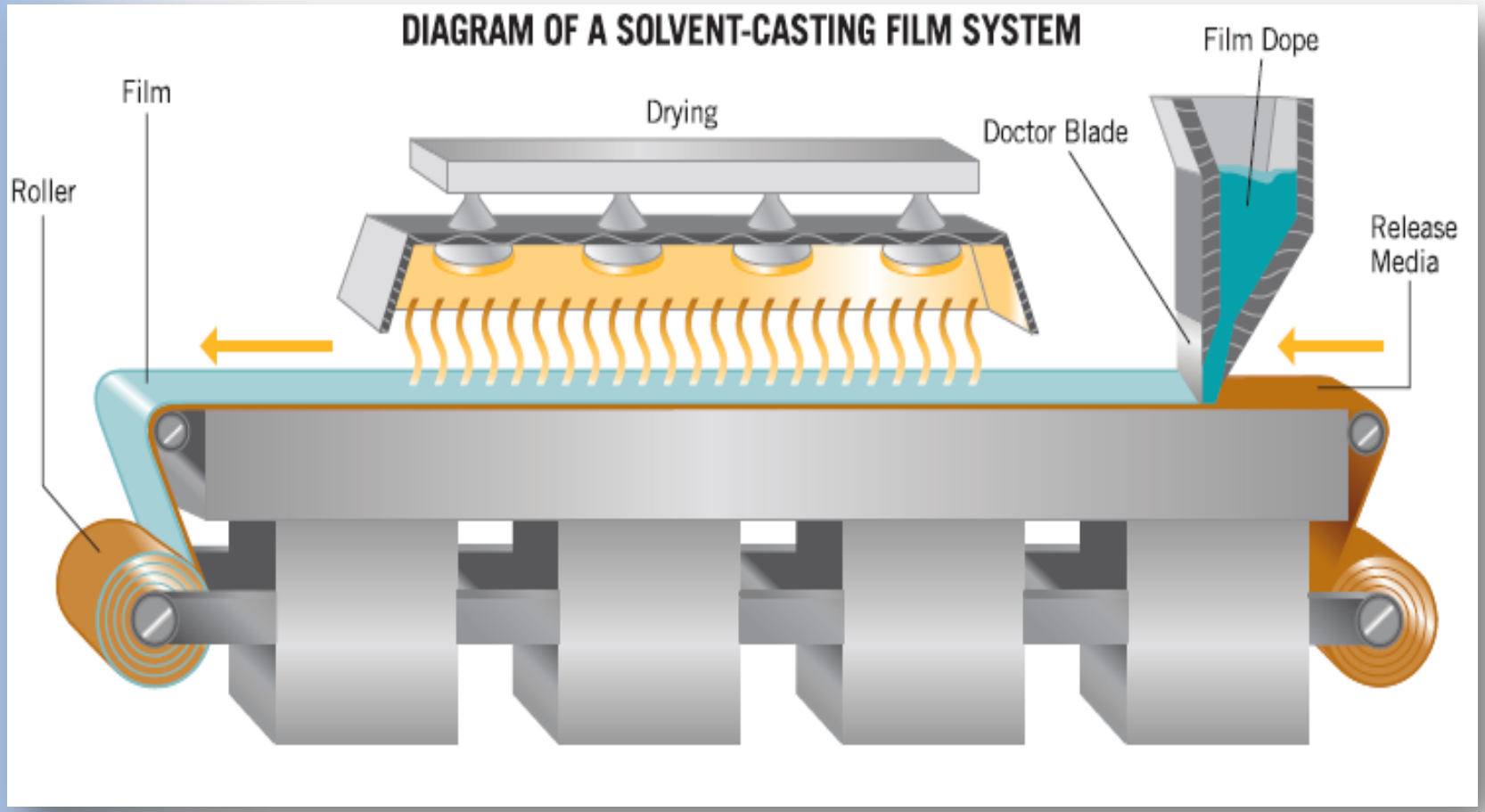


Oral Films: Methods for Preparation





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**
- Evaluation Tests
- Packaging Materials Consideration
- Clinical Considerations: Bioequivalence Studies

Intellectual Properties for Lyophilized Dosage Forms

Zydis

- RP Scherer
- At least 26 patent families relate to the Zydis® technology

Documents	Priority date	Title
US 5,046,618	19.11.1990	**Rapidly disintegrating tablet**
WO 91/09606 US 5,188,825 EP 435 684	28.12.1989	**Freeze-dried dosage forms and methods for preparing the same**
WO 94/07761 US 5,358,118 EP 662 918	30.09.1992	**Stepped-edge blister pack and use of steps**
EP 646 367	01.12.1992	**A multilayer laminated blister film**
WO 94/12142 US 5,729,958 EP 710 101	01.12.1992	**Method for manufacturing freeze dried dosage forms in a multilaminate blister pack**
WO 95/01782 US 5,631,023 EP 804 170	09.07.1993	**Method for making freeze dried drug dosage forms**
WO 96/13251 US 5,827,541 EP 737 064	28.10.1994	**Process for preparing solid pharmaceutical dosage forms of hydrophobic substances**

**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

Documents	Priority date	Title
US 5,219,574 US 5,401,513 WO 91/04018 EP 0 491 754	15.09.1989	**Magnesium carbonate and oil tableting aid and flavoring additive**
US 5,178,878 US 5,223,264 WO 91/04757 EP 0 494 972 EP 0 737 473	02.10.1989	**Effervescent dosage form with microparticles/ Pediatric effervescent dosage form**
US 5,503,846 WO 94/21239 EP 0 752 852	17.03.1993	**Base coated acid particles and effervescent formulation incorporating same**
US 5,607,697	07.06.1995	**Taste masking microparticles for oral dosage forms**
WO 98/14179 EP 1 007 012	01.10.1996	**Taste-masked microcapsule compositions and methods of manufacture**
US 6,155,423 WO 98/43893 EP 1 015 352	01.04.1997	**Blister package and packaged tablet**

**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

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

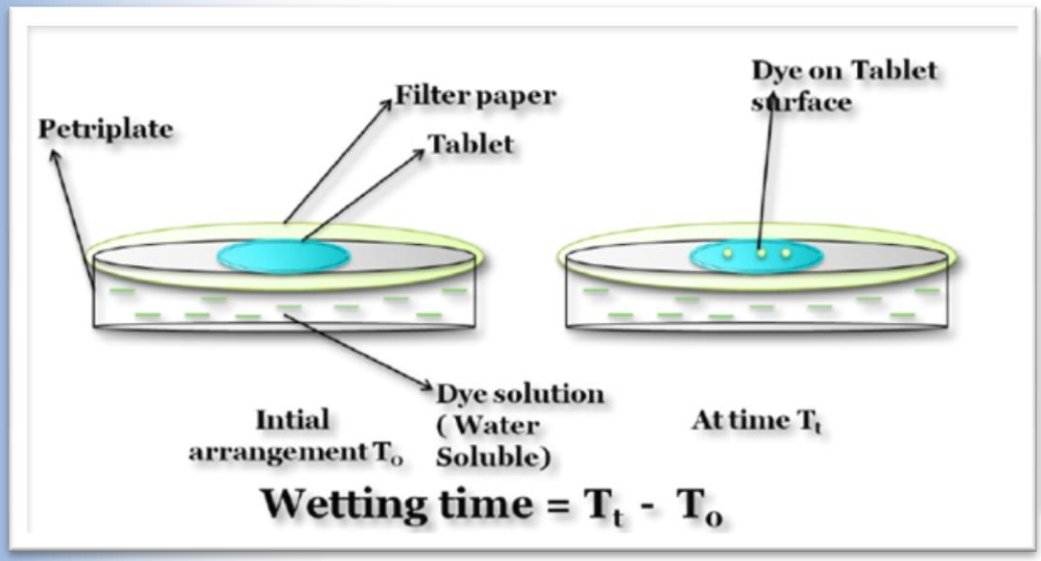
**Karsten Cremer, ORALLY DISINTEGRATING DOSAGE FORMS, 2001*

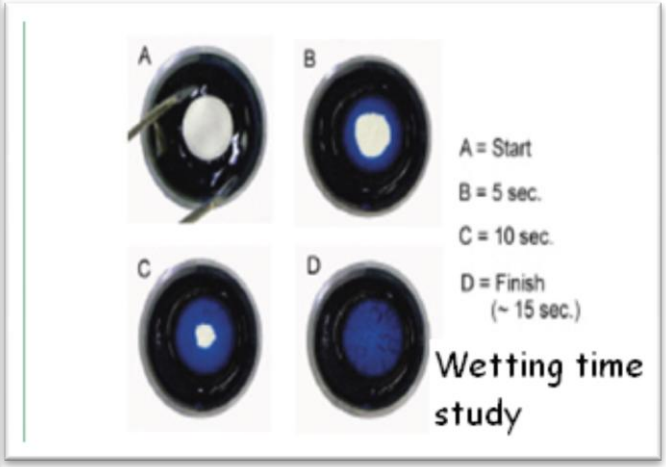
Evaluating Parameters of FDDDS

- 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





**J.Segado Ferran et al., 'Orally Disintegrating Tablets and Process for obtaining them', WO103629(2003)*

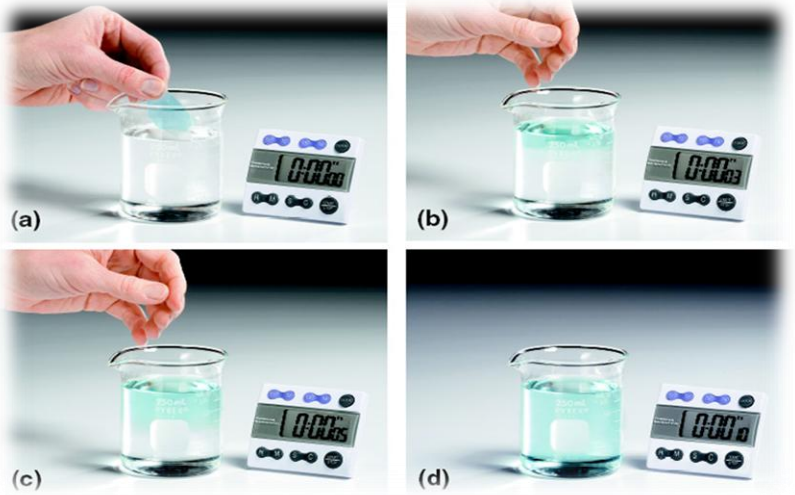
Evaluation Tests for FDDDS

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

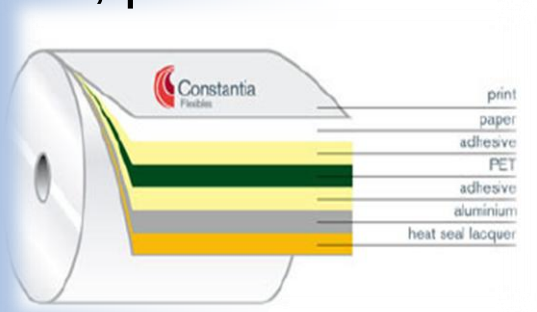




- Patients may need to be specifically instructed on how to open the package and take out a unit



- Child resistant and senior friendly foils, peelable foils



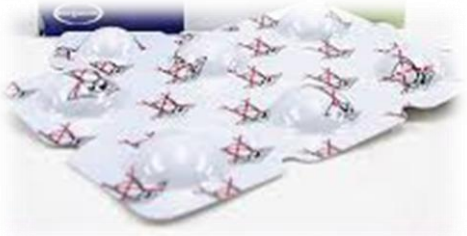


Packaging Materials for FDDDS:PakSolv™

- 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 FDDS

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.

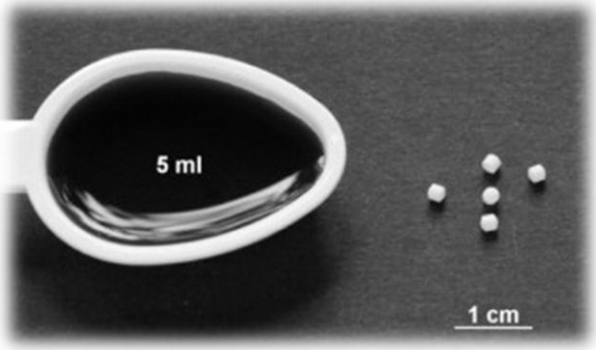


Future of FDDDS

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!

