

New Formulation Technologies for Patient Adherence: Solid Oral Dosage Forms

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Chief Scientific Officer
Colorcon**



Patient Adherence - Definitions & Considerations

- Adherence & compliance used interchangeably to describe the degree that a patient correctly follows medical advice in taking their medications
 - Adherence affected by capability, acceptability and willingness!
- Quality healthcare outcomes depend upon **patients' adherence** to recommended treatment regimens. Patient non-adherence can be a pervasive threat to health (NIH)
- Literature suggests only 50% adherence in developed countries



Google images

Patient Non- Adherence

- Non-adherence may be intentional or patient is unaware or due to complex regimen and depends on:
 - Patient age: pediatric & elderly
 - Disease condition: acute vs. chronic
- Causes of non-adherence
 - 40-60% could not understand directions
 - External forces:
 - Peer, media, relative influence & doubt of efficacy
 - Confusion thus **medication error** → stop or delay taking medication
 - Wavering trust – Consumer activists, reports on counterfeit medicines
 - Complex or difficult to take / administer
 - Cost and access



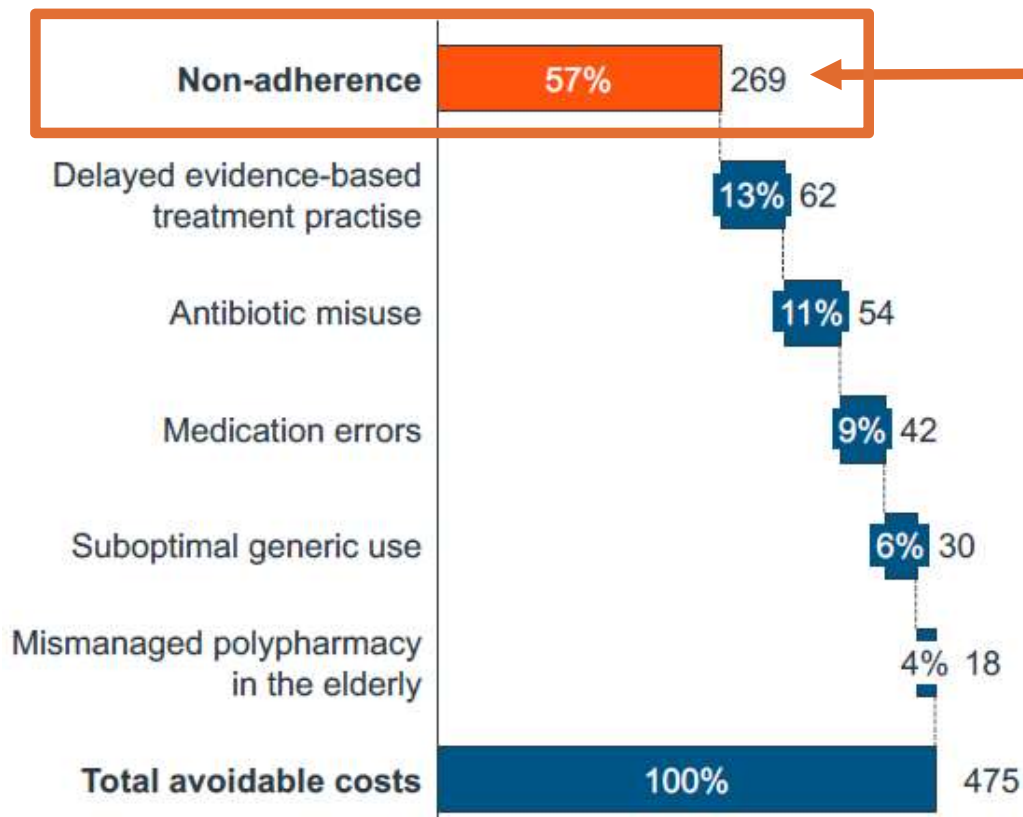
Guideline on pharmaceutical development of medicines for paediatric use. 1 August 2013, EMA/CHMP/QWP/805880

Reflection paper on the pharmaceutical dev. of medicines for use in the older population. 18 May 2017 EMA/CHMP/QWP/292439



One of sources: Oman Med J. 2011 May; 26(3): 155–159

Non-Adherence Results in Revenue Loss

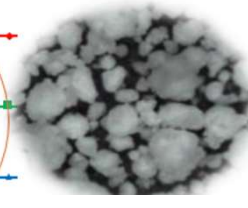
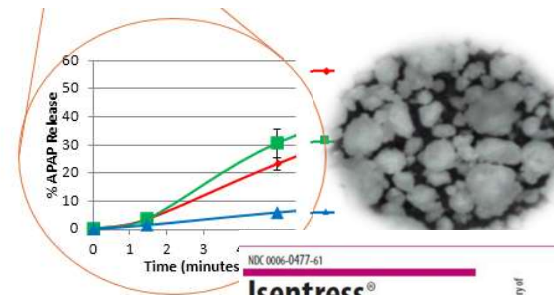
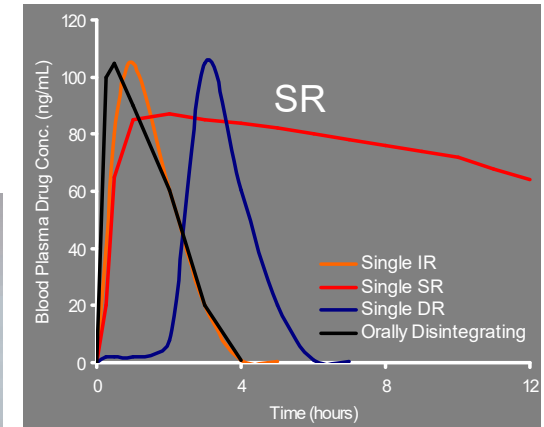


**Est. \$269 Billion
in Avoidable Medical Costs
(USA, 2012)**

Source: IQVIA European Thought Leadership; IQVIA Institute 2012 "Responsible use of Medicine"

Formulation Approaches to Enhance Patient Experience & Adherence

- Reduce the frequency & number of doses
 - Once daily dosing (Slow Release formulations)
 - Fixed Dose Combinations
- Improve taste – taste mask bitter drugs
- Reduce dosage size (challenge with SR)
- Improve trust using anti-counterfeiting
- Improve swallowability



NDC 0006-0477-61

Isentress®
(raltegravir) CHEWABLE Tablets

100 mg

For Pediatric Patients 2 to less than 12 Years of Age

Phenylethanolic: contains phenylethanolic (a component of aspartame) 0.10 mg per 100 mg chewable tablet.

Rx only

60 Tablets

Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08886, USA



Call to Reduce Counterfeit Medicines in the Market Call to Improve Supply Chain Integrity and Securitization

Law Enforcement Officer Walking On A Mountain Of Counterfeit Medicines



Schäuble: million products are falsified

Federal Minister of Finance Wolfgang Schäuble warns against counterfeit drugs on the Internet. More often than not, the customs confiscate false potencies, slimming products and anabolics from Asia. BY RAINER WORATSCHKA



Federal Finance Minister Wolfgang Schäuble (CDU) considered confiscated in customs Annual Press Arzneimittel.s
PHOTO: IMAGO / COMMON LENS

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Pharmaceutical industry

The Observer

Parallel trade in drugs puts EU patients at risk

Pharmaceutical manufacturers want a crackdown on the practice of buying cheap medicines to re-export at a higher price, a trade that creates shortages in countries such as Greece - and, arguably, allows in dangerous counterfeits. Oliver Morgan reports

Oliver Morgan
Sat 28 Jun 2008
19.01 EDT

If you suffer from epilepsy and you live in Athens you are less likely to receive the vital drugs you need for treatment than if you live in London, Berlin or Amsterdam. And, says Konstantinos Lourantos, president of the Association of Pharmacies of Attica, the fact that they are freely available in other parts of Europe contributes to their shortage in his country. The reason? Lourantos, whose

Guidance Has Been Issued To Have Anticounterfeiting Mechanisms In or On Solid Oral Dosage Forms

Guidance for Industry Incorporation of Physical- Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting

Additional copies are available from:
Office of Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 51, rm. 2203
Silver Spring, MD 20993-0002
(Tel) 301-796-3400

<http://www.fda.gov/CDER/CDER/CDER/Regulatory/Information/Guidance/03Guid03b.htm>



CONTRACT
PHARMA

MAGAZINE NEWS MANUFACTURING PACKAGING DEVELOPMENT

FEATURES

Will All Tablets and Capsules Have On-Dose Physical Chemical Identifiers Soon?

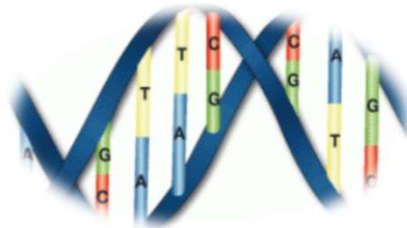
As the global problem of counterfeit and diverted drugs continues to grow worldwide, will our medicine soon carry secure identifiers woven into the very fabric of the drug product? Advancing technology is finally allowing drug makers the ability to implement on-dose authentication.



7

Authentication Solution - **A Film Coating with A Built-in Molecular Taggants**

For example:



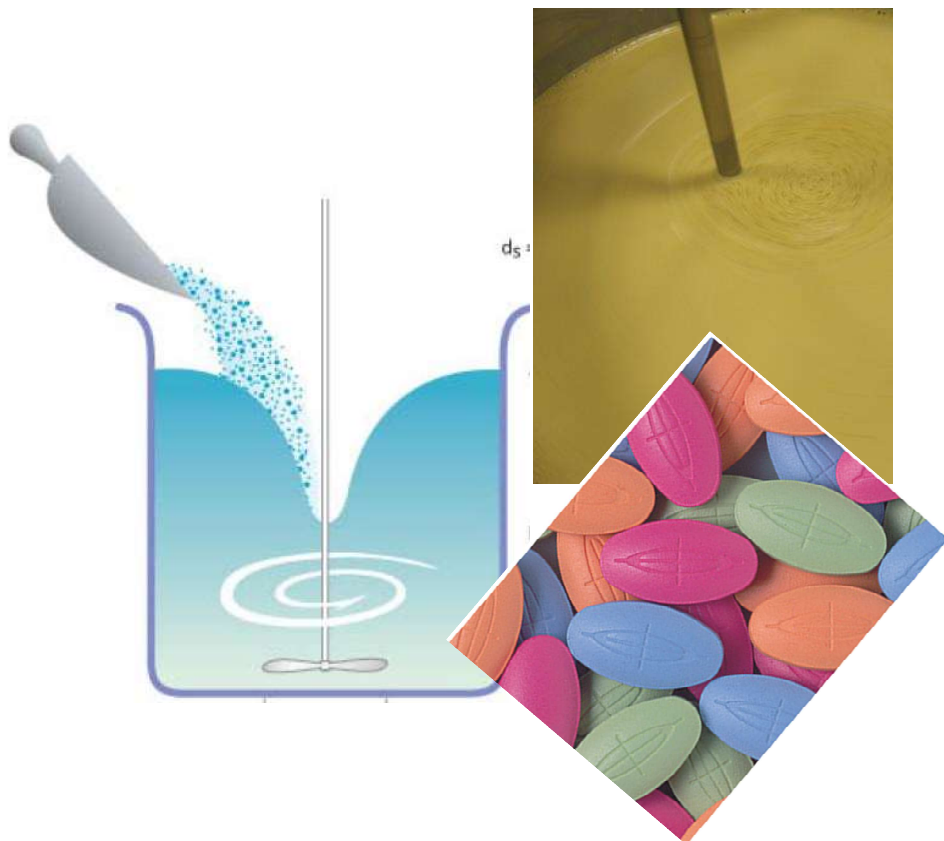
The Tablet Becomes the Barcode

A Molecular Taggant is A Physical Identifier (PCID) That Adheres to the FDA Guidance

- **The DNA Used is Too Small To Be Biologically Active**
- **Can Only Be Detected With A Corresponding Probe**
- **A Code That Cannot Be Broken**
- **Traceable At Parts Per Billion**

Pigmented Film Coating System To Be Mixed in Water

Apply The Coating and Identifier to the
Tablet or Capsule or in the printing ink



Improving Patient Experience & Adherence





International Journal of Pharmaceutics

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Developing methodology to evaluate the oral sensory features of pharmaceutical tablet coatings

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^a School of Pharmacy, University of Birmingham, Edgbaston, B16 2TT, UK

^b Institute of Clinical Sciences, University of Birmingham, Edgbaston, B16 2TT, UK

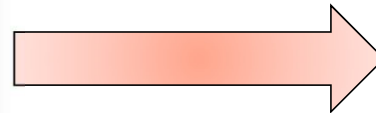
^c Colorcon Inc. Global Headquarters, 275 Ruth Road, Harleysville, PA 19438, USA

Received 21 December 2018, Revised 20 March 2019, Accepted 21 March 2019, Available online 22 March 2019.

Difficulty in Swallowing is a Significant Issue, Adversely Affects Adherence



**Harris interactive, 2004 study*



4 in 10 adults
report difficulty in
swallowing tablets*

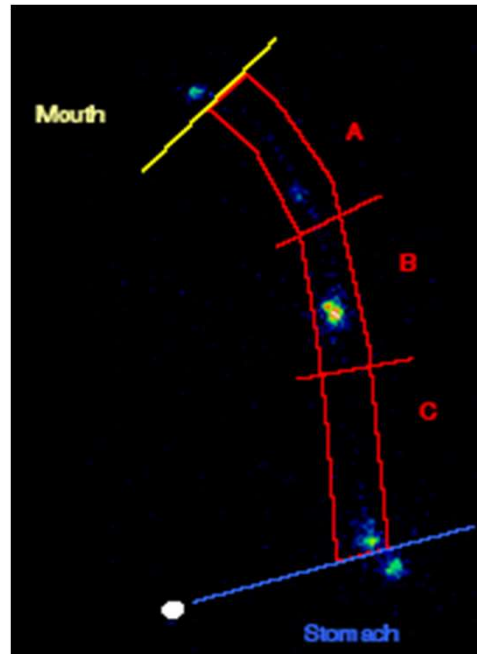
Delay Taking
a Dose

Discontinue
Use

Skip a
Dose

Size, shape and coating are all contributory factors

In Vivo Study: Supports Perception that Uncoated Tablets are More Difficult to Take

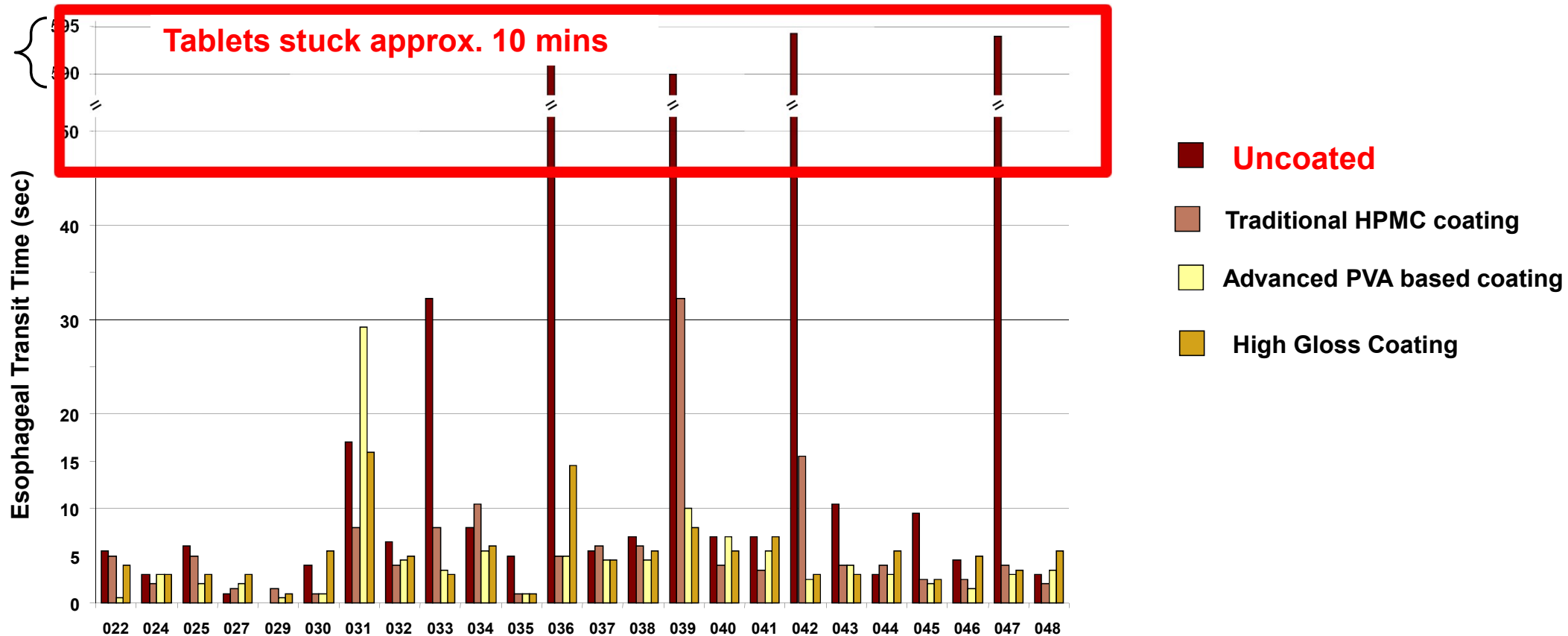


1000 mg Placebo



Bio-Images, Scotland, UK 2005

Only Uncoated Tablets Show Sticking in Esophageal Tracts



Market Demand Continues for a Solution to Improve Swallowability

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Factors Affecting Swallowability of Solid Dosages



- Phases of swallowing:
 - I. Sight*
 - II. Oral (role of tongue)*
 - III. Pharyngeal (avoid choking)*
 - IV. Esophageal*

Dosage form:

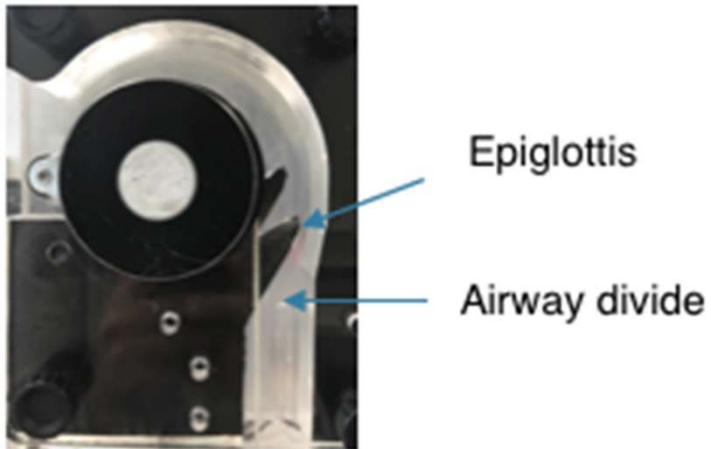
- Appearance - gloss, color, finish
- Size & shape - round, caplet, sharp edges, weight
- Texture - surface roughness / stickiness
- Taste - bitter / sweet



- Co-administration of water/liquid: presence/quantity

Method Development - Measuring Transit in Swallowability Tester

Artificial Throat Apparatus – mimics swallowing action by roller movement and biorelevant semipermeable membrane



Tablet reaching the epiglottis

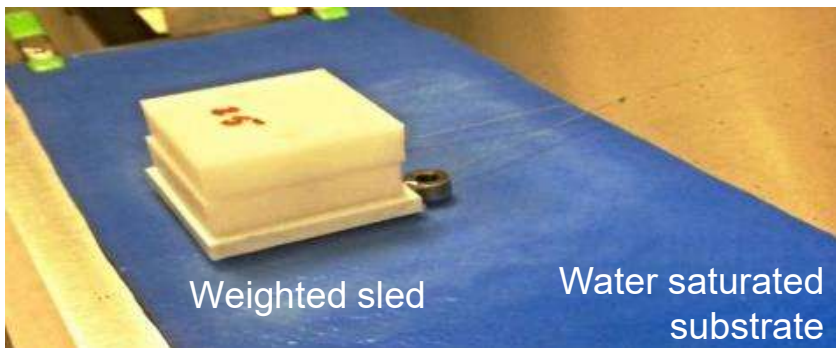


Tablet passing the airway divide

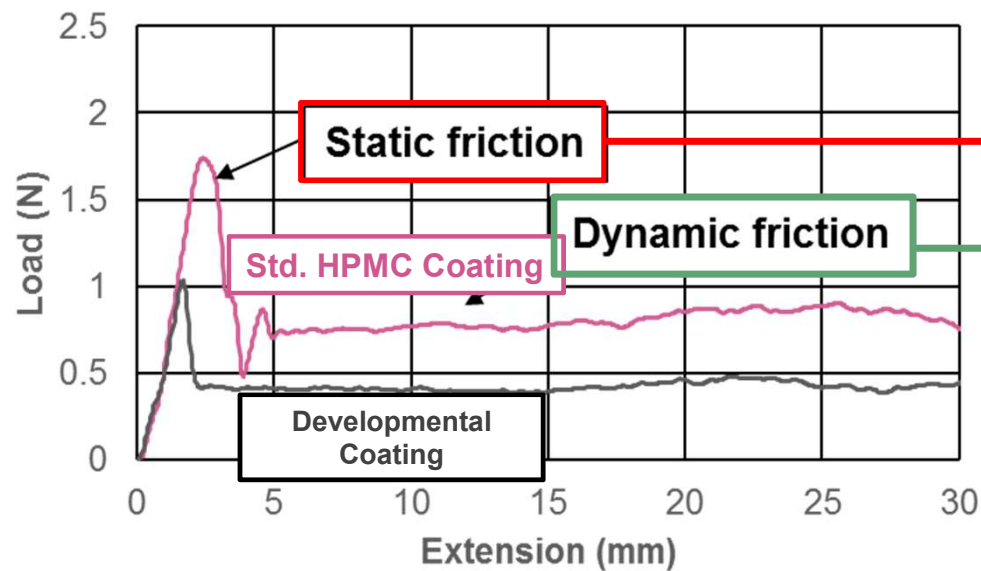
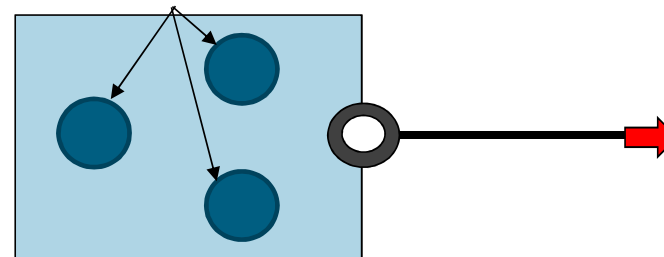
Roller Movement Duration (sec)		
Novel	PVA-based Coating	HPMC-based coating
0.17	0.33	Tablet Stuck
0.13	0.13	0.2
0.17	0.2	Tablet Stuck

Uncoated tablets stuck

Method Development for *In-Vitro* Measure of “Slip” Behavior



Coated Flat-faced Tablets

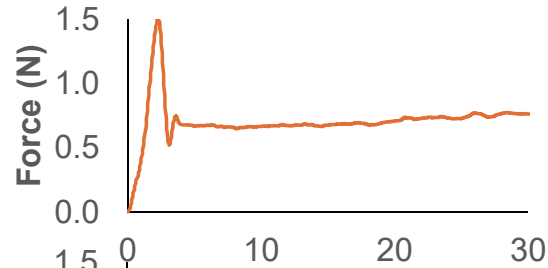


Get it moving

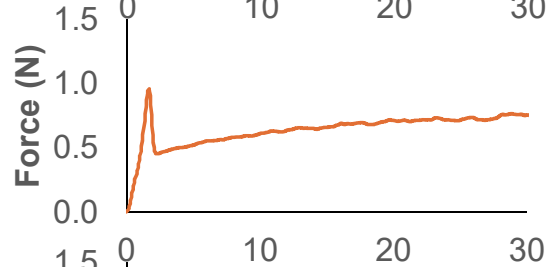
Keep it moving

Slip Duration

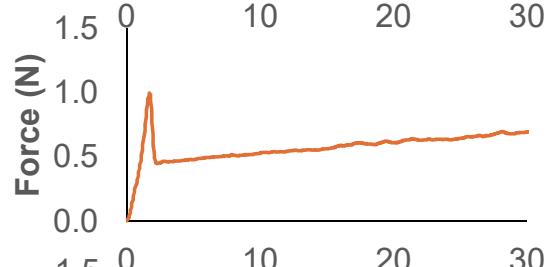
Black FC subcoat



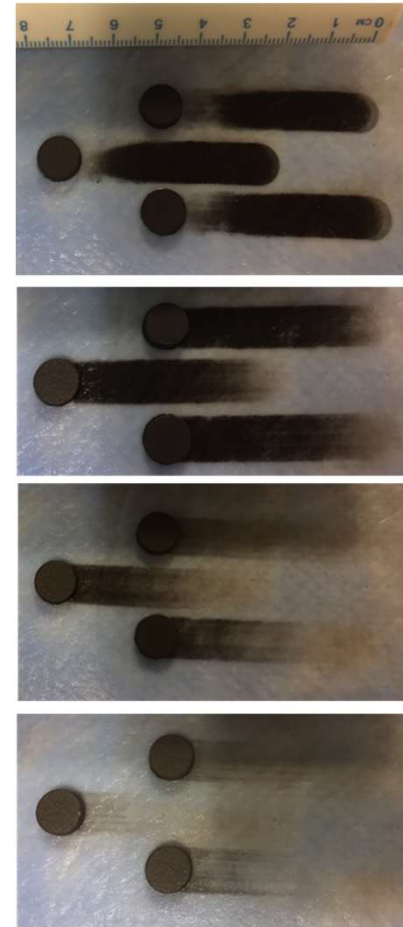
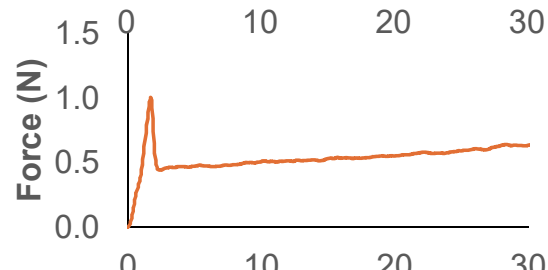
1% wg Slippery clear topcoat



2% wg Slippery clear topcoat



3% wg Slippery clear topcoat

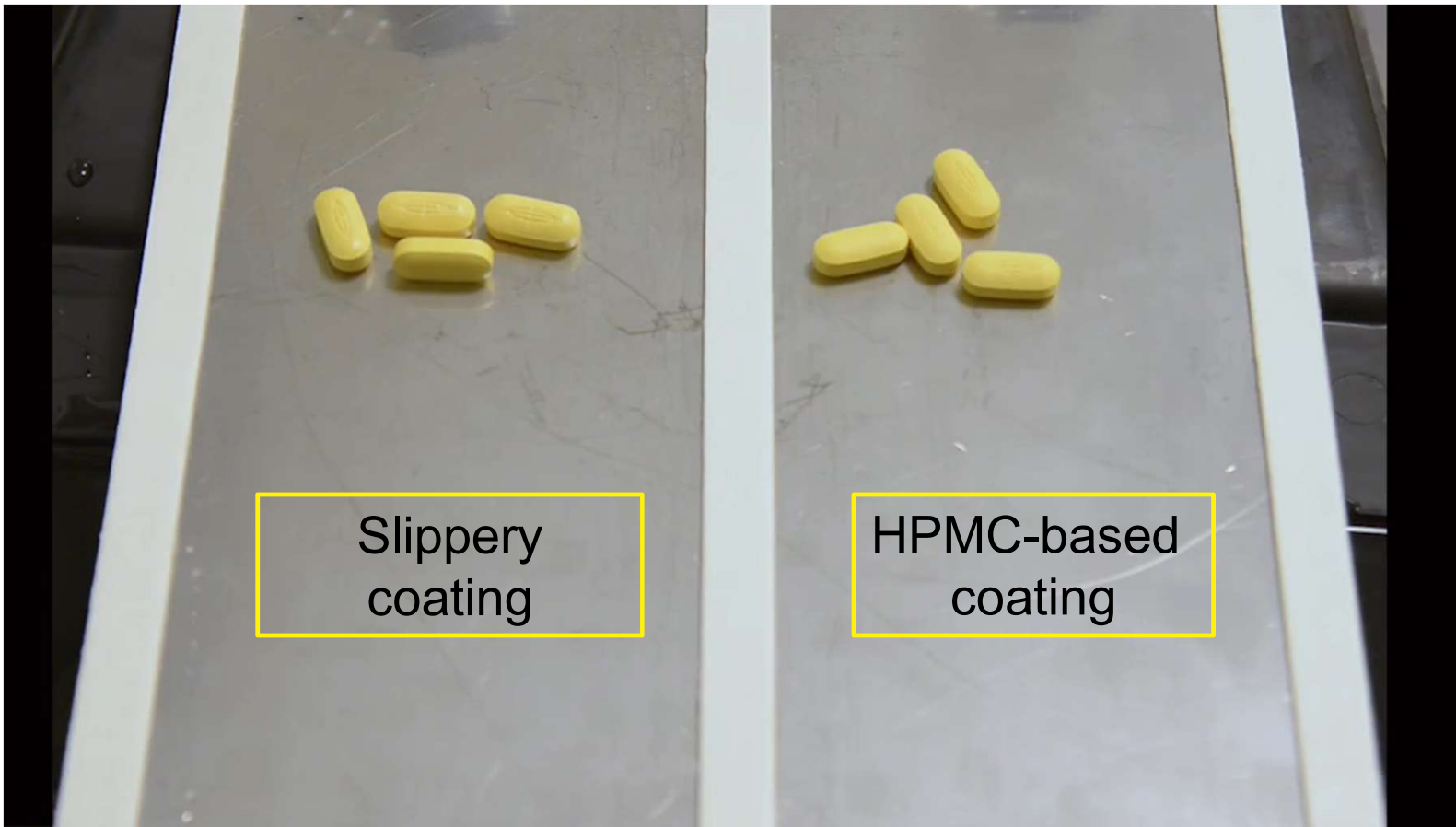




Film Coating Formulation Screening

- **Various pharmaceutical & food grade polymers screened looking for:**
 - Coherent film formation with sufficient mechanical properties
 - Easy to apply in common film coating machines – viscosity, spray ability & drying
 - Smooth appearance and colorant addition
 - Slipperiness when wetted
- **Many polymers screened:**
 - Cellulose ethers, polyvinyl alcohol (PVA), PVA-PEG graft cop-polymer, various gums
 - Combination of polymers & polysaccharides
- **Developed a novel coating system for optimum wet-slip**

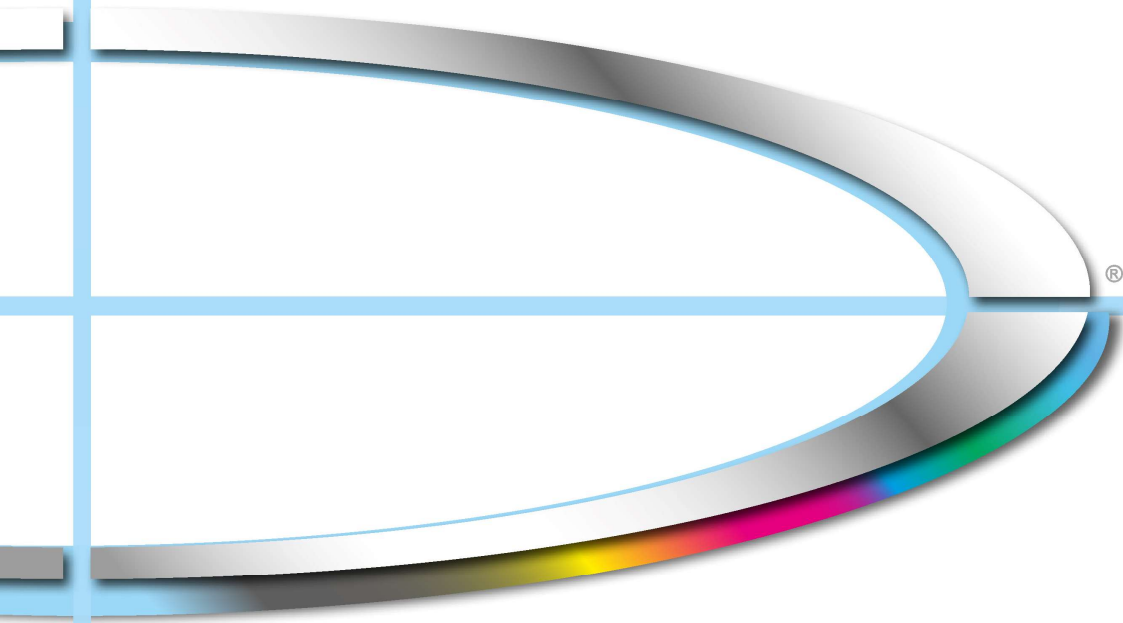
Developmental Coating Slides Easily with Water



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Human Swallowability Study

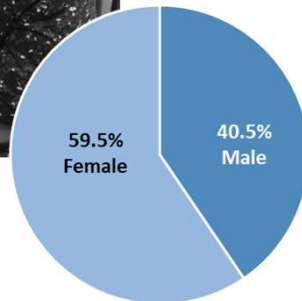
In collaboration with University
of Birmingham, UK, 2018



Study Design & Volunteer Population

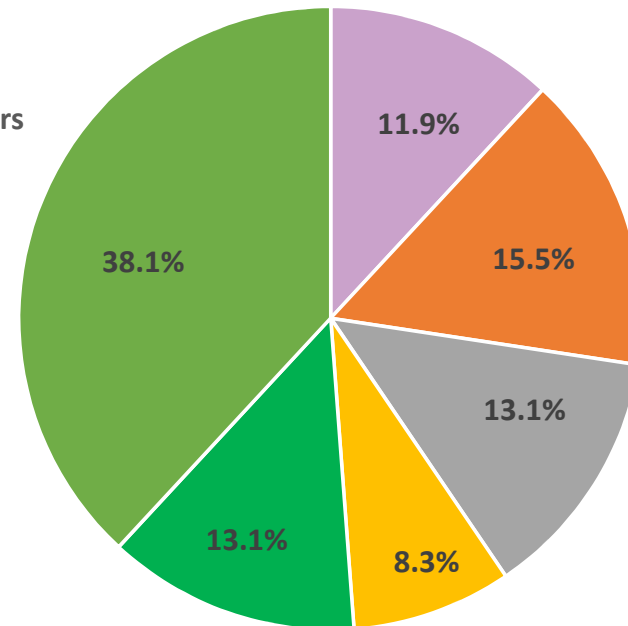
84 Volunteer: Ethical approval: UoB ERN-17-0883 (17-1074)

- Volunteers 18 to 75 years
- Consent & questionnaire
- Ability to swallow tablets



Age Range, Years

- <24
- 25-34
- 35-44
- 45-54
- 55-64
- >65



Formulation Development & Study Design

Film Coating (FC) Formulations:

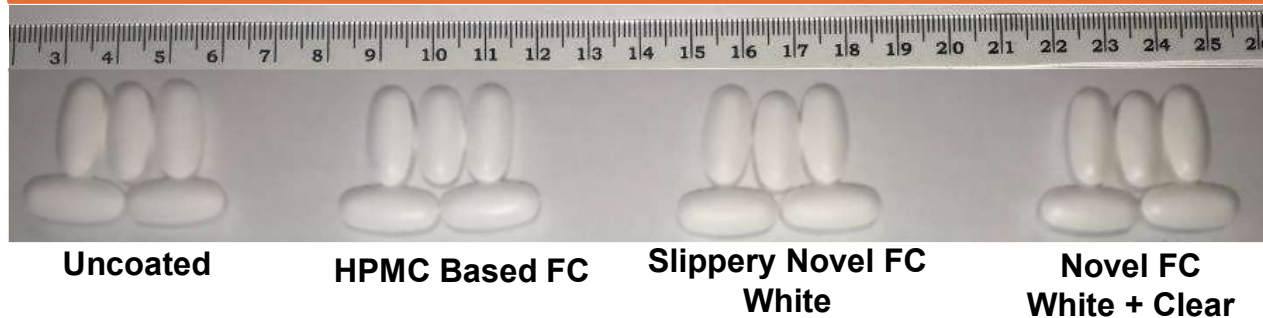
Main polymers used in this study:

- 1. HPMC
- 2. Novel slippery: HPMC & Guar Gum & polysaccharide (white)
- 3. Novel slippery: HPMC & Guar Gum & polysaccharide (Clear)

4 samples in a randomised order



Placebo tablets (950 mg, 19.3 X 9.2 mm)



Ease of Swallowing & Mouthfeel Assessment

Visual Analogue Scale (VAS) to rank



Ease of swallowing

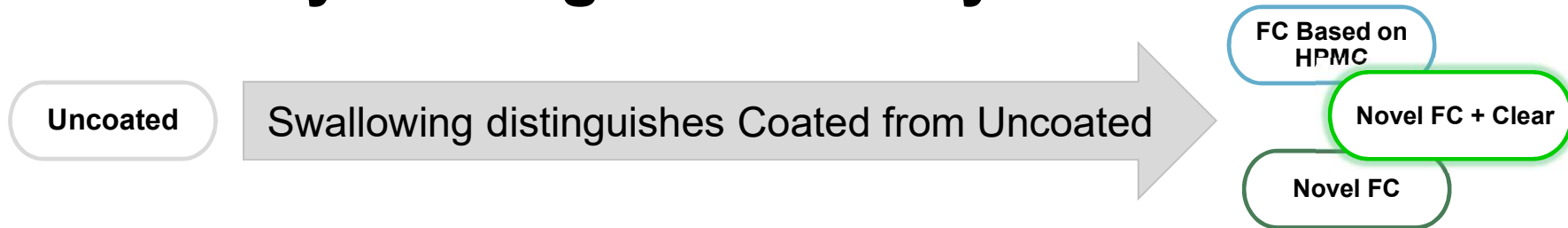
- volume of water used
- time taken to swallow

Mouthfeel (10 sec in mouth)

- smoothness
- adhesiveness (stickiness)
- slipperiness
- palatability

Three descriptions for each tablet

Study Findings - Summary



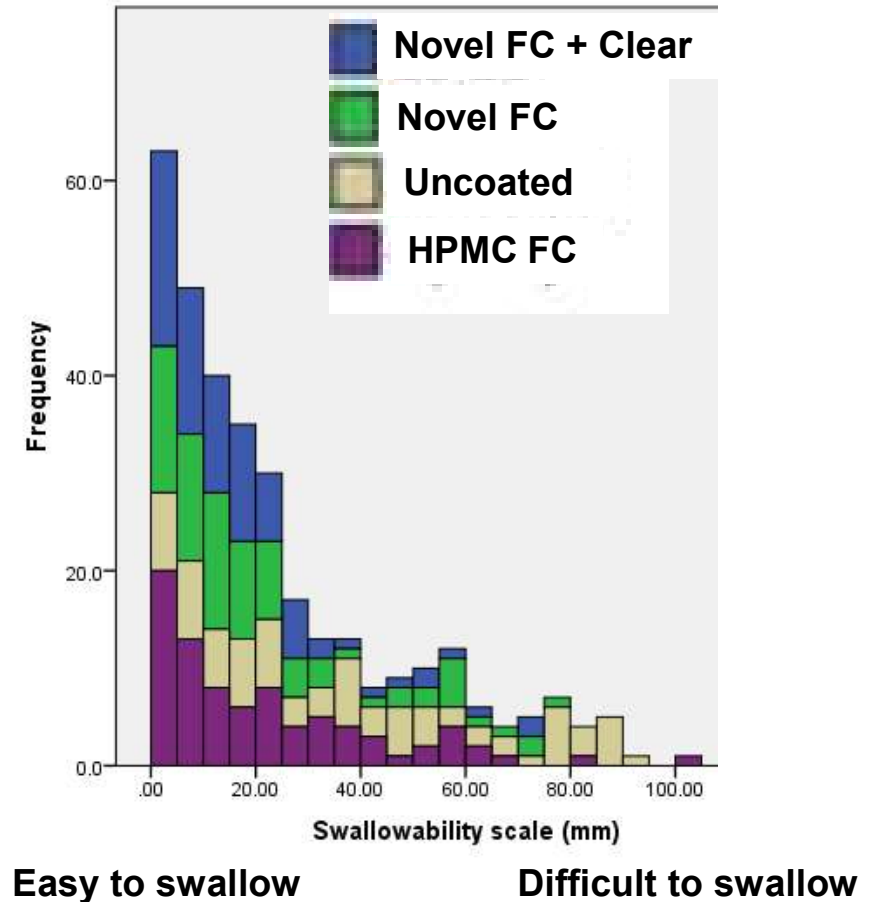
How easy was it to swallow?

Participants ranked tablets from hardest to easiest to swallow

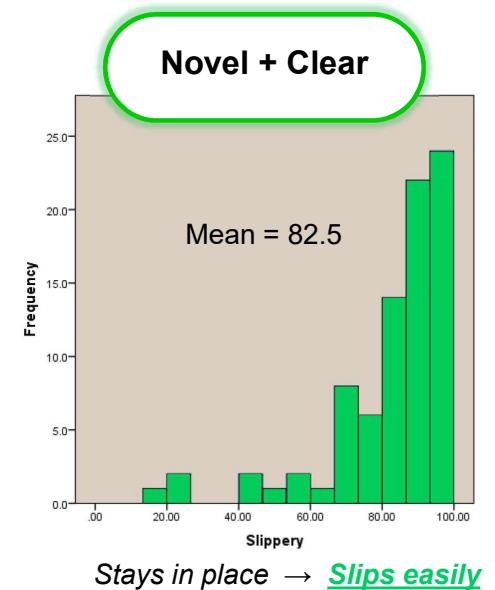
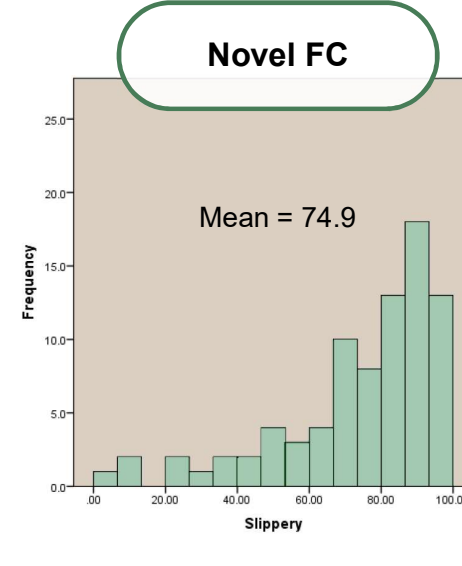
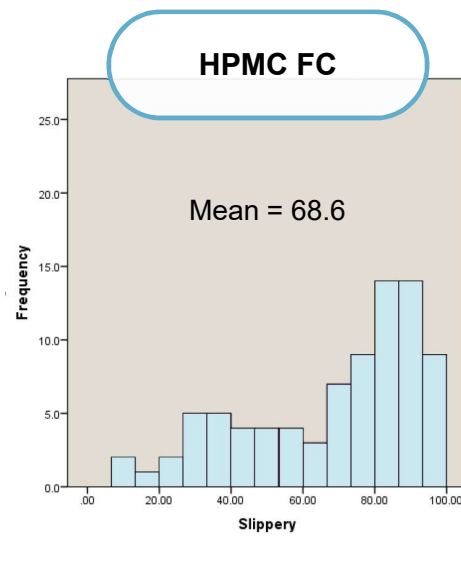
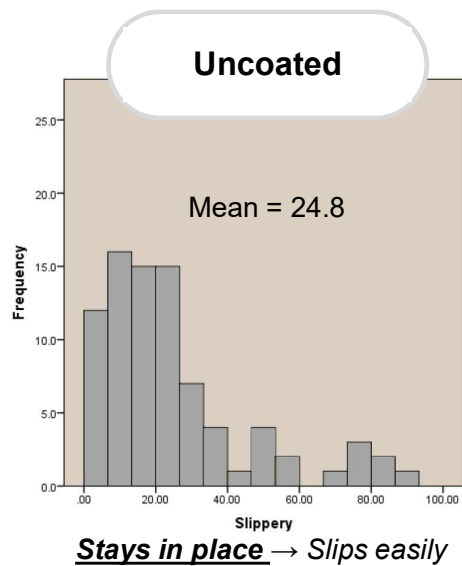


Study Findings – Scale & Statistical Analysis

- Data is NOT normally distributed
- Scale – Converted VAS into numerical values
- The graph shows scores of swallowability vs the frequency of score used. The height of bar represents all samples, the colours denote particular samples.
- Coated tablets scored much higher than uncoated.



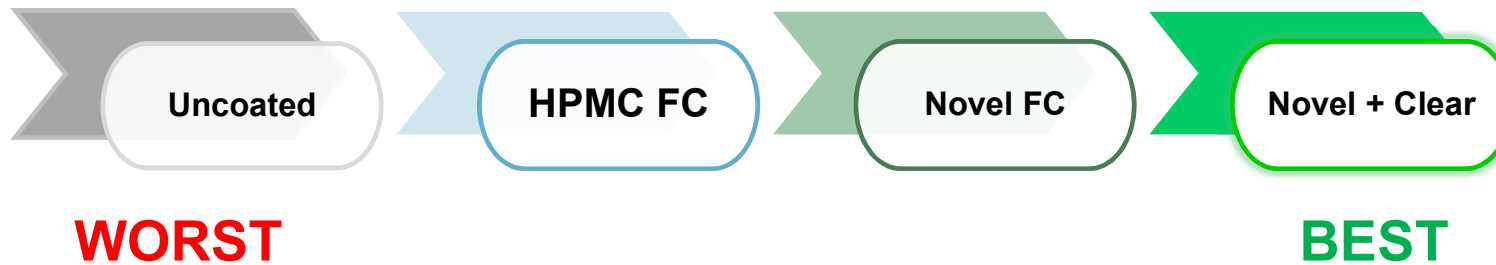
Volunteer Study – Slip Scale



- Uncoated tablets stayed in place in the mouth; coated tablets slipped easily
- Tablets coated with Novel FC + clear top-coat = significantly higher slip score

Mouthfeel : which tablet was most desirable

Participants ranked tablets from least to most desired mouthfeel



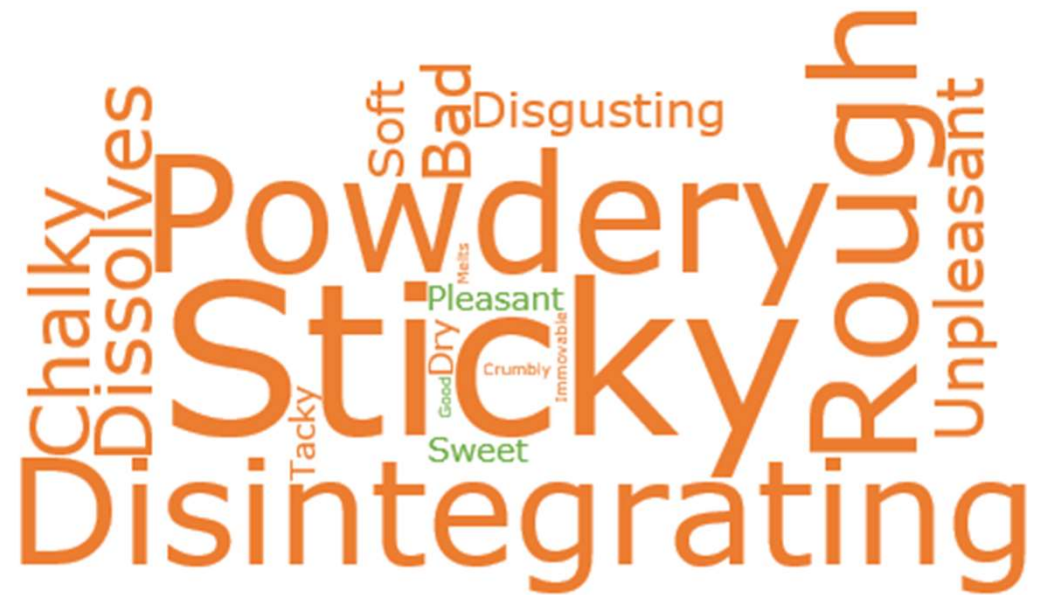
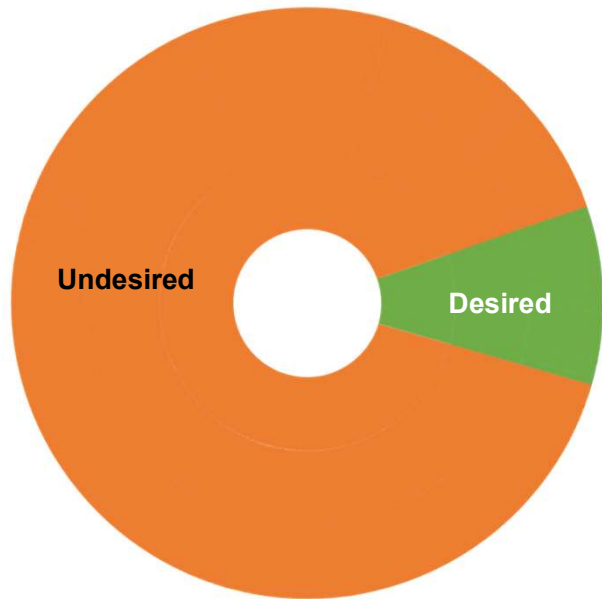


Analysis of Participant Commentary

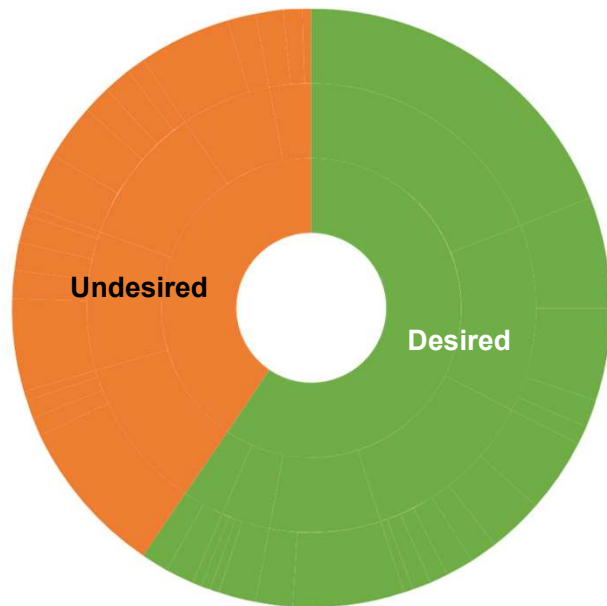
How Do You Feel About Swallowing This Tablet?

Participants were asked to provide three words to describe the experience of swallowing each sample tablet

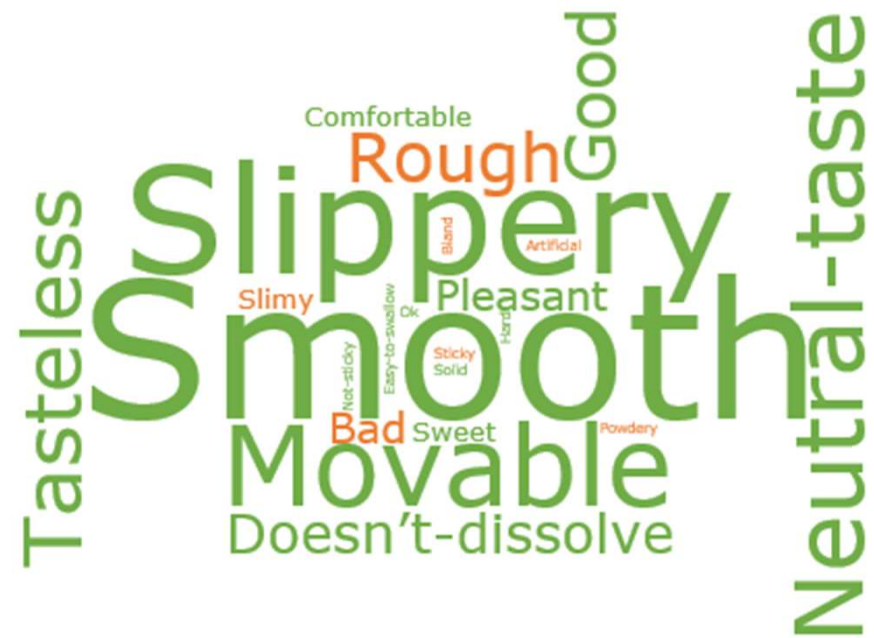
Uncoated Tablet



HPMC Based Coated Tablet



Novel FC Coated Tablet



Novel FC + Clear Coated Tablet



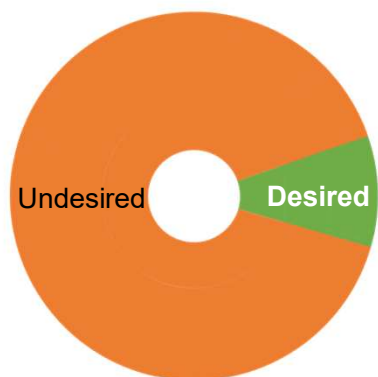
How Do You Feel About Swallowing This Tablet?

Uncoated

HPMC Based Coated

Novel Film Coat

Novel + Clear Film Coat



▪ **Powdery, Disintegrates, Sticky, Rough**

✓ **Smooth, Neutral Taste, Slippery, Good**

**Novel film coating provided a positive experience with:
Mouthfeel, Palatability & Acceptance**



Summary & Conclusions

- Patient adherence remains a big concern
- Various formulation approaches to enhance patient experience and adherence
- Critical to consider patients acceptance / capabilities for taking medication at early stage of development (Safety by Design)
- Coating tablets significantly enhances swallowability and patient acceptability
- Film coating allows inclusion of markers (anti-counterfeiting), colors for easy ID and stability and hide bitter taste of drugs