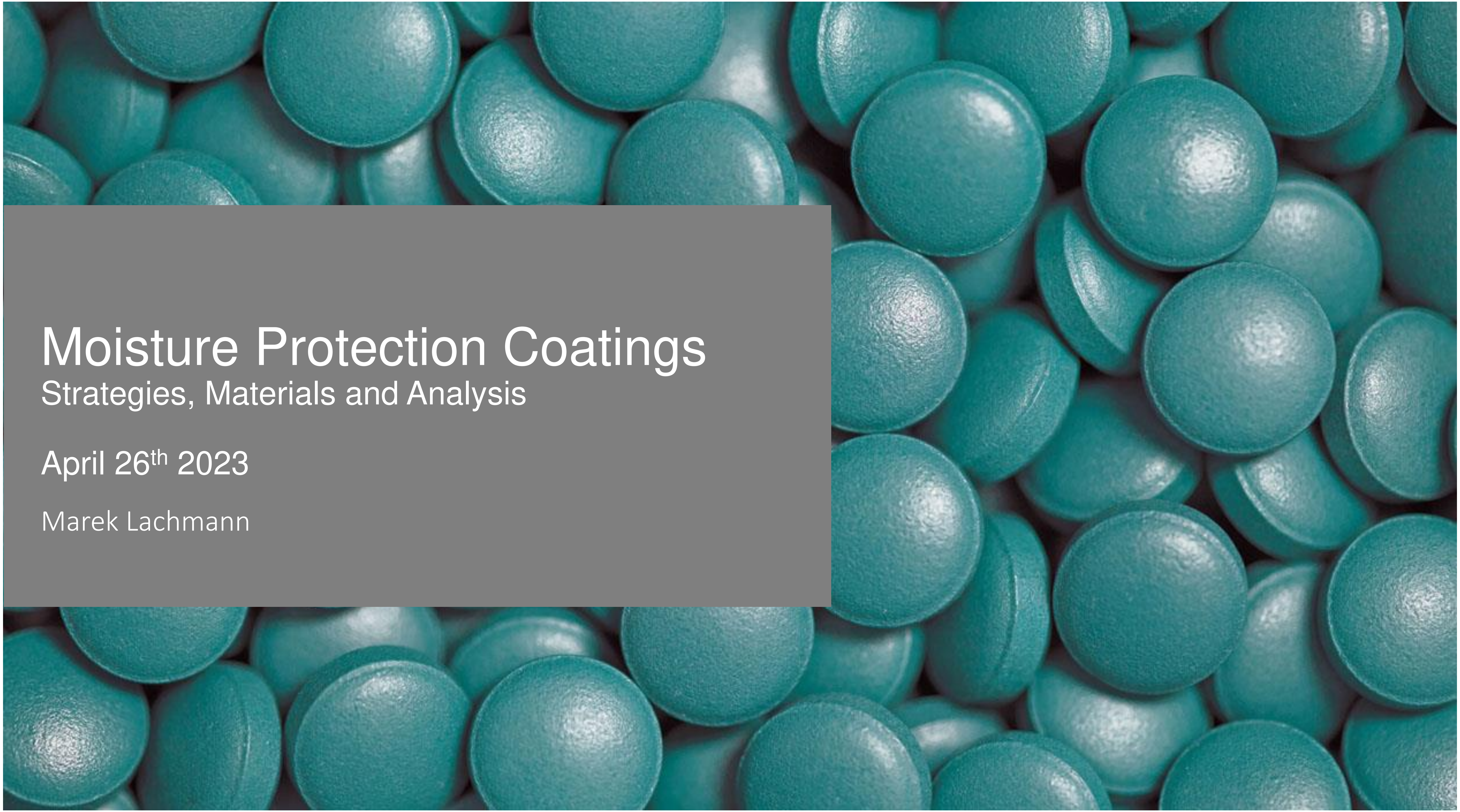


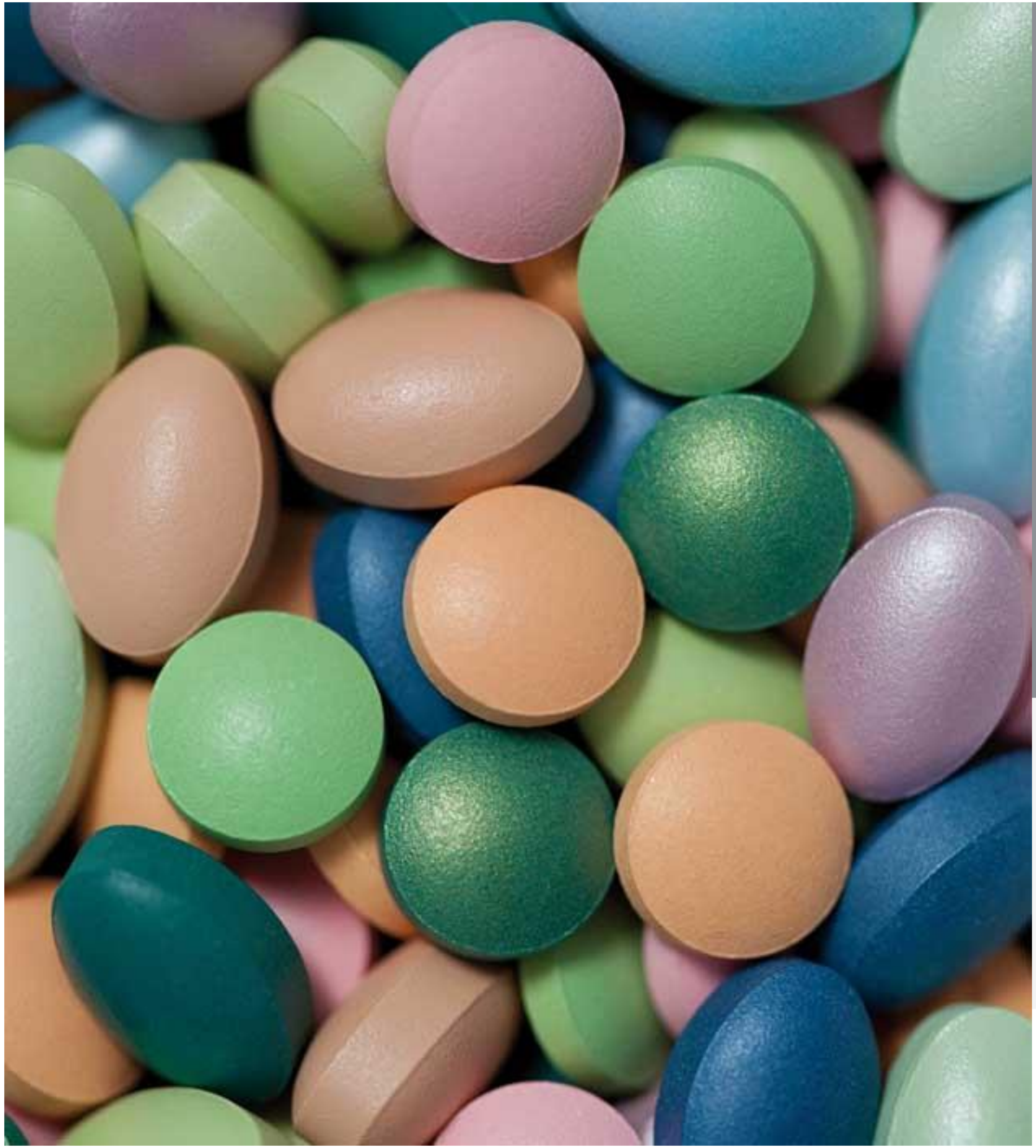
Moisture Protection Coatings

Strategies, Materials and Analysis

April 26th 2023

Marek Lachmann

Contents



Hydrolysis of APIs and Excipients

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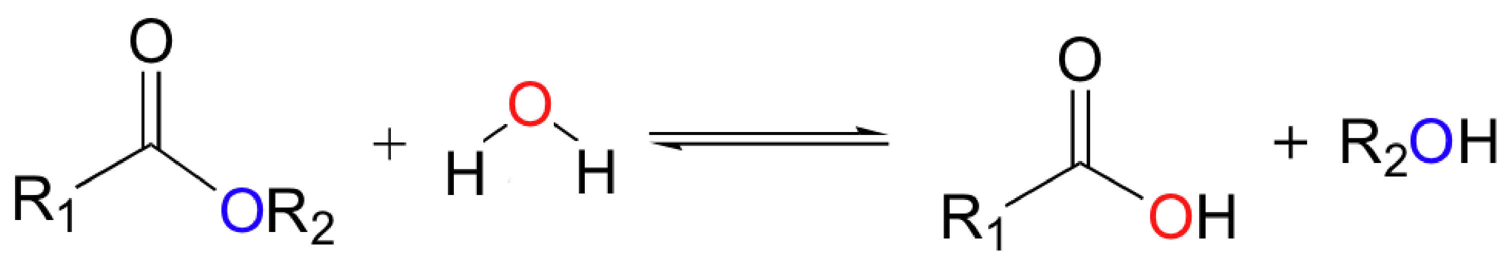
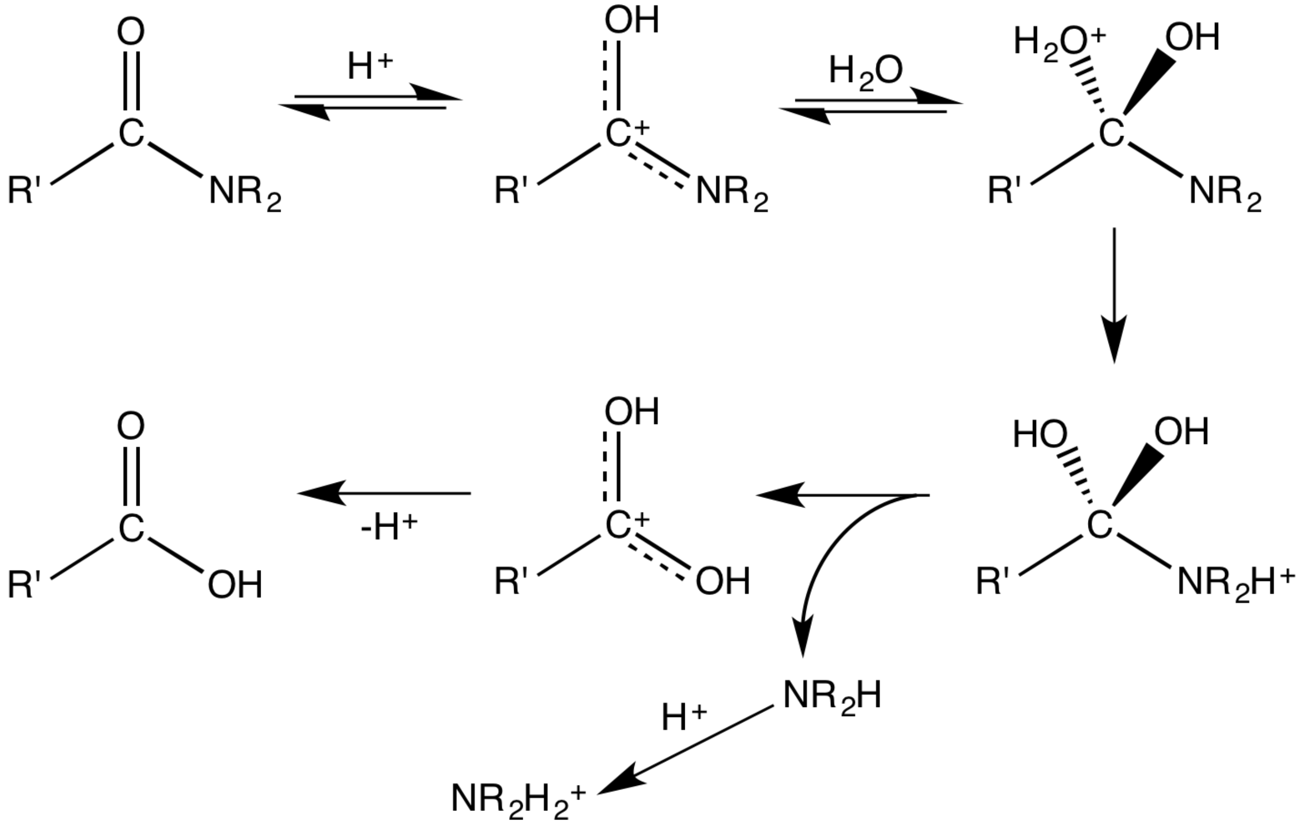
Hydrolysis of APIs and Excipients

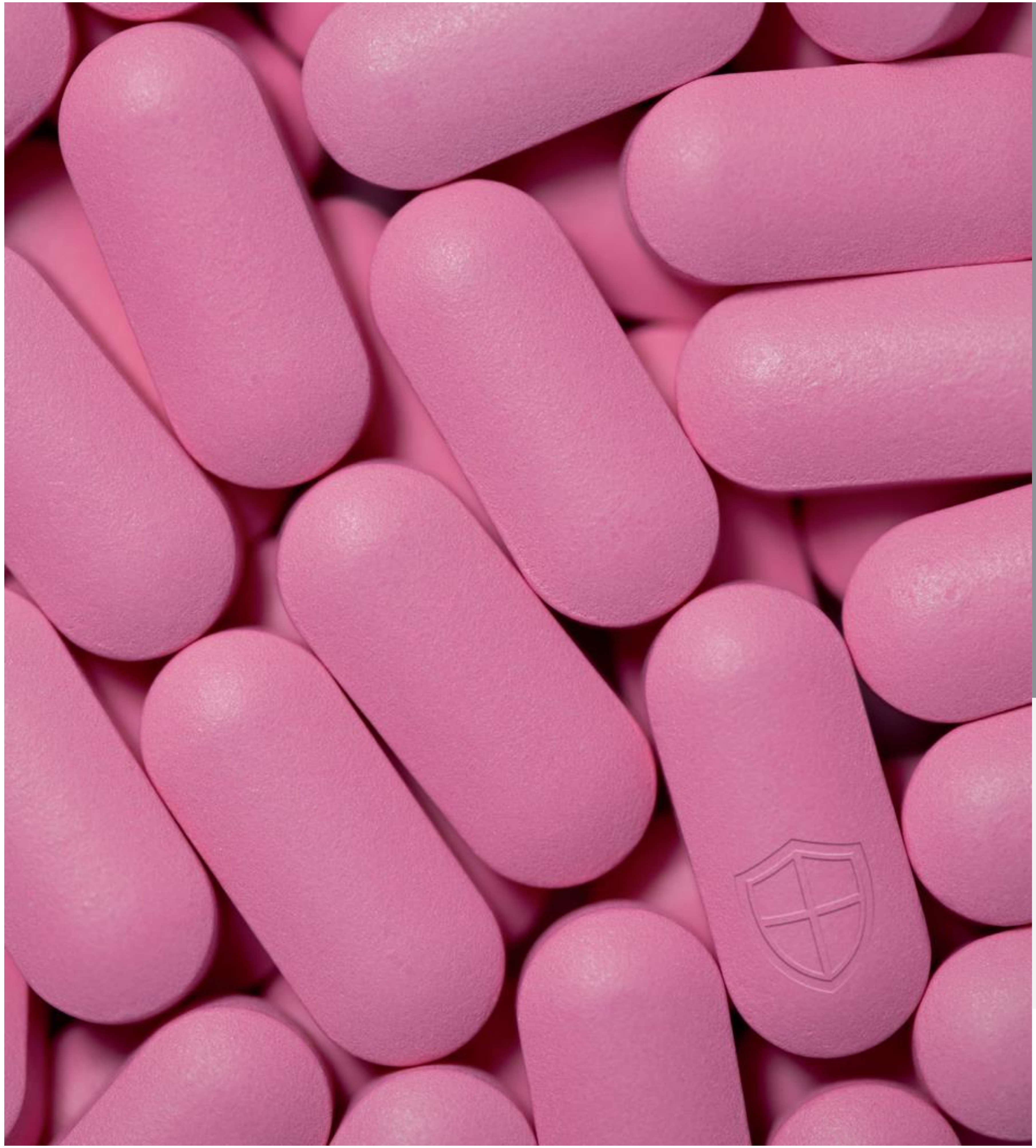
- Moisture can have a severe impact on the stability of active pharmaceutical ingredients (API) within pharmaceutical dosage forms
- Mostly the active ingredients, but also some excipients, might be prone to degradation processes due to hydrolysis
- The term is used broadly for substitution, elimination and solvolysis reactions in which water is a nucleophile
- During the reaction a hydrogen atom of the water molecule is attached to one part of the degraded (hydrolysed) molecule and the remaining hydroxyl group is bound to the remaining part of the hydrolysed molecule
- The graph on the right shows an example for a acid catalysed hydrolysis of an amide compound



Generic Hydrolysis Reaction [1]



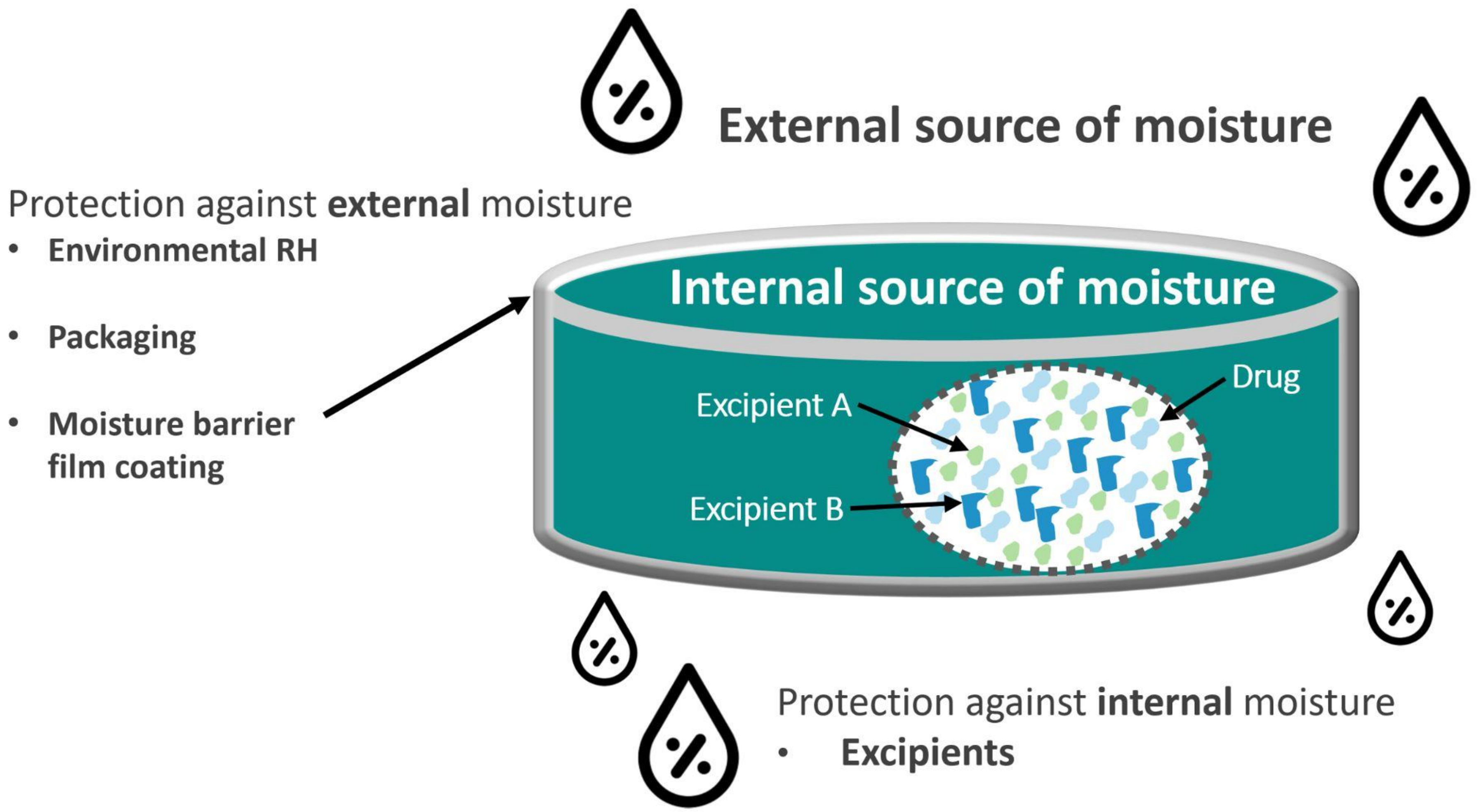
Mechanism for acid-catalyzed hydrolysis of an amide [1]



Protection Strategies

Protection Strategies

- Chosing the idal dosage form is essential to ensure API stability
- Most often solid dosage forms (e.g. tablets or capsules) are a good choice due to their low water content
- The next step in moisture protection strategy is to pick the right excipients for the formulation effort
- Generally external source of moisture can be distinguished from internal sources of moisture



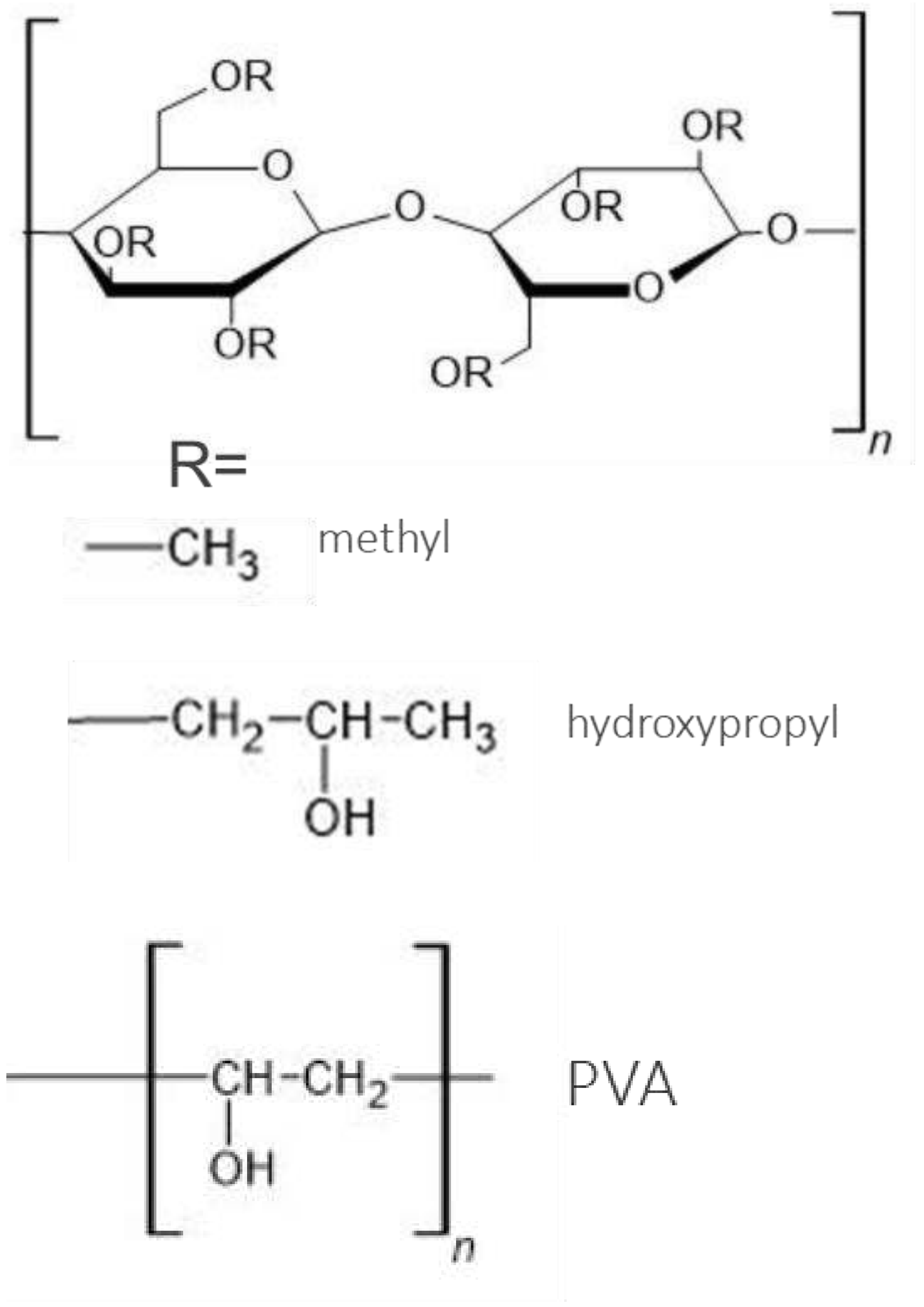
Moisture protection approaches (adapted from [3])

- The main external source of moisture is the water vapor in the environment surrounding the dosage form
- Internal moisture mostly originates from the ingredients (API or Excipient) that are used for the formulation
- However, the uptake of water vapor into the dosage form internalizes external moisture

Moisture Protection Coatings

Moisture Protection Coatings

- Moisture Protection Coatings are a good, reliable and easy way to protect the dosage form from external moisture (environmental humidity) once the dosage from is removed from the packaging
- Polymers used for moisture protection coatings include HPMC (Hydroxypropylmethyl Cellulose) and PVA (Polyvinyl Alcohol)
- These polymers are used on their own or in combination with hydrophobic additives such as fatty acids or the salts thereof



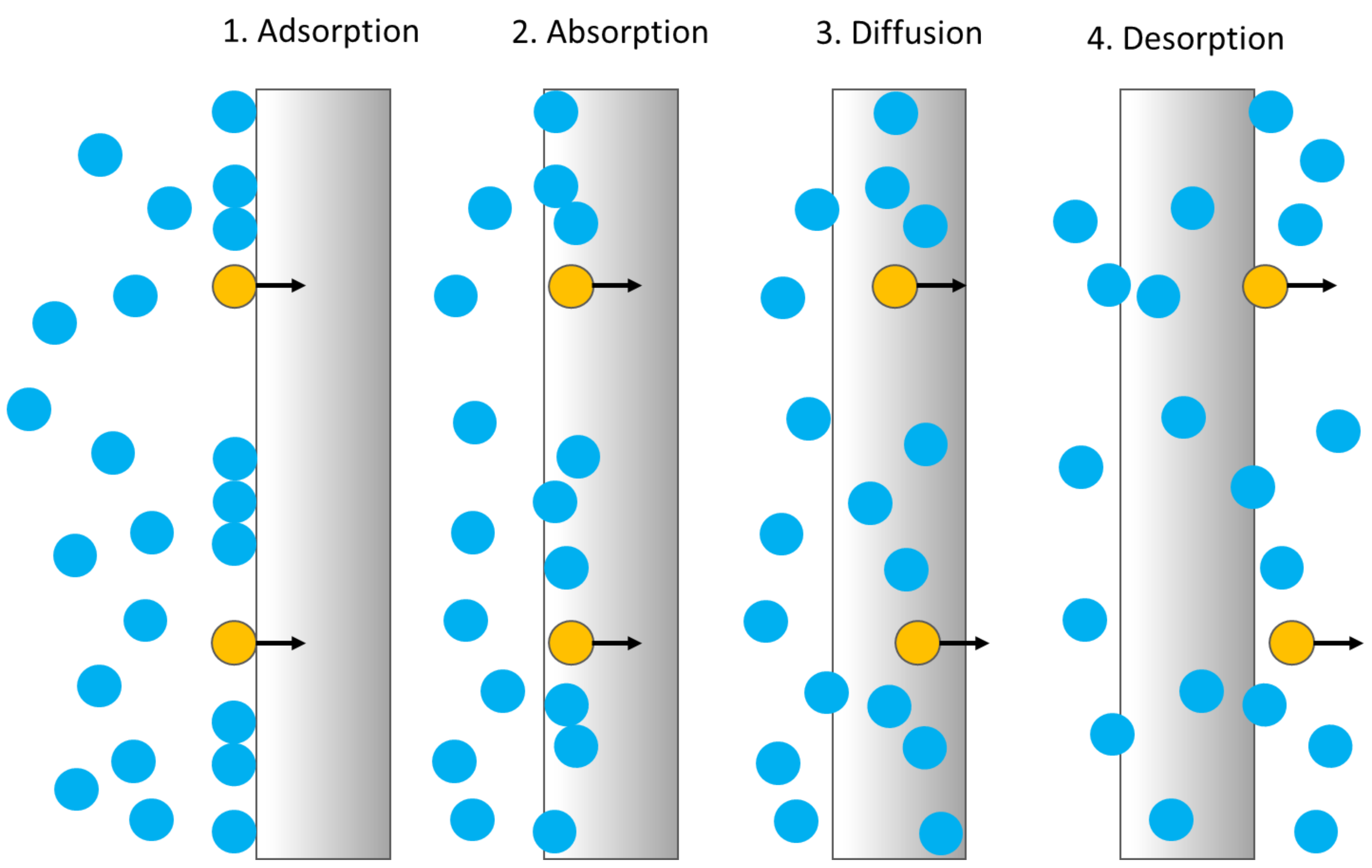
Illustrations of HPMC and PVA

Moisture Protection Coatings

- A moisture protection coating should enable to stop permeation of water vapor into the tablet
- Water vapor permeation through a film takes place in four steps

  1. water molecules are deposited on the surface of film and are hence adsorbed to the surface
  2. Water is absorbed into the film material by physical adsorption due to Van-der-Waals forces , chemical adsorption and because of electrostatic forces
  3. During the diffusion step the water molecules are transported through the film because of the concentration gradient, following Fick´s law

4. Finally the water is transported / taken up into the tablet by desorption from the film material



Scheme of the four steps of a water vapor permeation process through a film (adapted from [4])

Analytical Techniques

Analytical Techniques: Water uptake of coated, hygroscopic tablets

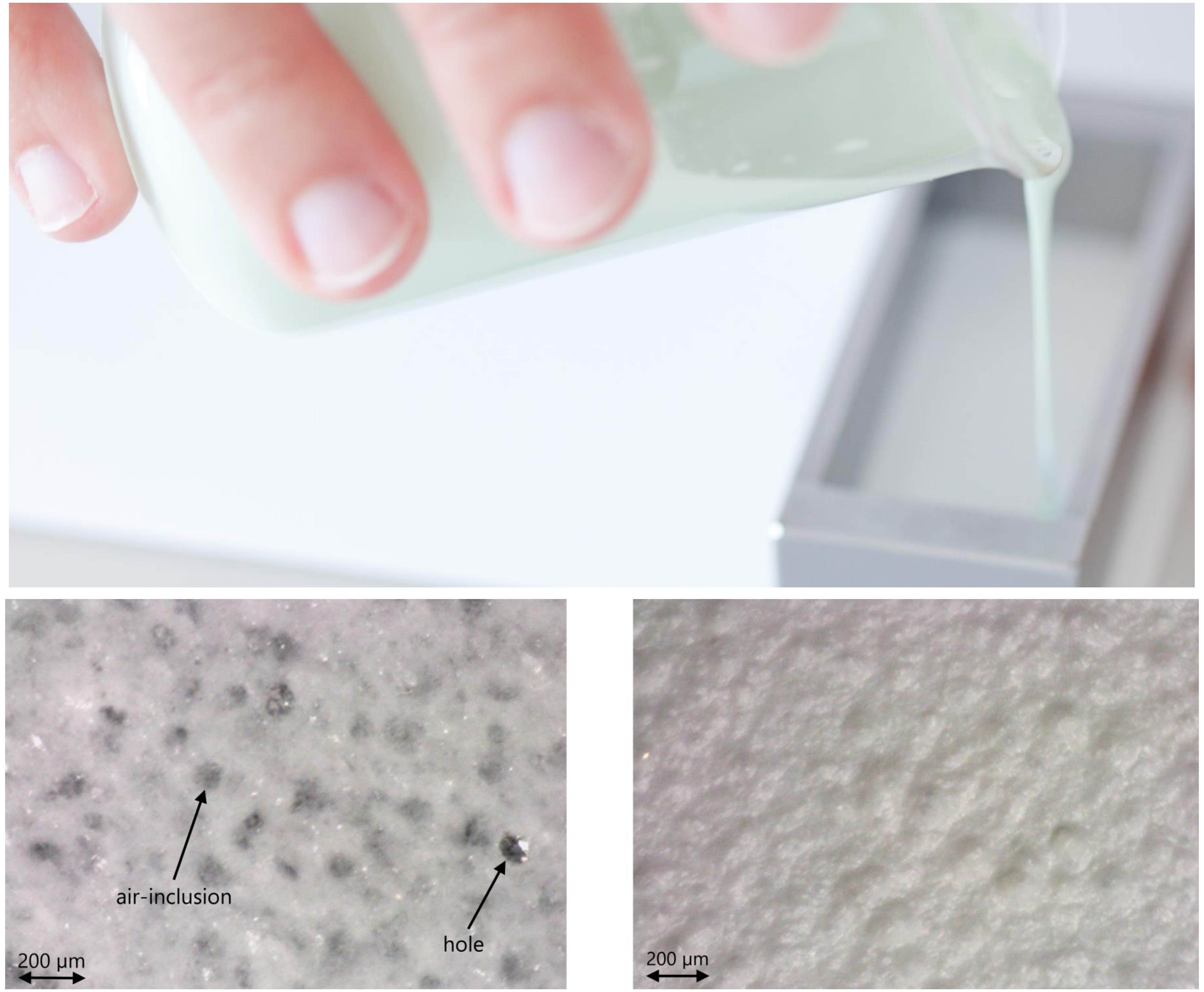
- Saturated salt solutions generate a constant, temperature dependent, humidity that can be used to create a defined environment for testing of water uptake
- For each batch of coatings and for each mass gain value ten tablets were placed in an open petri dish and stored at elevated humidity (70 % RH) at room temperature
- The section of table on the right shows examples of RH values generated by different salts at 20 °C

Solid phase	Percentage R.H.
$CO(NH_2)_2$	80·7[a]
NH_4Cl	80·0[a] 79·2[c]
$Na_2S_2O_3 . 5H_2O$	78·0[c]
$NaNO_3$	77·7[e]
$NaCl$	78·3[a] 76·5[a] 75·8[b]
$CH_3COONa . 3H_2O$	76·0[c]
$H_2C_2O_4 . 2H_2O$	76·0[c]
$NaClO_3$	75·0[c]
$K_2C_4H_4O_6 . \frac{1}{2}H_2O$	75·0[a] 74·1[b]
NH_4Cl-KNO_3 mixture	72·6[b, c]
$NaNO_3$-KNO_3 mixture	71·0[b]
$NaNO_3$-KCl mixture	70·0[d]
$CoCl_2 . 6H_2O$	67·3[b] 67·0[f]
NH_4NO_3	67·4[a] 64·0[f]
$NaNO_2$	66·0[f, c] Room temp. / 66·0[c]

Examples of relative humidity values at 20 °C [5]

Analytical Techniques: Film Casting

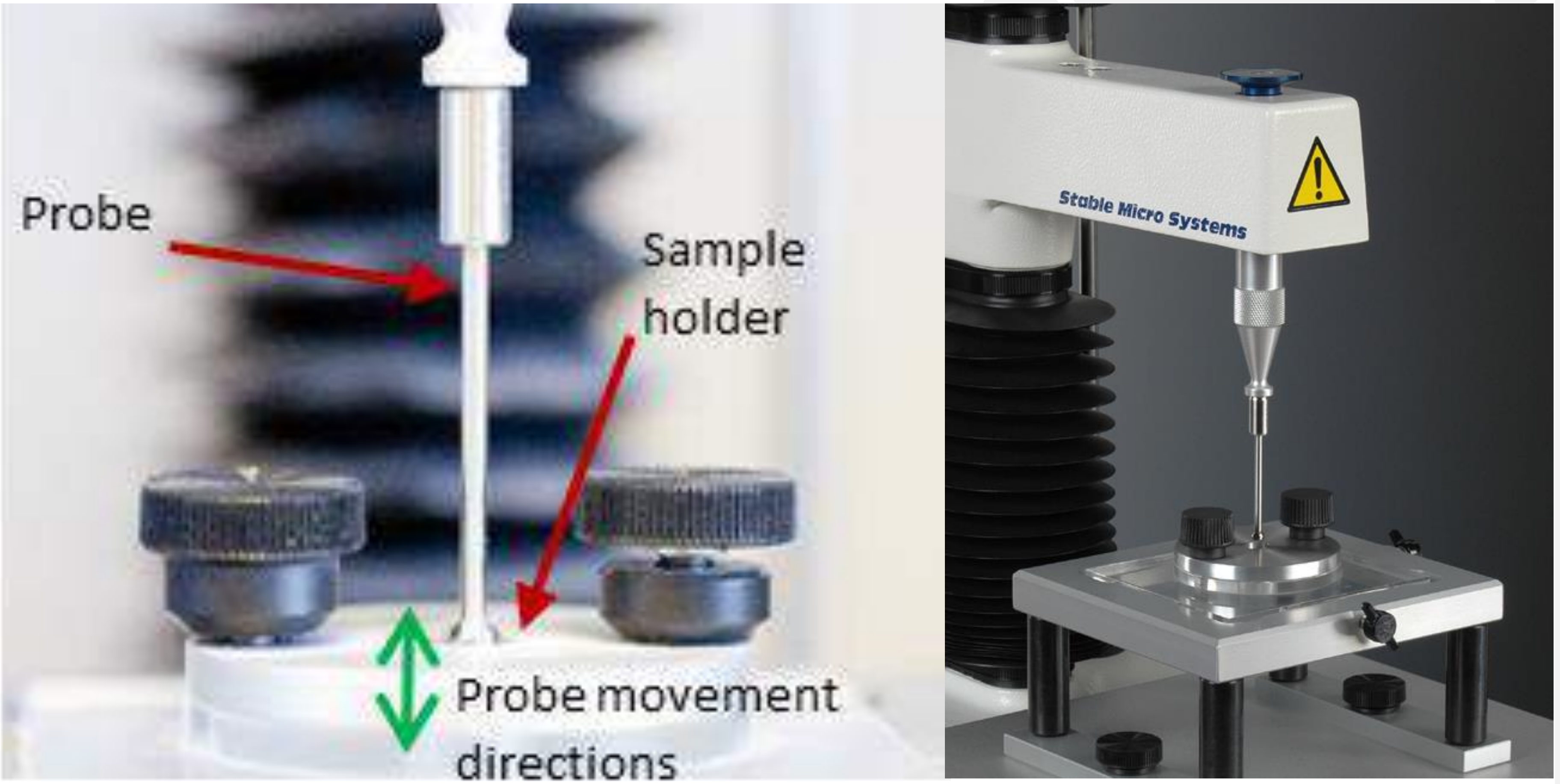
- Casting of films, especially if they need to be of the same thickness, is not an easy task
- The viscosity of the dispersion must be sufficiently low for complete removal of the air bubbles but must be high enough to allow for casting of a film that does not spread in an uncontrolled way
- Air bubbles can be removed from the dispersion by sonication or evacuation
- Once cast it is important to dry the films evenly and slowly
- Oven drying often results in cracked or curled films that are not good for further analysis



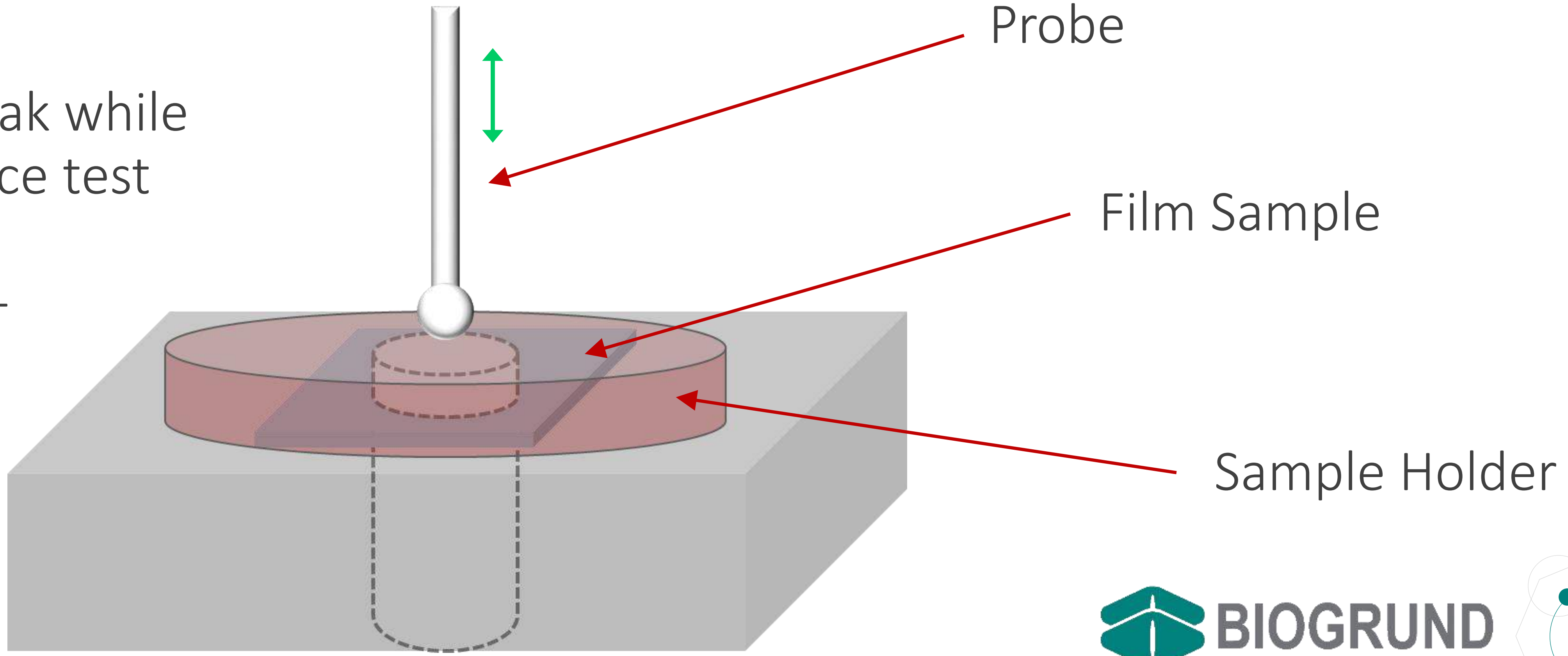
Film casting and microscopic pictures of films

Analytical Techniques: Film Support Rig

- The film support rig of the Texture Analyser allows fixation of a film sample over a hole
- The sample is held into place by a sample holder and the probe is approaching the sample at predetermined speed
- Reaching trigger conditions (specified force) the data recording is started and force, distance and time are recorded
- During the film burst test the film will break while during the relaxation test and the resilience test care must
  be taken to chose settings that avoid film-breakage



Pictures of film burst rig



Function of the film burst rig

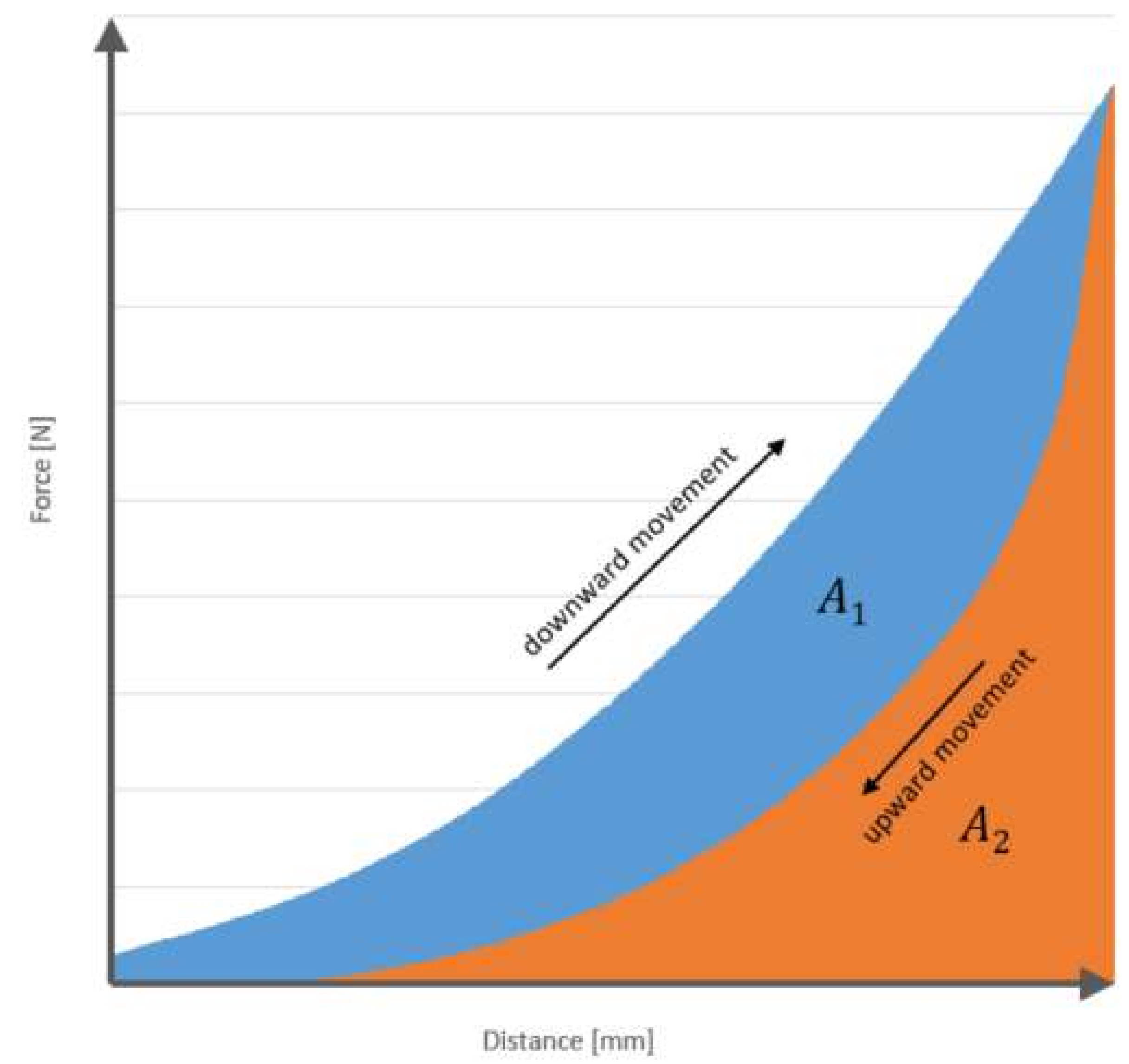
Analytical Techniques: Textur Analyser Resilience Test

- the resilience test gives an indication about the elasticity of the film formulation
- The resilience test also starts with a downward movement of the probe at a speed of 0.5 mm/s with the data recording started by a trigger force at 49 mN. After reaching trigger conditions, the probe moves 0.3 mm into the sample and then retracts at a speed of 0.5 mm/s
- During the upward movement of the probe the film samples enact a force on the probe which is a measure of the elastic properties of the film

$$Resilience\ [\%] = \frac{A2}{A1} * 100$$

- The Resilience is then calculated by using the areas under the curves for the downward and upward movements

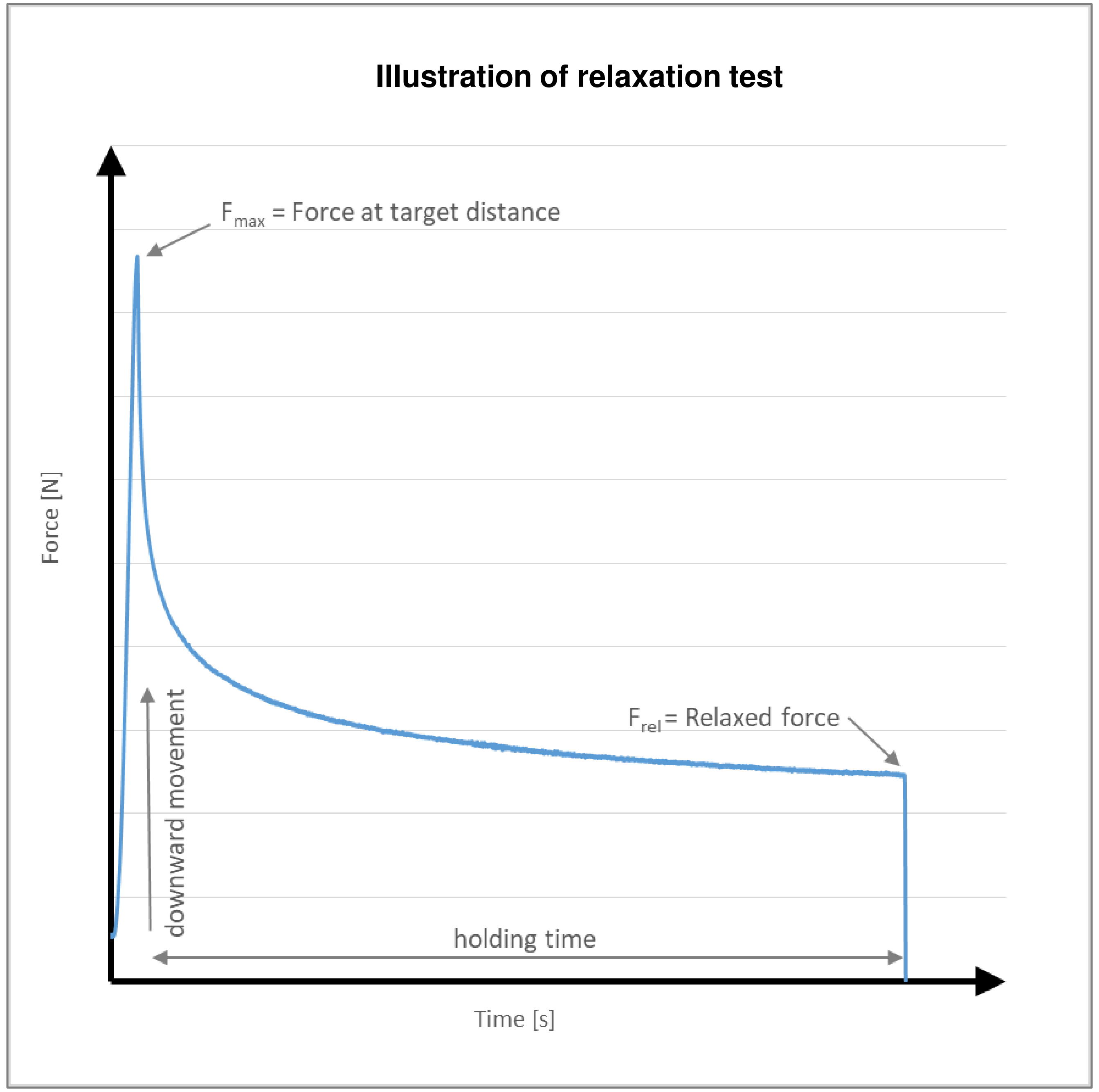
Illustration of film resilience test



Analytical Techniques: Texture Analyser Relaxation Test

- the relaxation test provides information regarding the plastic deformation under load
- For the relaxation test, the probe approaches the sample film at a speed of 0.5 mm/s with the data recording started by a trigger force at 49 mN. After reaching trigger conditions the probe moves 0.3 mm into the sample and then stays in that position for 30 s
- The retained force % is calculated from the relaxed force and the maximum force at the target distance

$$\text{Retained Force}[\%] = \frac{F_{\text{rel}}}{F_{\text{max}}} * 100$$



Analytical Techniques: Water Vapour Transmission // Permeability

- To test the water vapor transmission through a film sample a pristine specimen is cut into an accurate circle
- The sample is then placed onto a bottle containing 25 g of neat sodium hydroxide
- The sample is fixed in with a lid that has a hole of a defined diameter (3 cm)
- The bottles are placed in a climate chamber which generates accelerated storage conditions (40 °C, 75 % RH)
- The mass gain of the bottle is measured frequently (every 24 h) using an analytical balance
- Water vapour transmission and permeability are calculated as shown below [5]

$$Water\ Vapour\ Transmission = \frac{\Delta m}{\Delta t\ A} \qquad Permeability = \frac{\Delta m\ \delta}{\Delta P\ \Delta t\ A}$$

Sample bottle for water vapor transmission measurement

Case Study

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Case Study: Moisture Protection of Vitamin-C tablet formulation

Aims: Investigate moisture barrier properties of different film coatings

Compare mechanical properties of film coating formulations on isolated films

Tablet Composition:

Component	Percentage
Granular Vitamin – C	49.0
Iron oxide yellow	1.0
Microcrystalline cellulose	29.5
Pregelatinized starch	15.0
Hydroxypropyl cellulose, super fine powder	2.0
Croscamellose sodium	2.5
Magnesium stearate	1.0

Tableting Parameters: RoTab T rotary lab press; convex punches; ∅ = 10 mm;

Main Compression Pressure 400 MPa (20 kN)

Pre Compression Force 20 MPa (1 kN)

rotational speed 30 rpm

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Case Study: Moisture Protection of Vitamin-C tablet formulation

Coating Formulations:

No	Product	Polymer	comment
F1	AquaPolish® P white 010.107	HPMC	No moisture protection formulation, containing TiO_2
F2	AquaPolish® P white 010.142	HPMC	No moisture protection formulation, containing no TiO_2
F3	AquaPolish® P white 019.177 MS	HPMC	moisture protection formulation, containing TiO_2
F4	AquaPolish® P white 019.160 MS	HPMC	moisture protection formulation, containing no TiO_2
F5	AquaPolish® P white 610.19 PVA	PVA + PEG	moisture protection formulation, containing TiO_2
F6	AquaPolish® P white 612.02 PVA	PVA + PEG	moisture protection formulation, containing no TiO_2

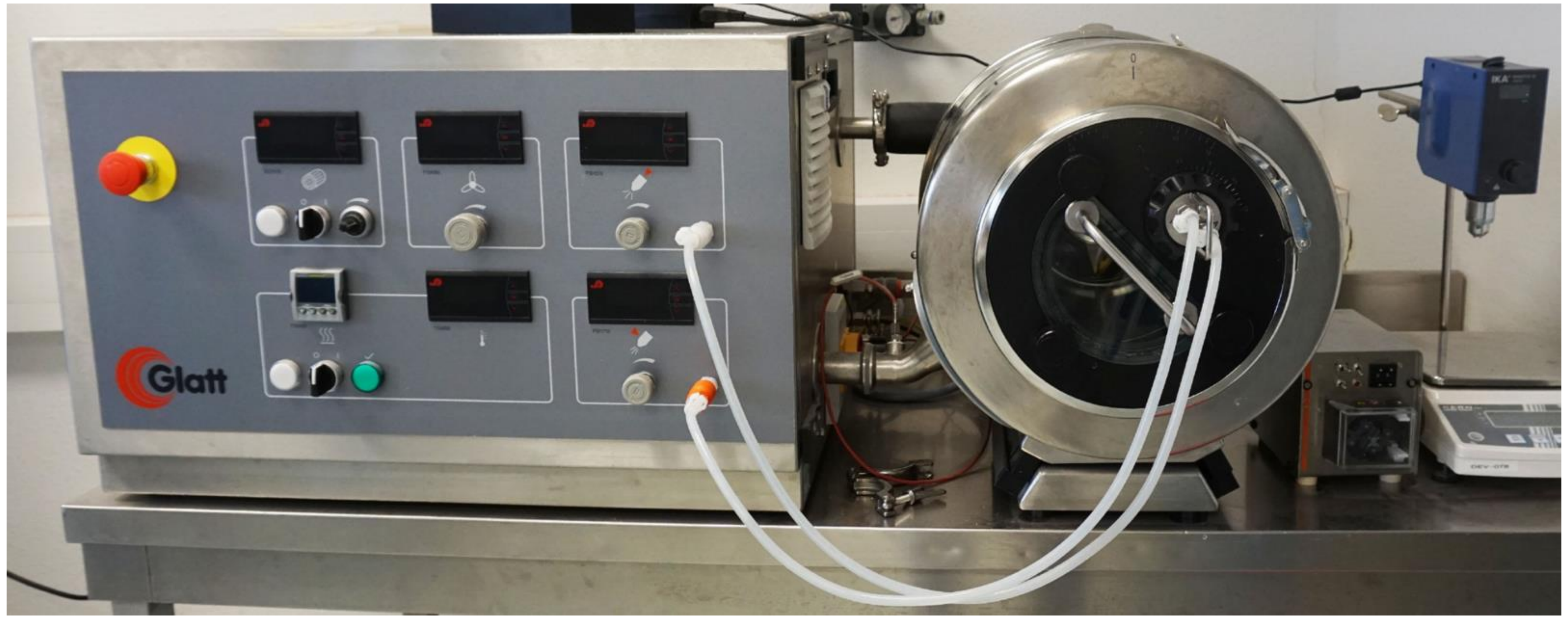
All formulations containing HPMC had a solid content of the dispersions of 15% and all PVA containing preparations of 20 %.

Case Study: Moisture Protection of Vitamin-C tablet formulation

Coating Process:

Parameter	Unit	PVA formulations	HPMC formulations
Inlet Air Temperature	°C	75 – 80	70 - 72
Tablet Temperature	°C	44 - 46	39 - 41
Drum Rotation	rpm	9	
Spray rate	g/min	3.0 – 3.4	3.5 – 4.0
Spray pressure	bar	1.0	
Pattern Pressure	bar	1.0	
Outlet Air temperature	°C	48 – 52	44 - 46

750 g of tablets were coated in a Glatt GC1 drum coater for each coating material under investigation to reach 3%, 5% and 7% of mass gain



Case Study: Moisture Protection of Vitamin-C tablet formulation

No	Product
F1	AquaPolish® P white 010.107
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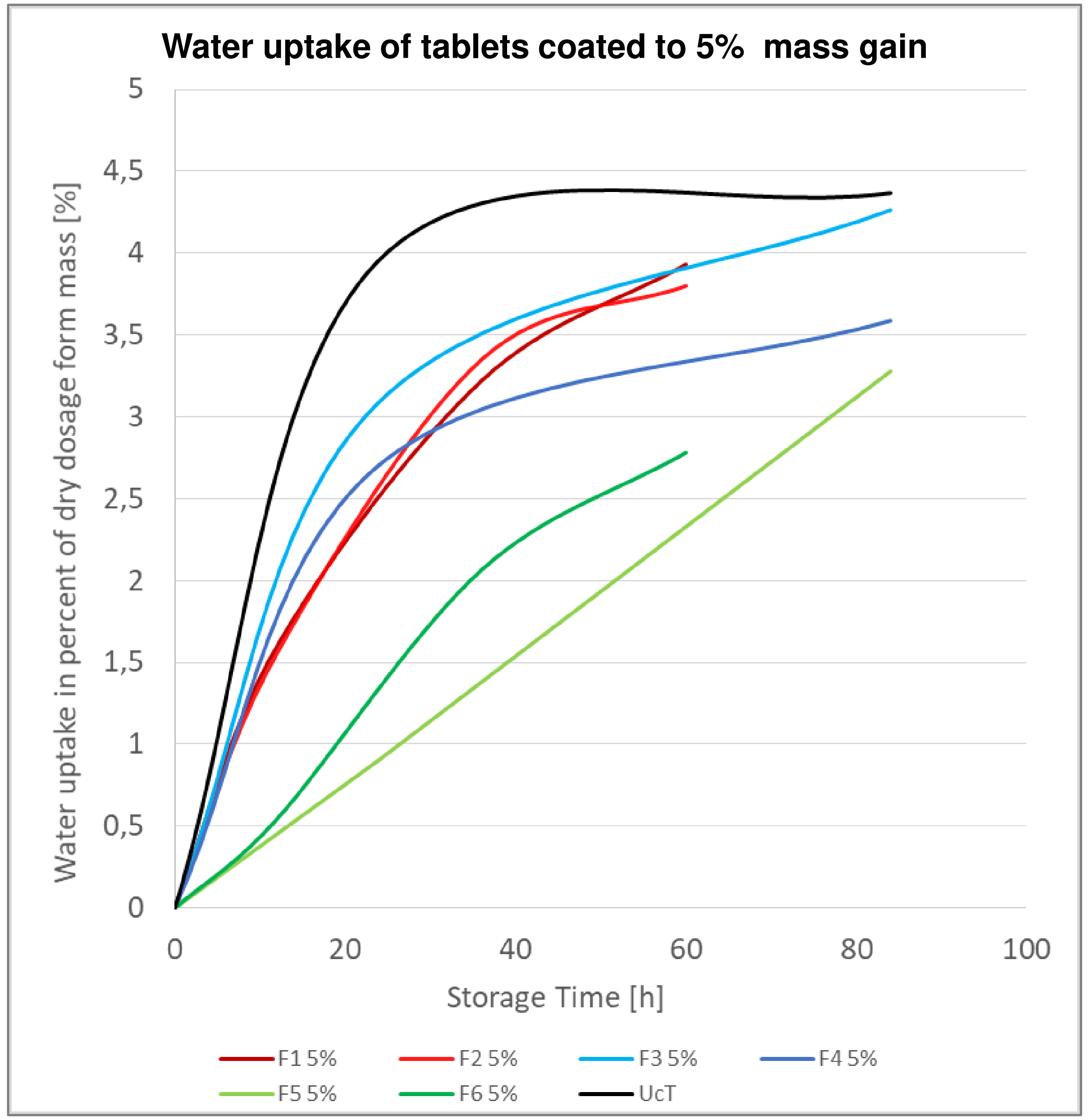
F3	AquaPolish® P white 019.177 MS
F4	AquaPolish® P white 019.160 MS
F5	AquaPolish® P white 610.19 PVA
F6	AquaPolish® P white 612.02 PVA

Results for Coated Tablets: water uptake of hygroscopic tablets

- Estimation the barrier functions by measuring the water uptake of tablets is difficult and prone to errors due to film thickness variations
- Moreover, the moisture content within a dosage form can be affected by the coating process itself (drying of the tablet during the coating process)
- The results for the water uptake experiments clearly show a superior performance of the PVA formulations in comparison to the HPMC coatings

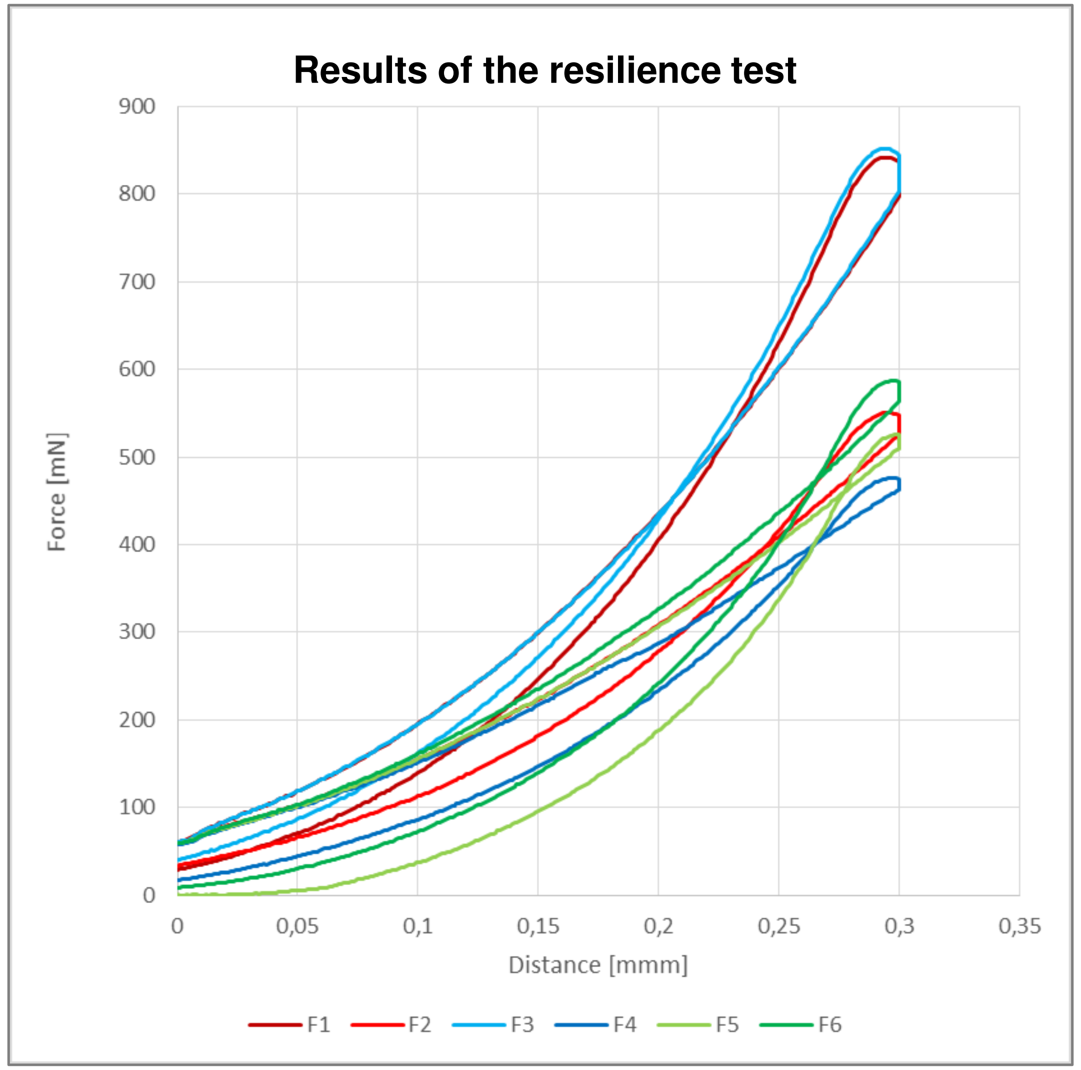


https://www.dino-lite.eu/en/component/eshop/am7915mzt-edge?Itemid=0

Case Study: Moisture Protection of Vitamin-C tablet formulation

Results for Isolated Films: resilience test

- The moisture protection coating with HPMC and TiO_2 (F3) shows the highest resilience followed by the HPMC formulation with TiO_2
- This indicates that the addition of the fatty compound (providing extra moisture protection) is not affecting the resilience of the film
- PVA coatings show the lowest resilience, leading to the conclusion that these film are less elastic than the other formulations



$$Resilience\ [\%] = \frac{A2}{A1} * 100$$

No	Force at Target Distance [mN]	Resilience [%]
F1	842(+/- 102)	84,30 (+/- 1.43)
F2	551 (+/- 46)	83,52 (+/- 7.37)
F3	852 (+/- 62)	89,32 (+/- 1.94)
F4	477 (+/- 147)	76,58 (+/- 7.81)
F5	526 (+/- 11)	60,13 (+/- 3.02)
F6	587 (+/- 16)	70,23 (+/- 5.62)

No	Product
F1	AquaPolish® P white 010.107
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F4	AquaPolish® P white 019.160 MS
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F6	AquaPolish® P white 612.02 PVA

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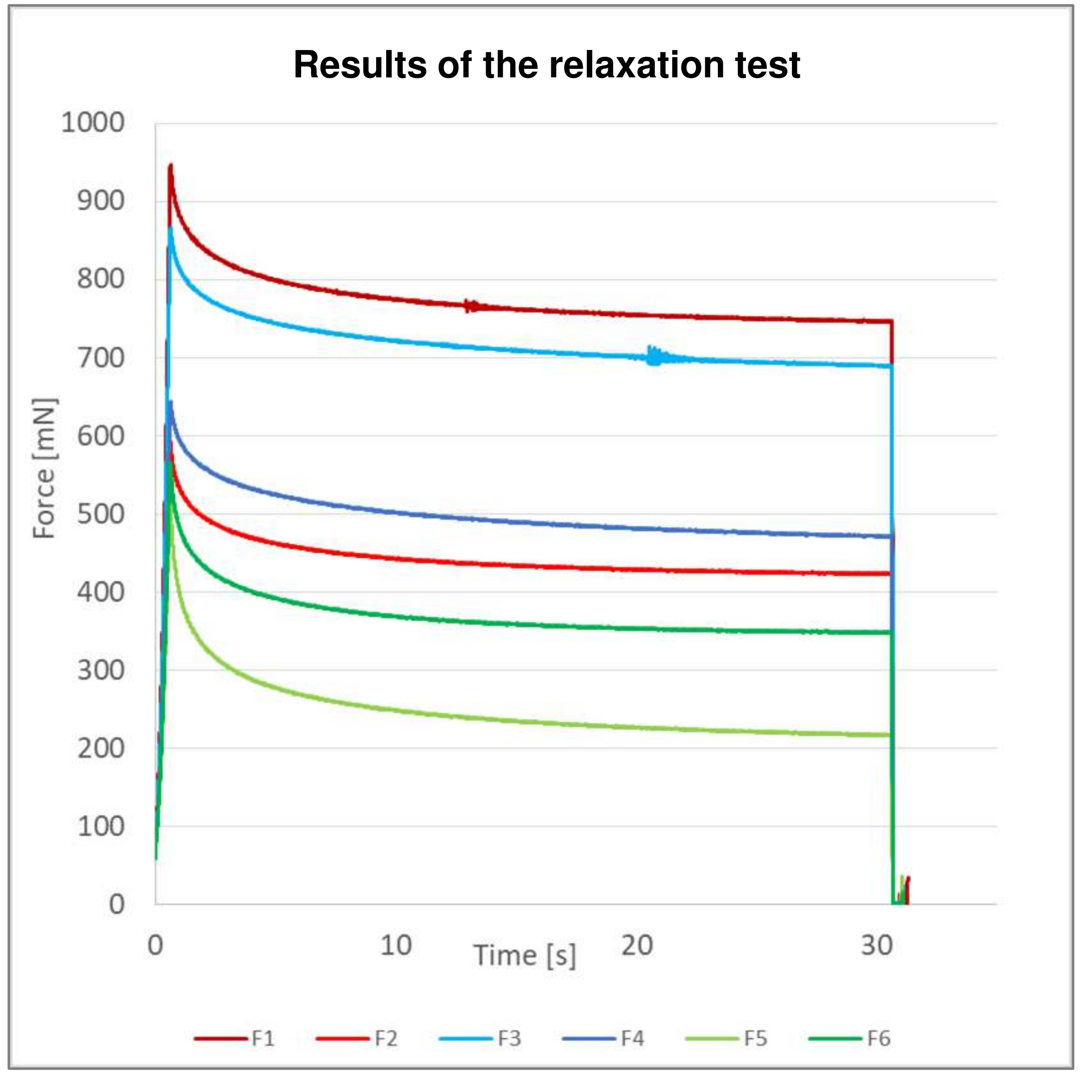
Case Study: Moisture Protection of Vitamin-C tablet formulation

Results for Isolated Films: relaxation test

- In correlation with the resilience test the PVA coatings showed the lowest retained force, indicating a more plastic deformation behavior
- Furthermore, there is a good correlation between the relaxation test and the resilience test for formulations F1 and F3
- In both cases the HPMC formulations require more force to cause deformation
- The retained force is high for all HPMC formulations



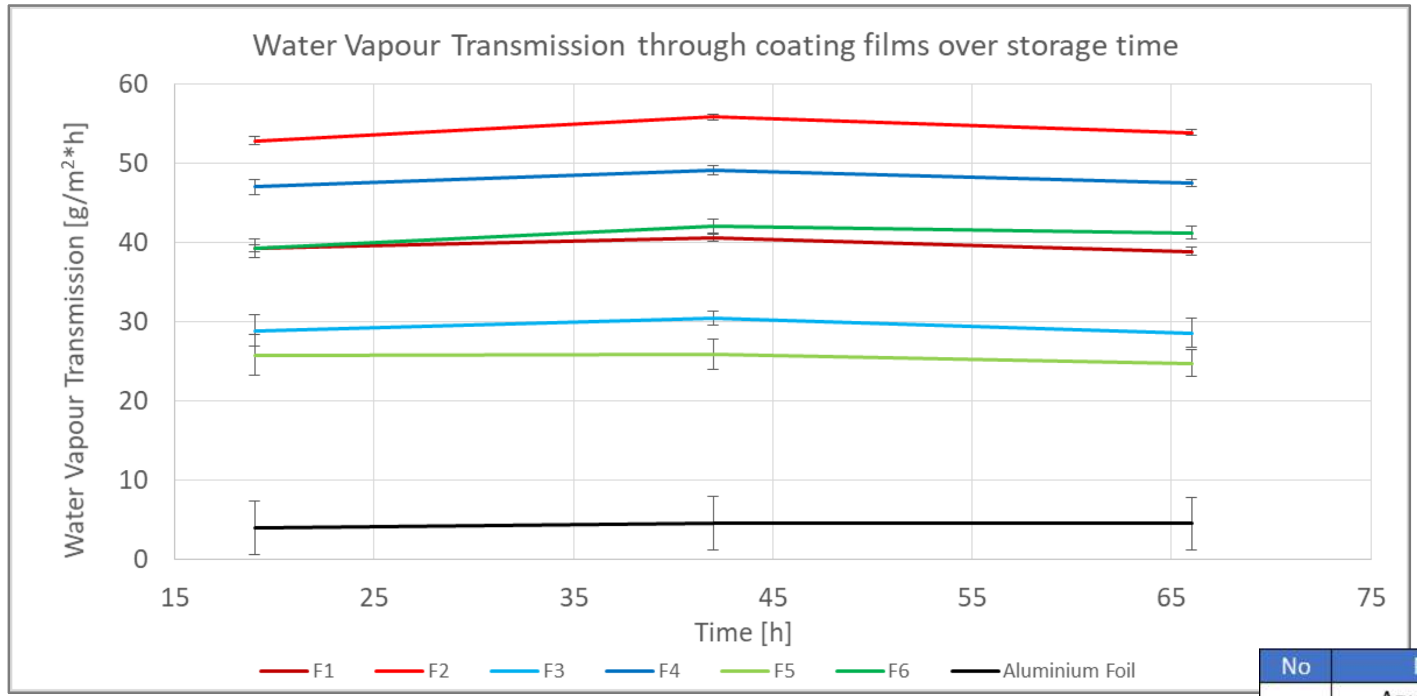
No	Force at target distance [mN]	Relaxed Force [mN]	Retained Force [%]
F1	947 (+/- 27)	601 (+/- 77)	63,6 (+/- 9.4)
F2	591 (+/- 23)	353 (+/- 17)	59,8 (+/- 4.6)
F3	866 (+/- 30)	544 (+/- 56)	62,8 (+/- 5.6)
F4	643 (+/- 66)	393 (+/- 29)	61,4 (+/- 4.6)
F5	524 (+/- 40)	194 (+/- 22)	36,9 (+/- 1.9)
F6	566 (+/- 27)	299 (+/- 36)	52,8 (+/- 4.2)

No	Product
F1	AquaPolish® P white 010.107
F2	AquaPolish® P white 010.142
F3	AquaPolish® P white 019.177 MS
F4	AquaPolish® P white 019.160 MS
F5	AquaPolish® P white 610.19 PVA
F6	AquaPolish® P white 612.02 PVA

Case Study: Moisture Protection of Vitamin-C tablet formulation

Results for Isolated Films: water vapor transmission and permeability

- Water vapor transmission is a good indicator for the barrier properties
- However, the value does not take into account the film thickness and therefore the permeability is the most important value to compare regarding the barrier function
- Both moisture protection formulations containing TiO_2 (F3 + F5, HPMC MS and PVA) show increased water vapor barrier properties
- Formulations containing no TiO_2 have show higher water vapor permeability
- Generally the PVA formulations perform best



$$Water\ Vapour\ Transmission = \frac{\Delta m}{\Delta t\ A}$$

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F1	AquaPolish® P white 010.107
F2	AquaPolish® P white 010.142
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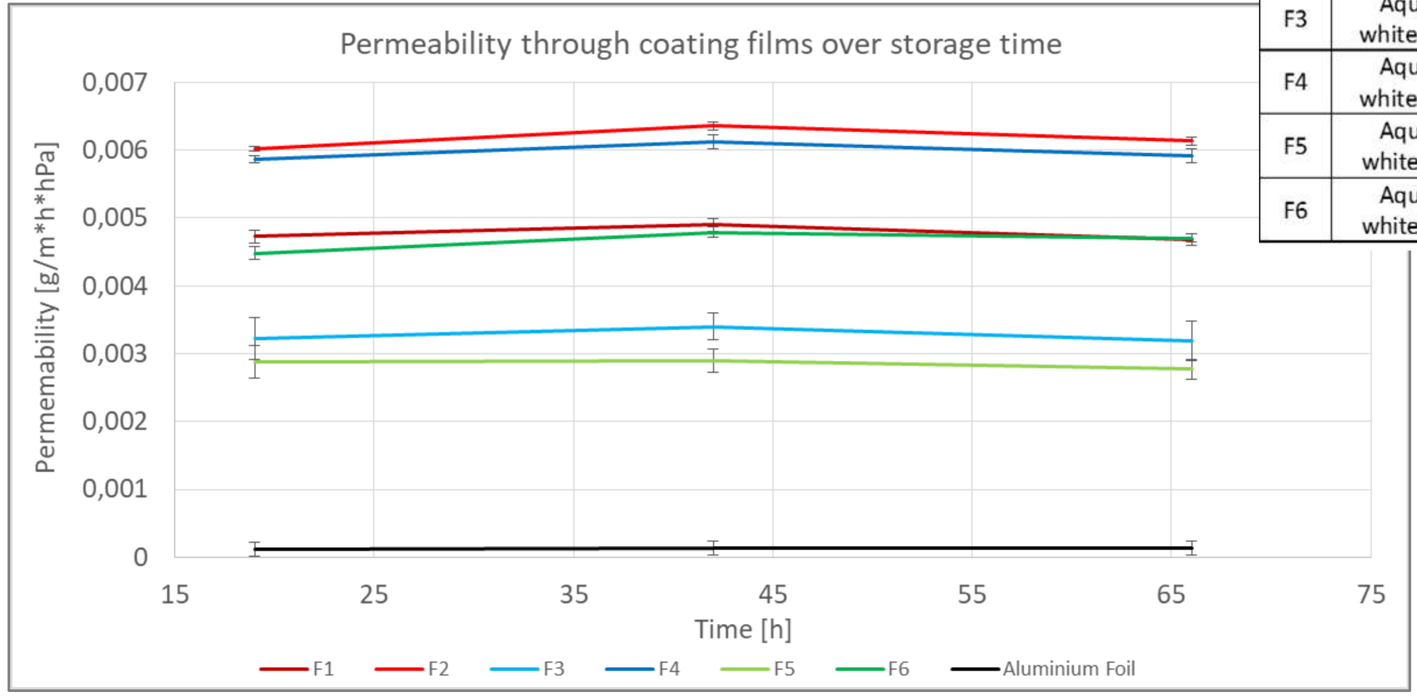


$$Permeability = \frac{\Delta m\ \delta}{\Delta P\ \Delta t\ A}$$

BIOGRUND

BIOGRUND products

BIOGRUND products

- *BIOGRUND offers a wide range of specialized coating solutions*
- *Moisture protection coatings containing HPMC and PVA are available*
- *Customized, customer need centered solutions are always available*
- *At BIOGRUND we are always happy to help you to overcome your formulation challenges*

BIOGRUND Materials

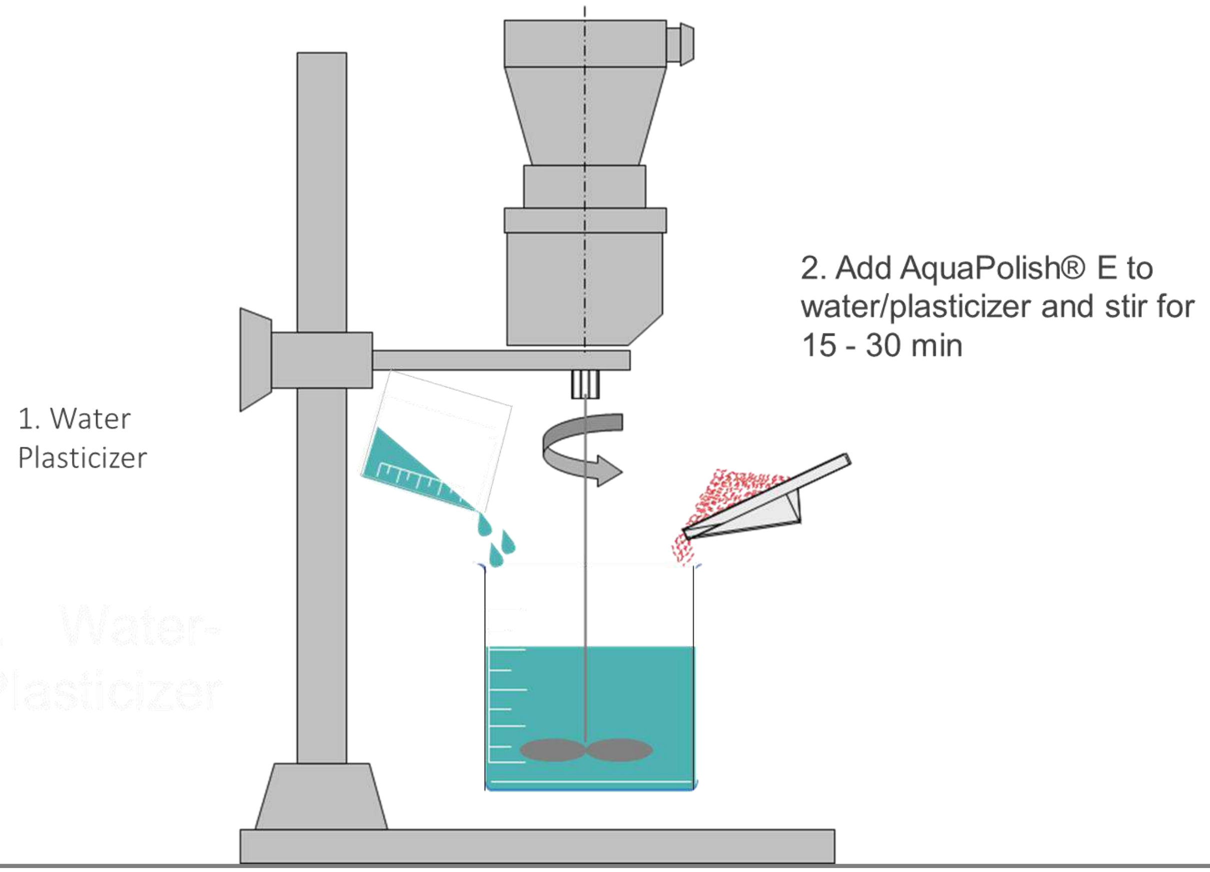
Film Coating Product	Quality (food = F; pharma = P; dual use = D)	Polymer(s) // compendial name	Functionalities	recom. substrate temperature [°]	recom. weight gain [mg/cm2]	recom. weight gain [%]	solid content [%]
Aquapolish® PRO	D	Polyvinyl alcohol-Macrogol-co-polymer and PVA	mositure protection	45 - 47	2,0 - 12,0 (round tablet) 4,0 - 20,0 (oblong tablet) 10,0 - 20,0 (hard capsule)	4 - 7	25
Aquapolish® MS	D	HPMC (Hypromellose)	enhanced moisture protection	38 - 42	1,5 - 10,0 (round tablet) 3,0 - 17,0 (oblong tablet) 8,0 - 17,0 (hard capsule)	5	15
Aquapolish® PVA	D	PVA (Polyvinyl alcohol)	highly flexible coating	45 - 47	2,0 - 4,5 (round tablet) 2,0 - 9,0 (oblong tablet) 11,0 - 22,0 (hard capsule)	3 - 5	20
Aquapolish® E	P	HPMC AS (Hypromellose acetate succinate)	enteric coating	32 - 34	4,5 - 7,0 (round tablet) 5,5 - 12,0 (oblong tablet) 5,5 - 24,0 (hard capsule)	8 - 10	15 inkl. TEC
	P	Methacrylic acid-ethyl acrylate copolymer Type B	enteric coating	28 - 30	5,0 - 7,5 (round tablet) 6,5 - 12,5 (oblong tablet) 6,5 - 25,0 (hard capsule)	8 - 12	22 inkl. TEC
	F	Sodium Alginate	enteric coating	32 - 34	25,0 - 37,5 (round tablet) 32,0 - 63,0 (oblong tablet) 31,0 - 125,0 (hard capsule)	8 - 12	10 - 12
BonuLac®	D	Shellac	enteric coating	36 - 40	6,5 - 10,0 (round tablet) 8,5 - 17,0 (oblong tablet) 8,5 - 34,0 (hard capsule)	4 -7	17 - 19
Aquapolish® SR	D	EC (Ethylcellulose)	sustained release	36 - 40	8,0 - 12,0 (round tablet) 10,0 - 20,0 (oblong tablet) 10,0 - 40,0 (hard capsule)	5 - 10	10

BIOGRUND products

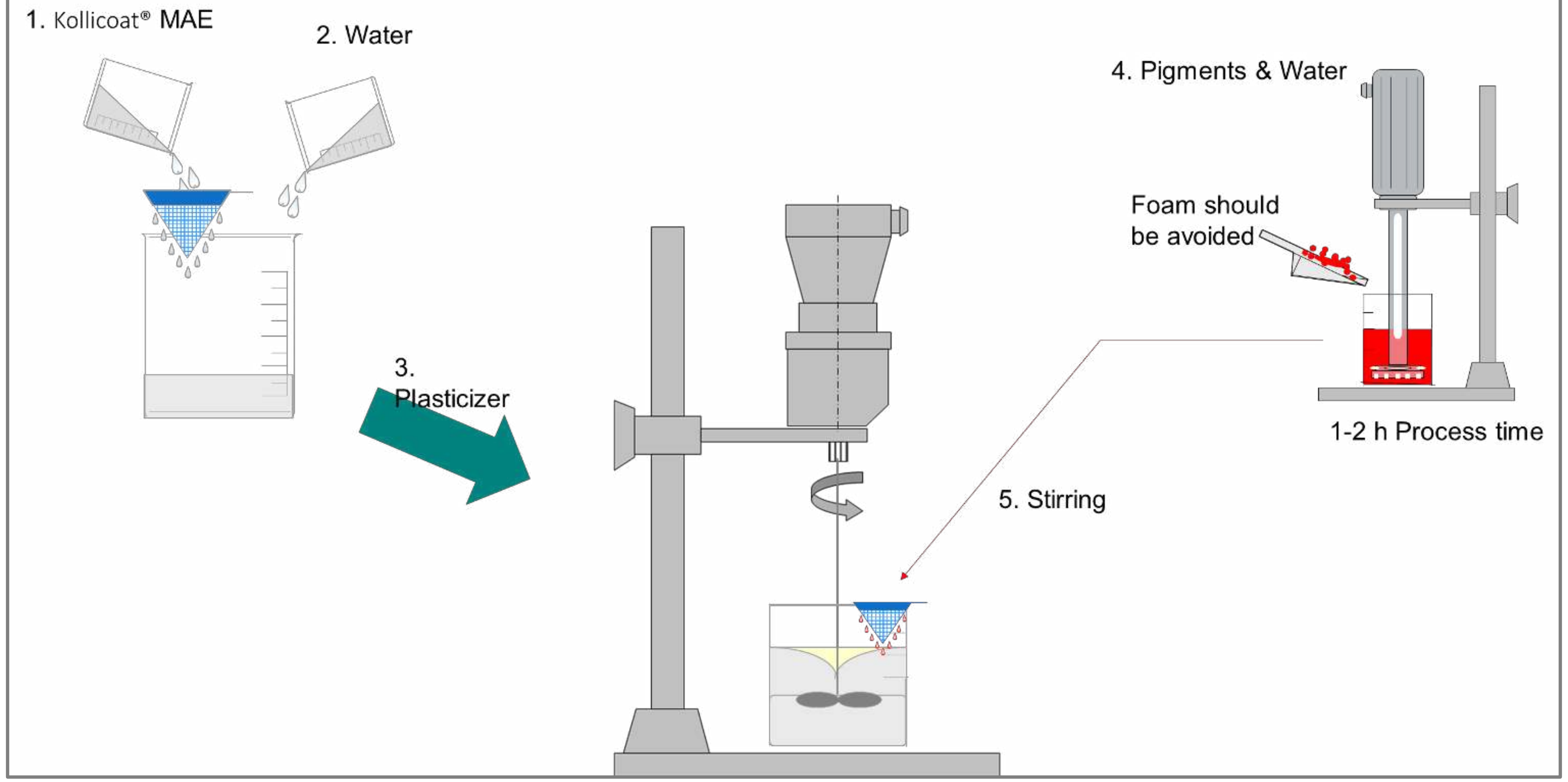
- *BIOGRUND ready to use mixtures* reduce processing time / preparation time

Fast preparation of Aquapolish E formulation (enteric coating)

The solid content is 15 - 25 % depending on the formulation of the AquaPolish® E formulation. Maybe an additional plasticizer is needed.



Example of preparation on an enteric coating from separate comopnents



Summary

Summary

- *There are a number of strategies to protect moisture sensitive ingredients*
- *The choice of excipient for the core / tablet / capsule is of great importance*
- *Additives such as CompacCel® MAB can help to overcome the moisture challenge at the tablet formulation level*
- *Coating with moisture barriers is the easiest, fastest and most cost effective way to protect the dosage form once it is removed from the packaging*
- *BIOGRUND offers several options for moisture protective coatings*
- *HPMC based formulations are available as well as PVA based formulations*
- *TiO2 containing formulations can be found in the portfolio as well as more modern TiO_2 –free options*
- *In most cases formulations without TiO_2 necessitate slightly higher addition of coating (4- 5% instead of 3%) to ensure coverage of darker tablets*
- *For ideal barrier function HPMC MS coatings are usually applied to 5 % mass gain and PVA coatings at slightly lower levels (3-5%)*

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www.biogrund.com

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