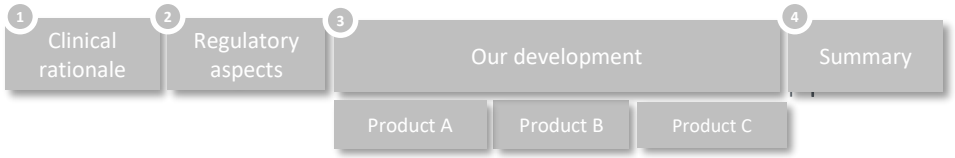
Crushed tablets

- Industry perspective

Jan Šůs
Zentiva, k.s.

Outline

- Clinical rationale for tablet crushing
- Regulatory aspects - requirements for crushed tablets in EU
- In-house experience
- Summary



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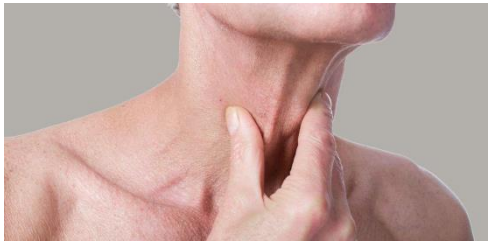
Dysphagia
- prevalence



„a swallowing disorder“

- common in **elderly** and **pediatric patients**
- cca 30% of hospitalized elderly patients (Layne et al., 1989)
- up to 68% for residents in long-term care units (Steele et al., 1997)

% of patients with following disease:

- **Parkinson´s disease** : 35 - 82%
- **multiple sclerosis**: 24-34%
- **Stroke**: 29-68%
- **Dementia**: 13% to 57%
- **head and neck cancer**: 50%
- **gastroesophageal reflux disease**: 14%
- **traumatic brain injury**: 38%–65%

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Dysphagia
- causes and complications

Causes:

- **hyposalivation**
- **weakening of the swallowing muscles**
- **disease** (Parkinson's disease, multiple sclerosis, stroke, cancer, dementia etc.)
- oral mucositis, oral candidiasis
- **drugs** (anticholinergics, chemotherapeutics etc.)
- **radiation therapy** to the head and neck
- **psychological aversion** to swallowing solid dosage forms

Complications:

- **↓ adherence to treatment**
- **malnutration, dehydration**
- **aspiration**
  - **→ pneumonia**
  - **→choking**

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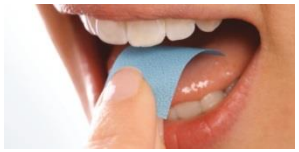
Alternatives for dysphagia patients

1 **Alternative dosage form/ route of administration**

- liquids
- lozenges
- orodispersible form.
- buccal form.
- effervescent tbl
- patches
- inhalers
- intravenous form.



2 **Tablet crushing/ Capsule content spilling**

Administration with food/ beverages

Nasogastric/ gastric tube administration

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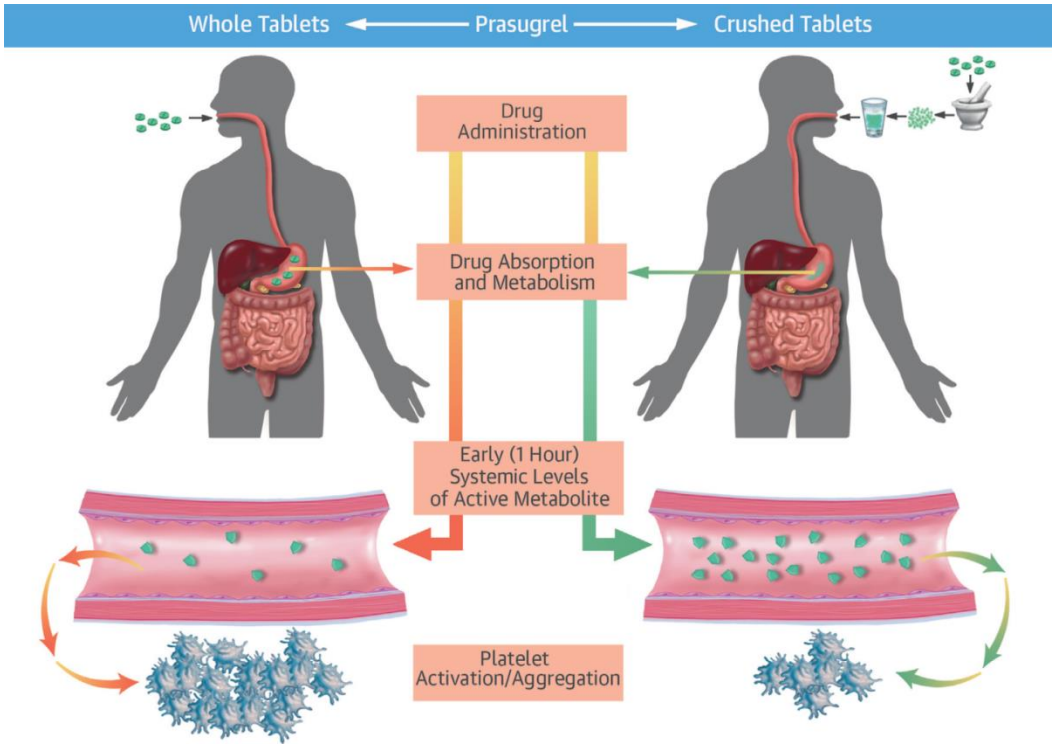
Alteration of PK properties
- faster onset of action

- e.g. painkillers
- prasugrel currently studied



Rollini, F. et al. J Am Coll Cardiol. 2016;67(17):1994–2004.

Some medicines should not be crushed!

1

Carcinogenic or teratogenic molecules
(methotrexate, tamoxifene, cyclospine)
Hormones
Corticosteroids

→ **POWDER AEROSOLISATION RISK**

2

Irritative compounds
(biphosphonates, isotretinoin, nitrofurantion, ganciclovir, solifenacin)

→ **IRRITATION OF EYES, SKIN or GIT**

3

Compounds with very bitter taste
(quinine, ibuprofen, cefurocime axetil, ciprofoloxacine, pseudoephedrine)

→ **UNACCEPTABLE TASTE**

Some medicines should not be crushed!

4 Enteric-coated tablets → **IN-VIVO DEGRADATION – LOSS OF EFFICACY**
(prazols, pancreatine, erythromycine)
PLACE OF ACTION NOT REACHED
(sulphasalazine)
STOMACH IRRITATION
(enteric-coated ASA or diclofenac)

5 Modified-release tablets → **HIGH BOLUS DOSE - PATIENT´S SAFETY RISK**
(morphine, carbamazepine, verpamil)

6 Light-sensitive molecules → **INSTABILITY**
(nifedipine)

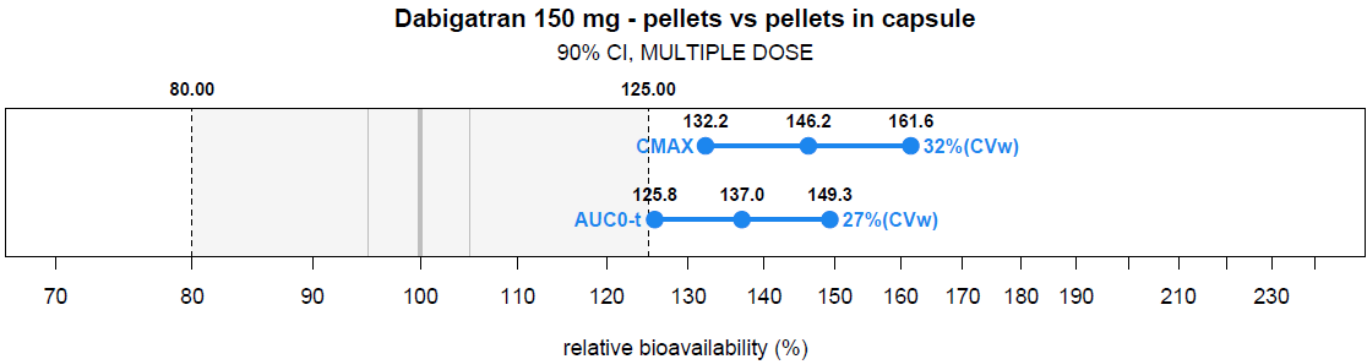
Some medicines should not be crushed!

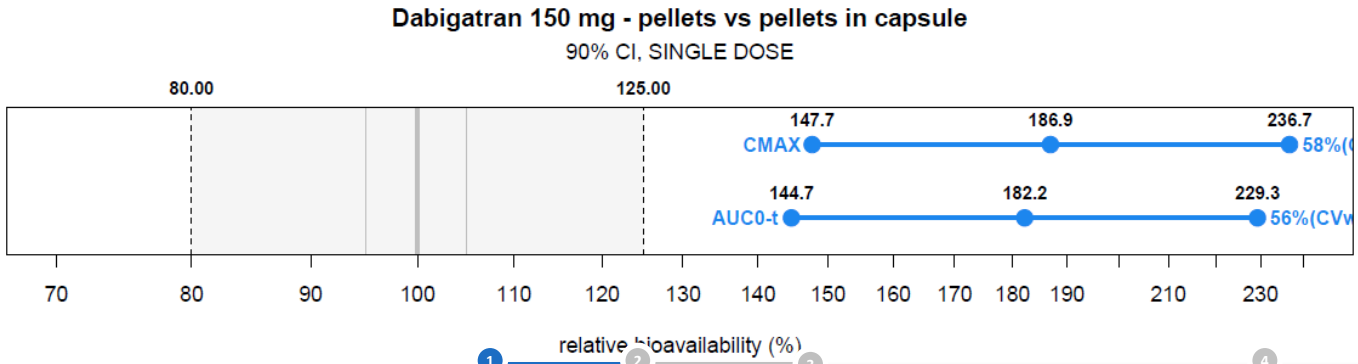
7

Altered bioavailability
(dabigatran)

→

OVERDOSE or
UNDERDOSING





EMA requirement for crushed tablets

- EMA Q&A on Clinical pharmacology and pharmacokinetics

If the SmPC of the reference product allows for the possibility to administer the tablet crushed/disintegrated (and dispersed in food), **bioequivalence should also be demonstrated, in principle, for a test product with this additional mode of administration**.

Rationale:

The **bioavailability of an API(s) may be altered if products are crushed/ disintegrated** to assist swallowing and also if a crushed/disintegrated tablet is mixed with food.

This change in bioavailability may be formulation/ product-specific as well as drug-dependent.

Therefore, a test product that is shown to be bioequivalent when administered as a whole tablet in a fasted state, **may exhibit significantly different bioavailability compared to the reference product, when both are administered crushed/disintegrated** (and dispersed in food).

EMA requirement for crushed tablets

- EMA Q&A on Clinical pharmacology and pharmacokinetics

A crushed tablet study can be waived if <u>all</u> of the conditions below are fulfilled:

- successful **bioequivalence with uncrushed products**
- **BCS** classification of the drug substance as **class 1 or 3**
- **comparative evaluation of excipients**, particularly regarding potentially surface active excipients
- comparative multimedia **in-vitro dissolution**
- comparative **disintegration testing**

In-vitro/ in-vivo testing

- current requirements

Limiting step:
- Gastric emptying

Limiting step:
- solubility
- intrinsic dissolution

CLASS I	CLASS II
High solubility High permeability	Low solubility High permeability
CLASS III	**CLASS IV**
High solubility Low permeability	Low solubility Low permeability

Permeability

Solubility

In-vitro testing
- ✓ *In-vitro* dissolutions
- ✓ Disintegration
- ✓ Evaluations of excipients

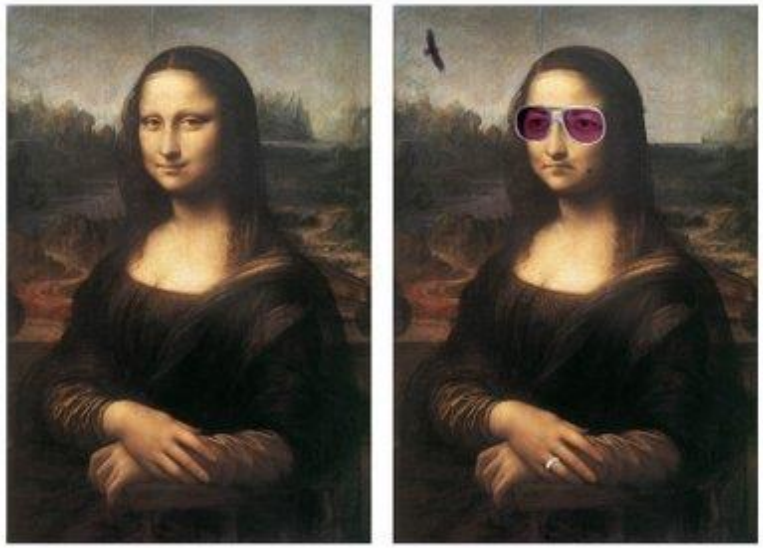
In-vivo testing
- ✓ *Crushed tablet BEQ study*

Limiting step:
- intestinal membrane permeation

Limiting step:
- solubility
- intrinsic dissolution
- intestinal membrane permeation

Goal

- Full interchangeability with originator
- Absence of the claim for alternative administration in the SmPC = disadvantage for the product



Product A

- Justification of crushing of highly soluble drugs

BCS 1 | BCS 3

Deficiency letter:

In line with the reference product, the SmPCs/PILs state that as method of administration the ***tablets may be disintegrated and mixed with water or food prior to administration in patients with difficulties swallowing tablets whole****.*

Bioequivalence was demonstrated with tablets taken whole and ***it is unclear if/how disintegration would affect the pharmacokinetics of the generic product****, neither as compared to the intact tablet nor as compared to the reference product, when administered in this way.*

The applicant is requested to justify that the relevant statement in the SmPC is applicable to the generic Zentiva product.

Disintegration study

Method of administration:

Tablets can be disintegrated in approximately 100 mL of water, orange juice or grape juice and taken immediately.

	Reference			Test		
	Orange Juice	Grape Juice	Water	Orange Juice	Grape Juice	Water
1	6:45	7:56	3:58	4:58	6:32	1:32
2	6:58	7:48	3:45	5:09	6:39	1:45
3	7:10	8:01	4:18	5:32	6:42	1:50
4	7:25	8:15	4:35	5:24	6:49	1:13
5	7:16	8:32	4:38	5:44	6:03	1:26
6	7:28	8:35	4:48	5:29	7:05	1:57
Average	**7:20**	**8:18**	**4:52**	**5:38**	**6:65**	**1:17**

In-vitro dissolutions

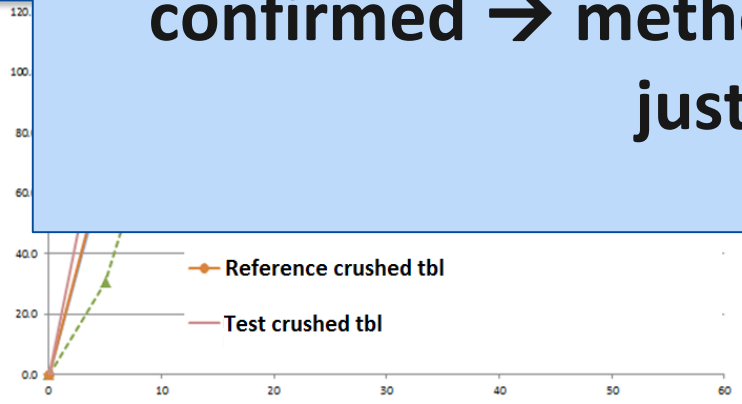
API 1 | **API 2**

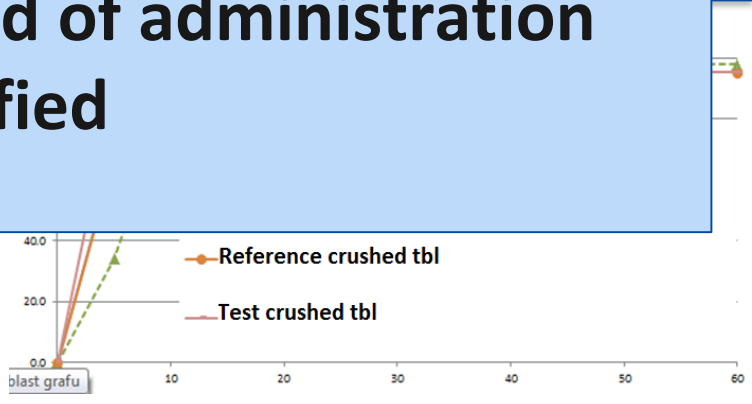
0.1N HCl

Comparable dissolution tests between:

- Test whole tablet
- Test crushed tablet
- Reference whole tablet
- Reference crushed tablet

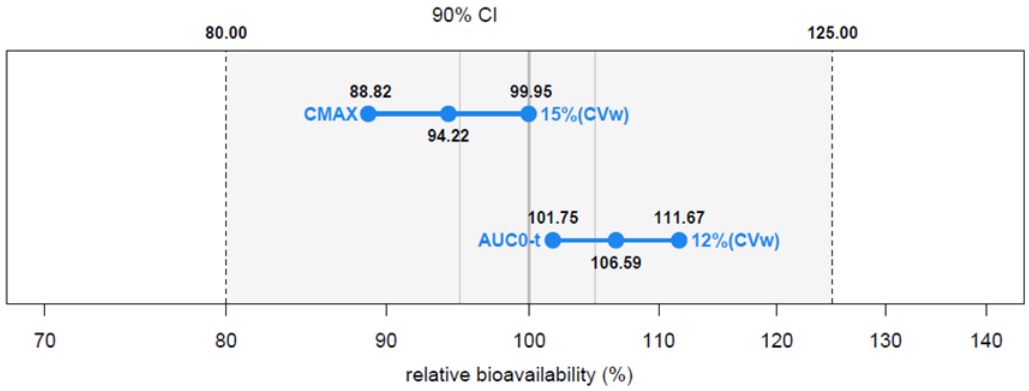
Good solubility of both products confirmed → method of administration justified





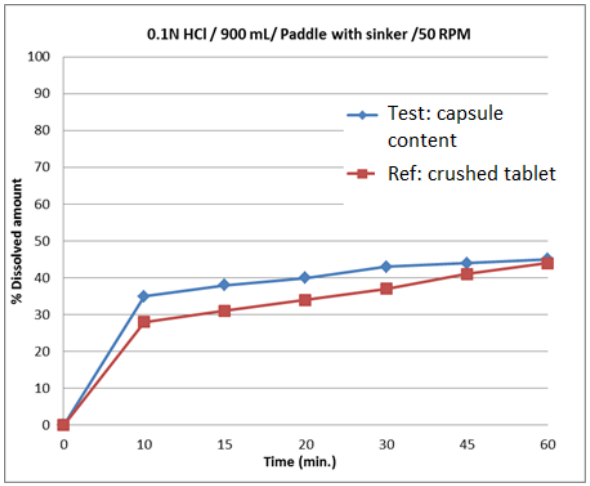
In-house experience – Product B
- basic information

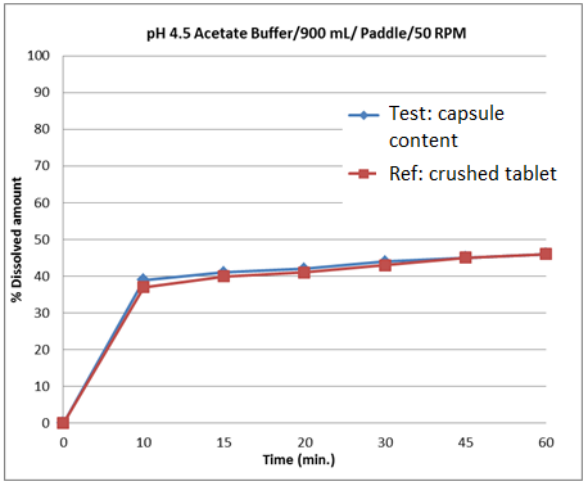
- **BCS II**
- **Method of administration:**
  - Administration with food
  - For patients who are unable to swallow whole tablets, tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed tablets, the dose should be immediately followed by food.
- **Originator**: tablet, **Zentiva product**: hard capsule
- **BEQ study successful for „whole capsule“**

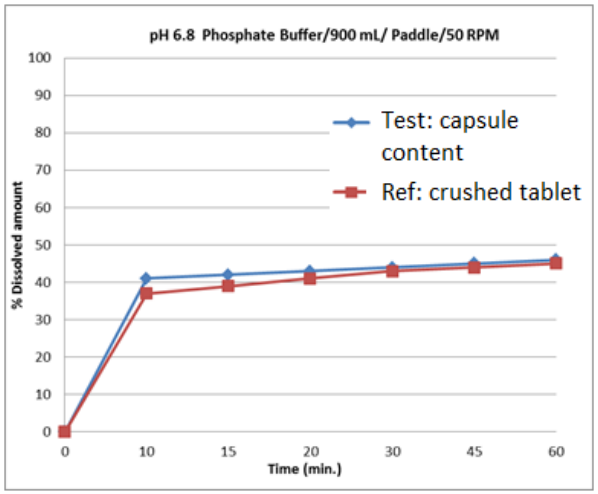


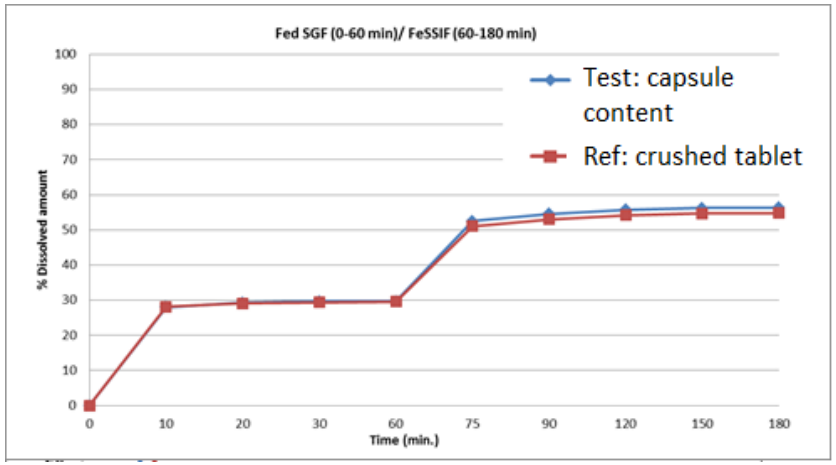
In-house experience – Product B

- in-vitro dissolutions









Study design - factors to consider
- FOOD ADMINISTRATION – when?

Food administration follows the SmPC:

For patients who are unable to swallow whole tablets, the tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. ***After the administration of crushed tablets, the dose should be immediately followed by food.***

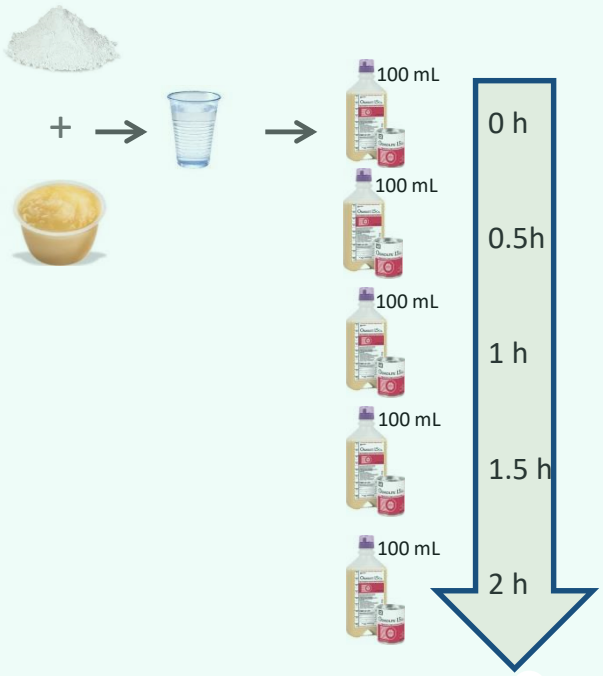
Food to be consumed within 30 min after dosing

vs. standard fed study design (breakfast consumption wihin 30 min before dosing)

Study design - factors to consider
- FOOD ADMINISTRATION – what?

Originator´s study:

- Osmolite® 1.5 Cal (nutrition drink)
- real world patients with swallowing problems will rather prefer nutrition drink than solid meal



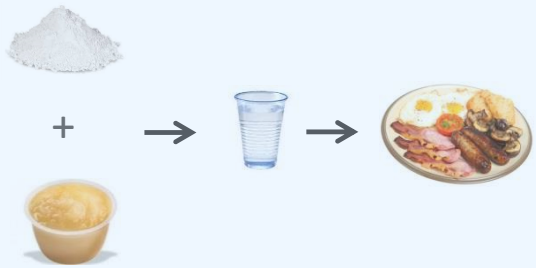
Zentiva´s study:

- Standardized high-fat high- calorie breakfast

(no specific recommendation on the composition of the meal in the SmPC)

- No nutrition drink contains required composition of meal (150 kcal of protein, 250 kcal of carbohydrate and 500-600 kcal of fat)

(Possibility of in-house preparation, but risk of diarrhoa and GIT problems)



Study design - factors to consider

- how to crush?

- ✓ **Standardization**
- ✓ **Minimal losses**
- ✓ **No cross contamination**
- ✓ **Smooth dosing procedure**

Study design - factors to consider
- tablet crusher

Crushers with disposable vessels

Disposable cups

Ocelco Plastic Pillcrusher

Rhino Crush

First Crush Automated Gen2

Disposable bags

Metal handheld crusher

Silent Knight Pill Crusher

Powdercrush

Crushers Without disposable vessels

Hand twisting

Ultra Fine Cut N Crush

Ergo-grip crusher

Pill Crusher PharmaSystems

Mortar and Pestle-like

Ball and socket tablet pulverizer

Blade

Vitacarry automatic pill grinder

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Thong MY, Manrique YJ, Steadman KJ (2018) Drug loss while crushing tablets: Comparison of 24 tablet crushing devices. PLoS ONE 13(3): e0193683

Study design - factors to consider
- tablet crusher

Silent Knight ® Pill Crusher

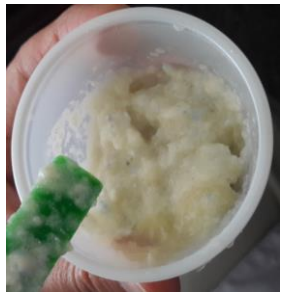
standardized crushing force for each tablet

slight risk of **rupture** of the pouch and **contamination** of the crusher

→ **doubles pouches**
→ **gentle shake of the pouch after each crushing motion**
→ **standby crusher**

Tablet crushing and administration procedure 1 (Reference)

Crushing
(5 times)



CRITICAL STEP

Hard to rinse all the material

Rinsing of pouch

The rest of water consumed

Rinsing of dosing cup

At least 7 rinses needed

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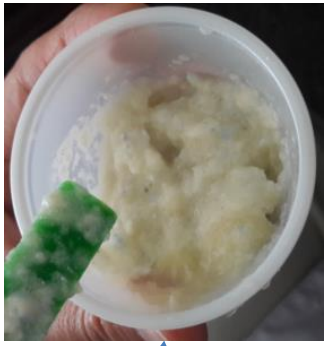
Tablet crushing and administration procedure 2 - FINAL

Crushing (5 times)

cca 1/2



Rinsing of dosing cup

The rest of water consumed

Rinsing of pouch

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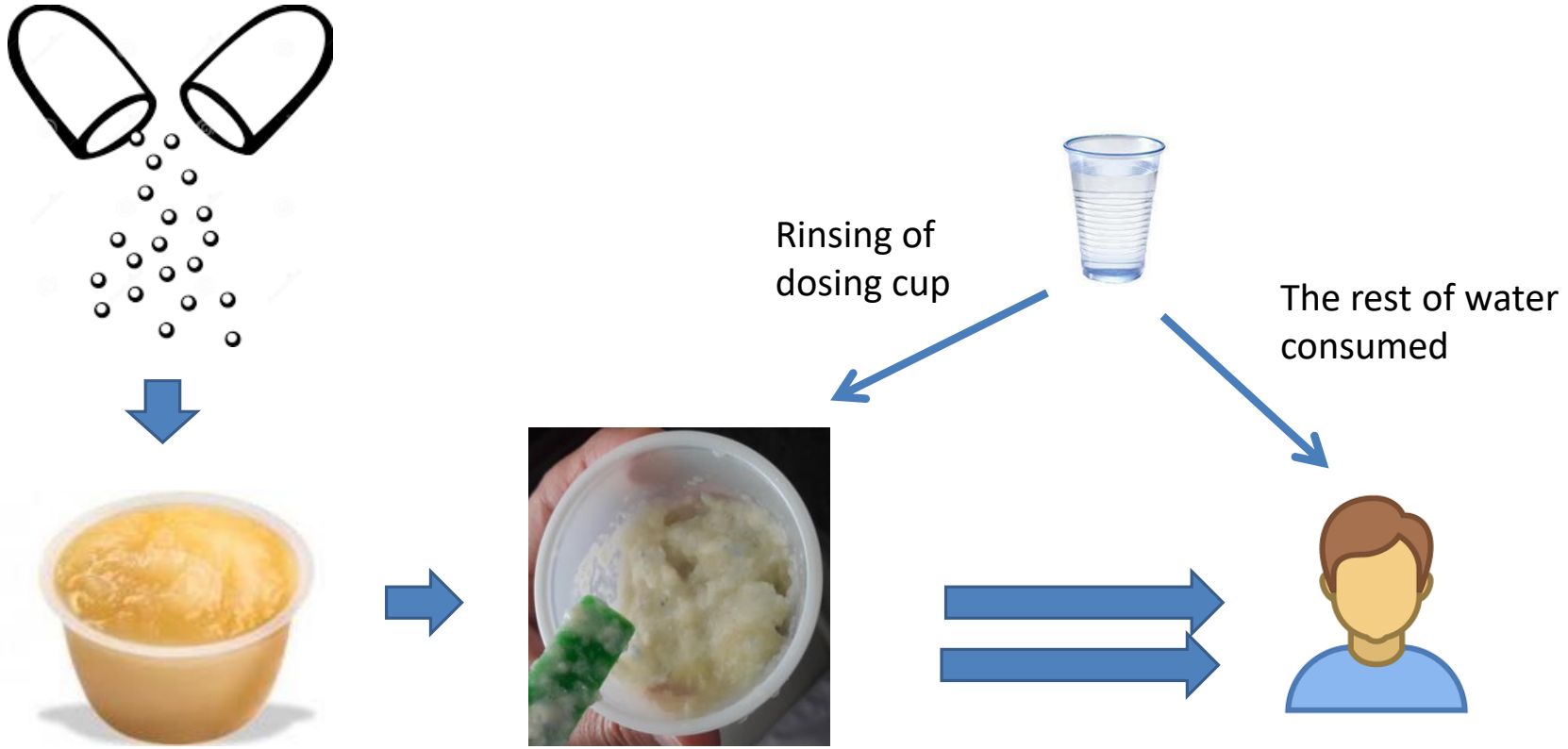
Capsule administration procedure (Test)



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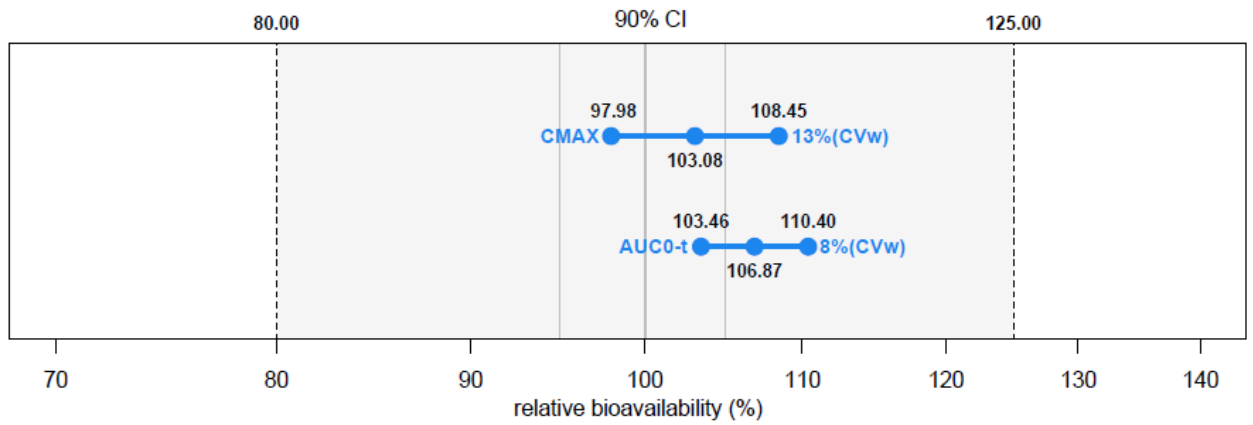
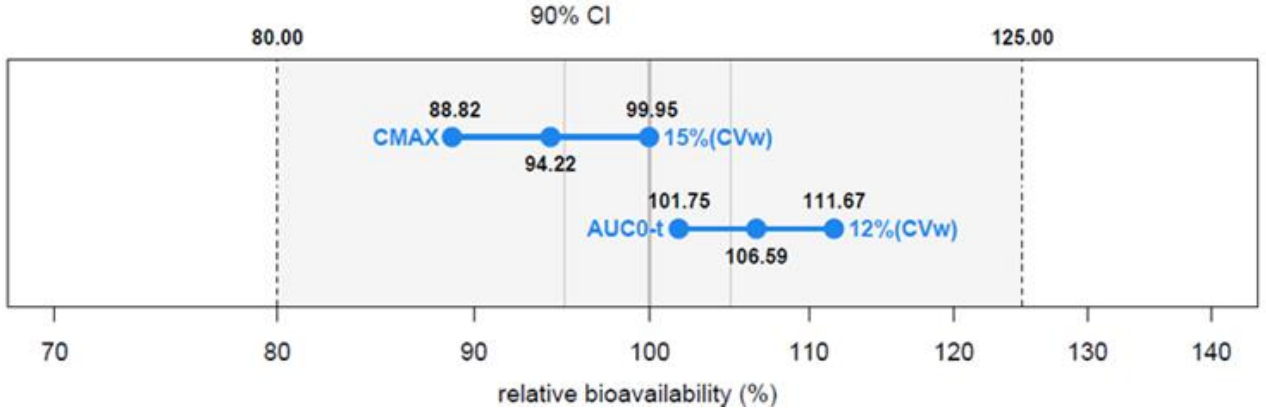
Product B - Study results

✓ **Spilled capsule content vs. Crushed tablet**



✓ **Whole capsule vs. Whole tablet**

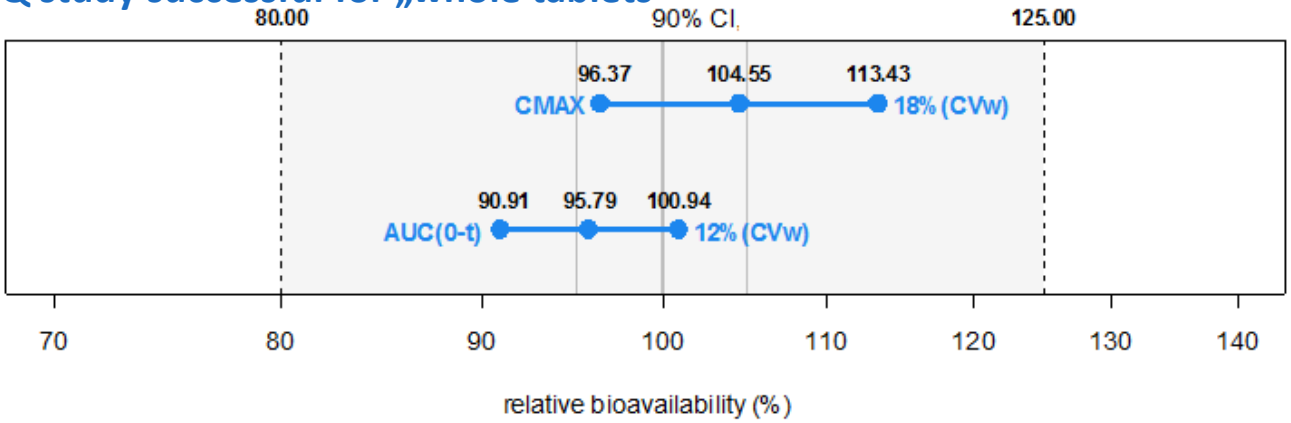


Dosing of crushed tablet
- important points

- **to avoid time pressure** – sufficient intervals between administration
- **precautions for a case of pouch rupture:**
  - double pouches
  - sufficient amount of spares
  - standby crusher
- **to minimalize the losses during the manipulation**
  - training of personell

In-house experience – Product C
- basic information

- **BCS II**
- **Method of administration:**
  - Administration with or without food
  - For patients who are unable to swallow whole tablets, the **film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce**.
- **Originator**: tablet, **Zentiva product**: tablet
- **BEQ study successful for „whole tablets“**



Product C
- crushed tablet administration

Administration by **individual crusher for each subject**

→ no risk of pouch rupture

Pill Crusher PharmaSystems®

Tablet crushing and administration

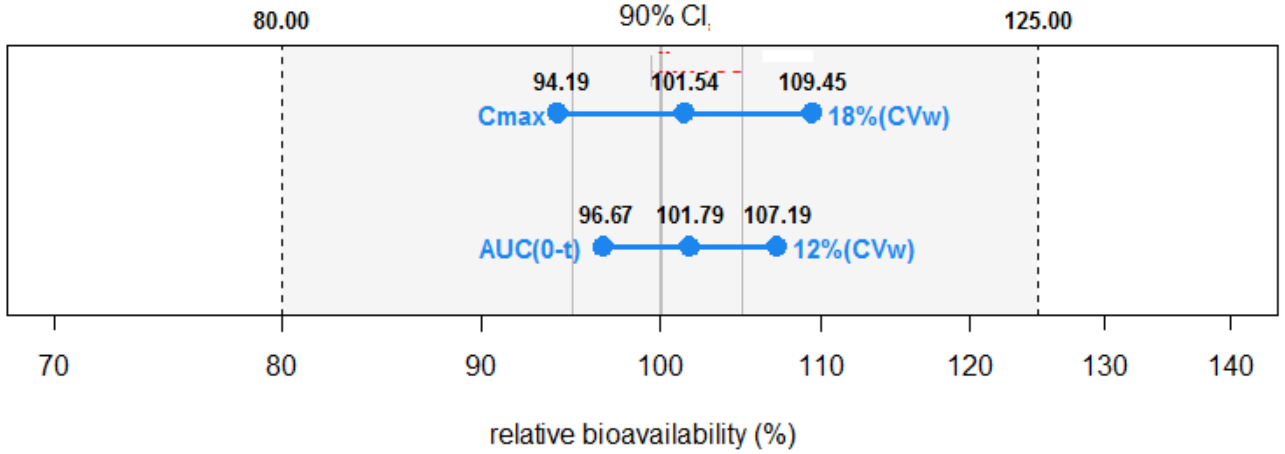
Product C

Crushing (3 times)

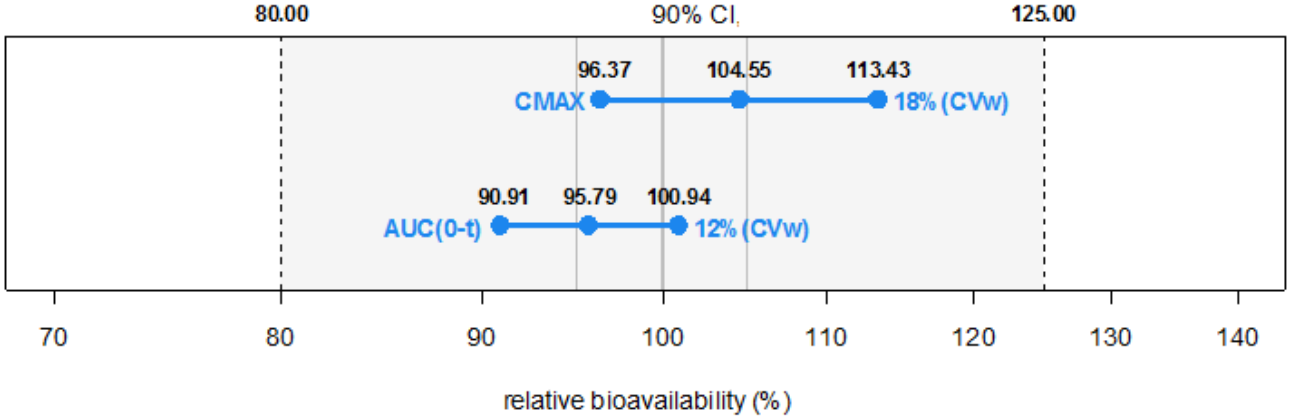
The rest of water consumed

Product C - Study results

✓ Crushed tablet study



✓ Whole tablet study



In-vitro/ in-vivo testing

- EMA Q&A on Clinical pharmacology and pharmacokinetics

Limiting step:
- Gastric emptying

Limiting step:
- solubility
- intrinsic dissolution

In-vitro testing
- ✓ *In-vitro* dissolutions
- ✓ Disintegration
- ✓ Evaluations of excipients

Permeability

CLASS I	CLASS II
High solubility High permeability	Low solubility High permeability
CLASS III	**CLASS IV**
High solubility Low permeability	Low solubility Low permeability

In-vivo testing
- ✓ *Crushed tablet BEQ study*

Limiting step:
- intestinal membrane permeation

Limiting step:
- solubility
- intrinsic dissolution
- intestinal membrane permeation

Solubility

Apixaban draft product-specific guideline

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **Neither of the two** **Background:** Apixaban is a compound with incomplete absorption, but the available data on solubility does not allow its BCS classification. If the applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, apixaban could be classified as BCS class III drug and a BCS-based biowaiver could be applicable.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 5 mg
	Background: Apixaban shows linear pharmacokinetics in dose range 2.5 - 10 mg. If it can be demonstrated that apixaban is highly soluble, in principle any strength may be used.
	Number of studies: One single dose study with intact tablets. An additional study may be required with crushed tablets, unless scientifically justified.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00 – 125.00%

Gefitinib draft product-specific guideline

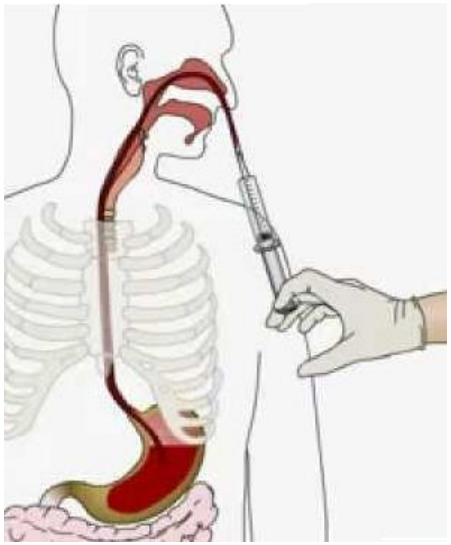
BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Gefitinib is a low solubility drug.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 250 mg **Background:** This is the only available strength.
	Number of studies: One single dose study.
	Other aspects: Additional in vitro studies should demonstrate similarity with the reference product when tablets are administered as dispersion in water and as dispersion through a nasogastric tube.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max}
	90% confidence interval: 80.00 – 125.00%

Nasogastric tube

- in-vitro studies

***In-vitro* NG tube testing**

- Sedimentation testing
- Particle size distribution study
- Comparative recovery testing
  - oral syringe and nasogastric tube
  - funnel and G tube



→ robustness of in-vitro testing required

- Medium (water/ apple juice)
- Pre-soaking time
- Tube size
- Tube material

- SOPs for the exepriments
- Risk assessment of various administration conditions

Crushed tablet studies
- Key points

- Crushed tablet administratio are appropriate for patients with dysphagia
- Not all the tablets shall be crushed!
- Crushed tablet administration is needed for:
    - full interchangeability with reference product
    - claiming the same alternative method of administration as originator
- **Crushed tablet study is required for badly soluble products (BCS 2 and 4), but there may be some exceptions..**
- **Crushed tablet study may be waived for well soluble products (BCS 1 and 3) based on *in-vitro* testing**
- Administration of full dose must be ensured during dosing of the subejcts
- Study specifics to be evaluated case by case

Acknowledgement

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Thank you for your attention!!!