Excipient Quality & Trouble Shooting

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Partnering innovation, adding value.

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- Definition of Excipient
- Excipient Needs
- Understanding Excipient
- Central Role of Dissolution
- Factors affecting in-vitro dissolution
- Role of Excipient in Dissolution
- Critical Quality Attributes
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- Conclusion
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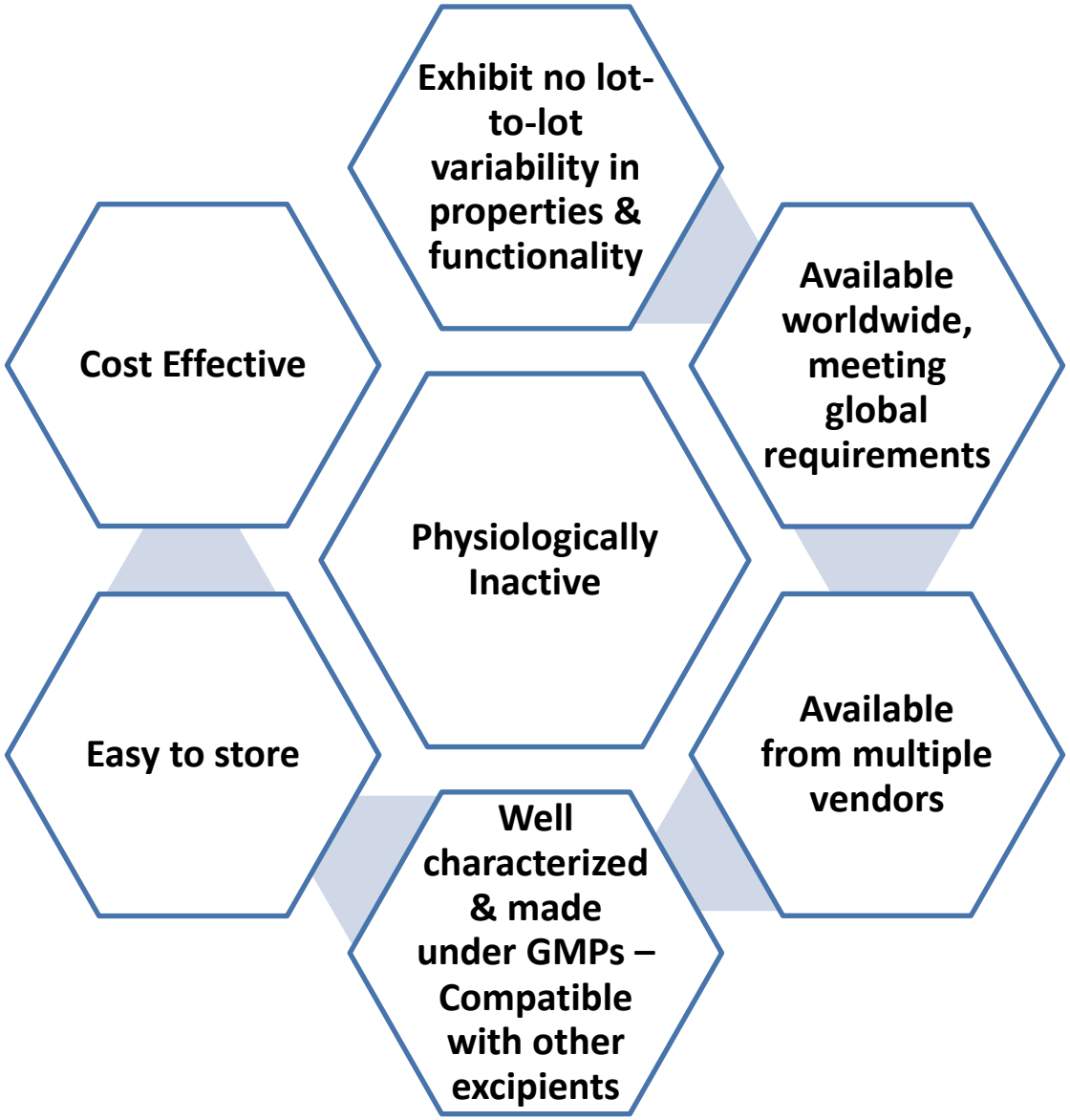
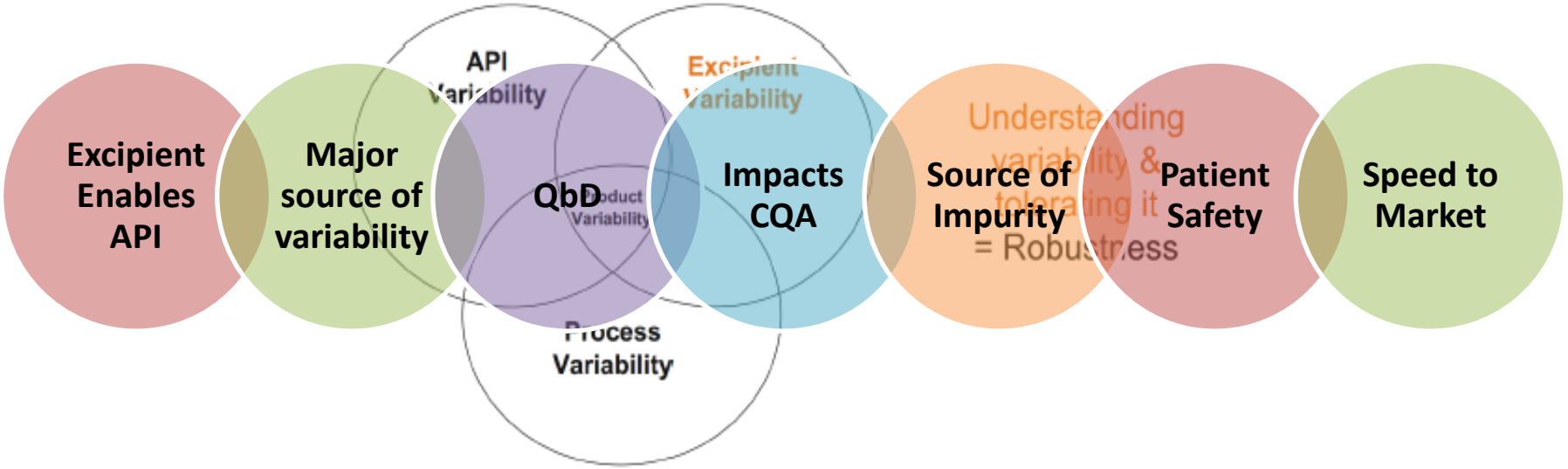
Definition of Excipient

Any substance, other than the active drug that has been appropriately evaluated for safety and is included in a drug delivery system to either aid the processing of drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, or assist in product identification or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Excipient Needs



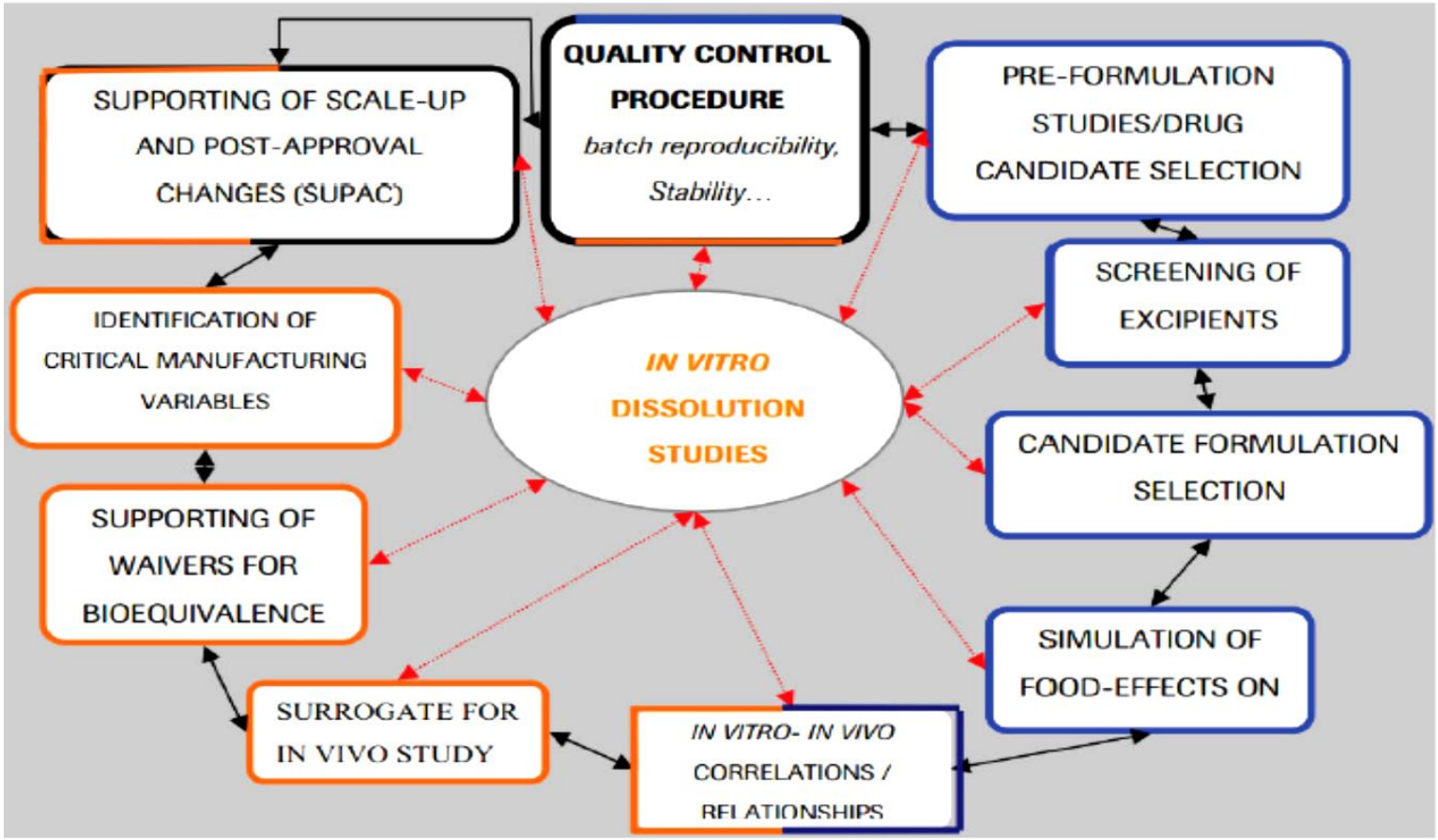
Understanding Excipients



$$\sigma^2_{Product} = \sigma^2_{API} + \sigma^2_{Excipients} + \sigma^2_{Process} + \sigma^2_{Interactions}$$

Ref: C. Moreton

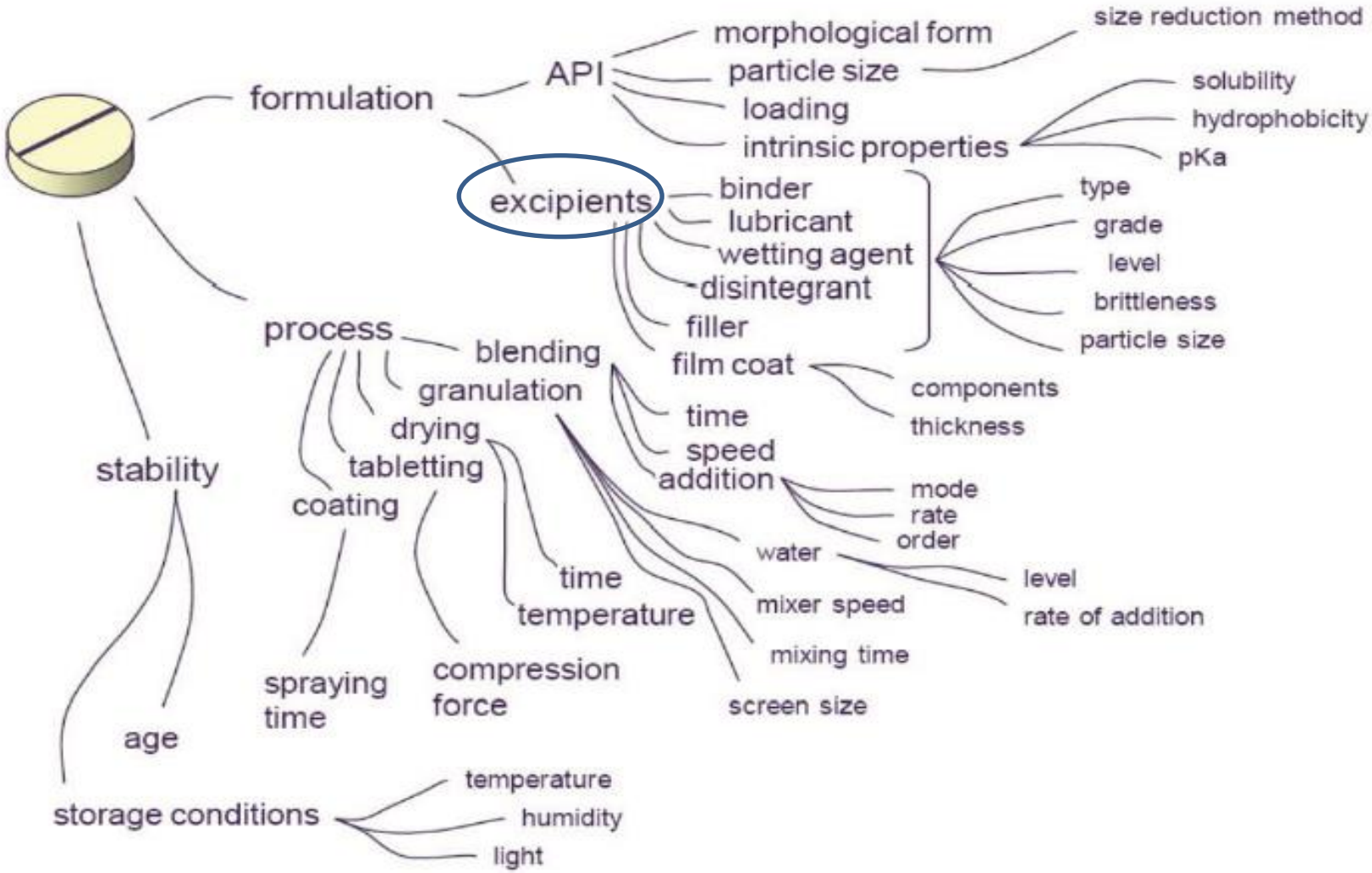
Central role of Dissolution



Ref: Emmanuel Scheubel

Early phase of development — Late phase — Market

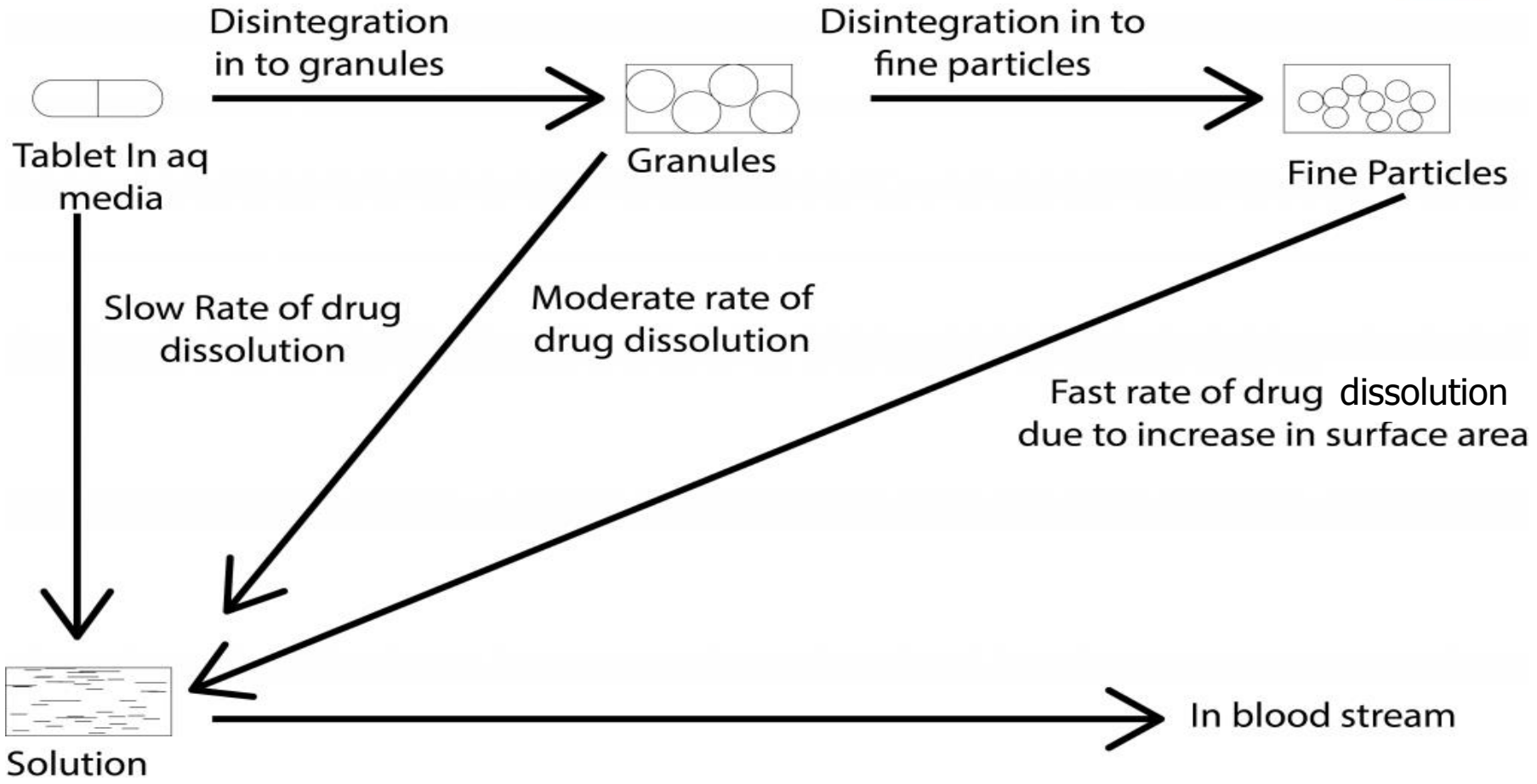
Factors affecting in-vitro dissolution



Dr Donald Murphy, Astra Zeneca UK, IRR Conference, May 07, Budapest

Role of Excipients in Dissolution

"Disintegrant"



Schematic representation of tablet disintegration and subsequent drug dissolution

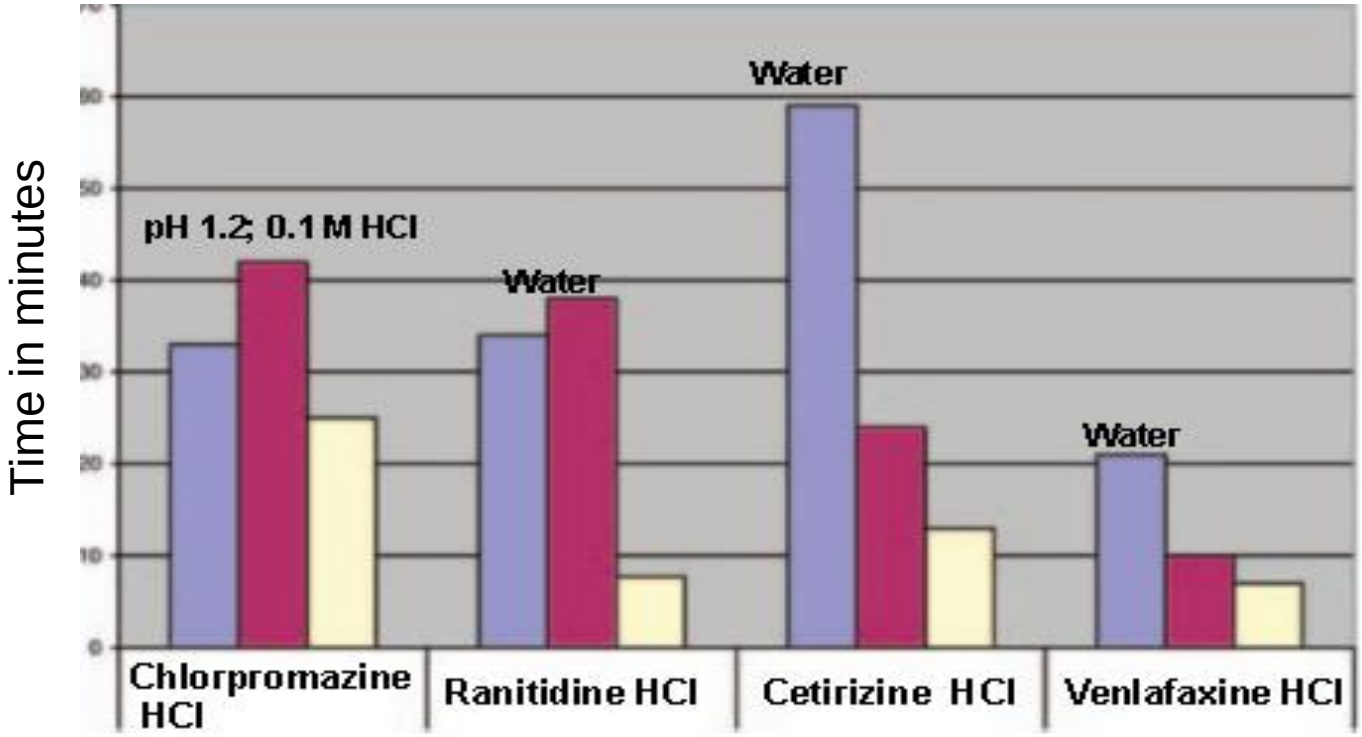
Types of Disintegrants

Disintegrants	Mechanism	Effective Concentration
Starch and Modified Starch	Swelling	5-10%
Microcrystalline cellulose	Swelling	10-20%
Croscarmellose Sodium	Wicking and swelling	1.0-4.0%
Sodium Starch Glycollate	Rapid and extensive swelling	4-6 %
Crospovidone	Wicking, swelling and deformation	2.0-4.0 %
Sodium Bicarbonate in combination acid	Effervescent Disintegrant Gas formation	-

Super disintegrants are effective in lower concentrations and offer significant improvements over disintegrants like starch and MCC
eg: Sodium Starch Glycolate, Croscarmellose Sodium, Crospovidone

Effect of Super-disintegrant

T80 of water-soluble cationic drugs



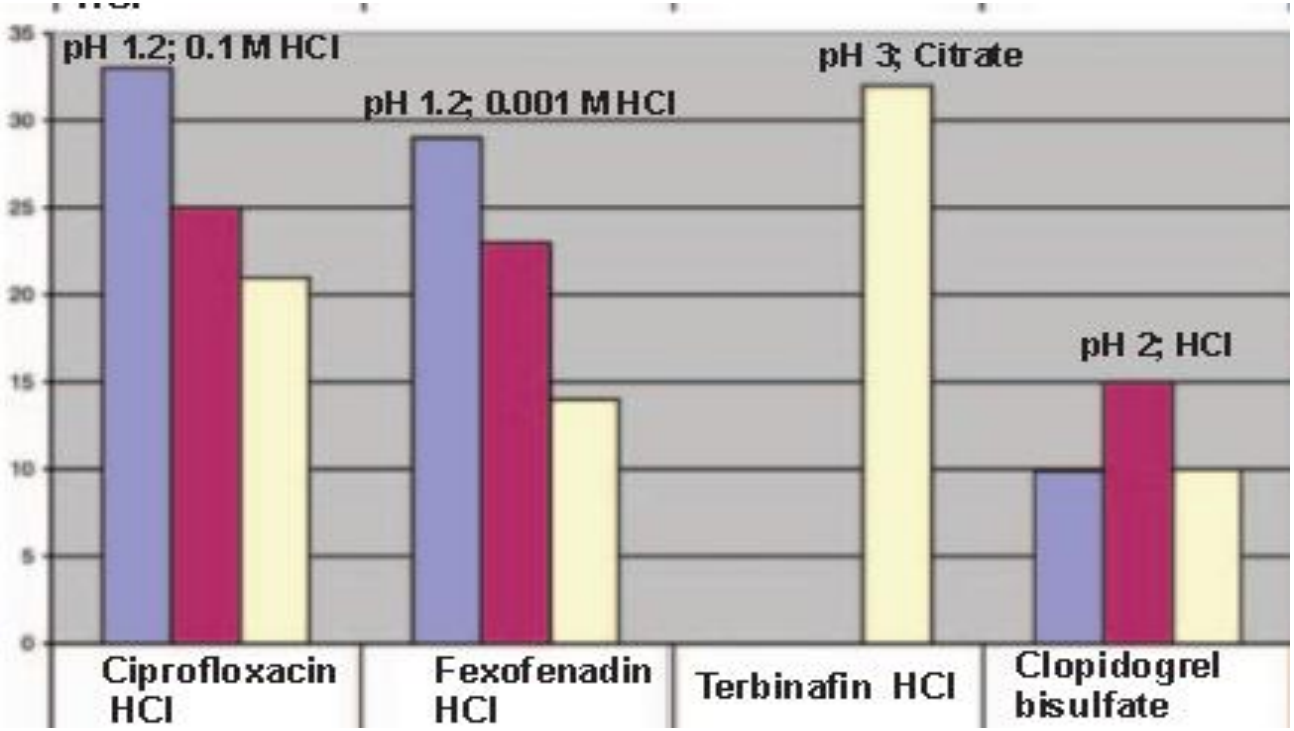
Ingredient	Weight %
Active drug	18
Superdisintegrant	2
Magnesium stearate	0.5
Talc	0.5
Avicel pH 102	q.s. 100

CCS
SSG
xPVP

Balasubramanium et al, Disso Tech, May 2008; 18-25

Effect of Super-disintegrant

T80 of poorly soluble cationic drugs.



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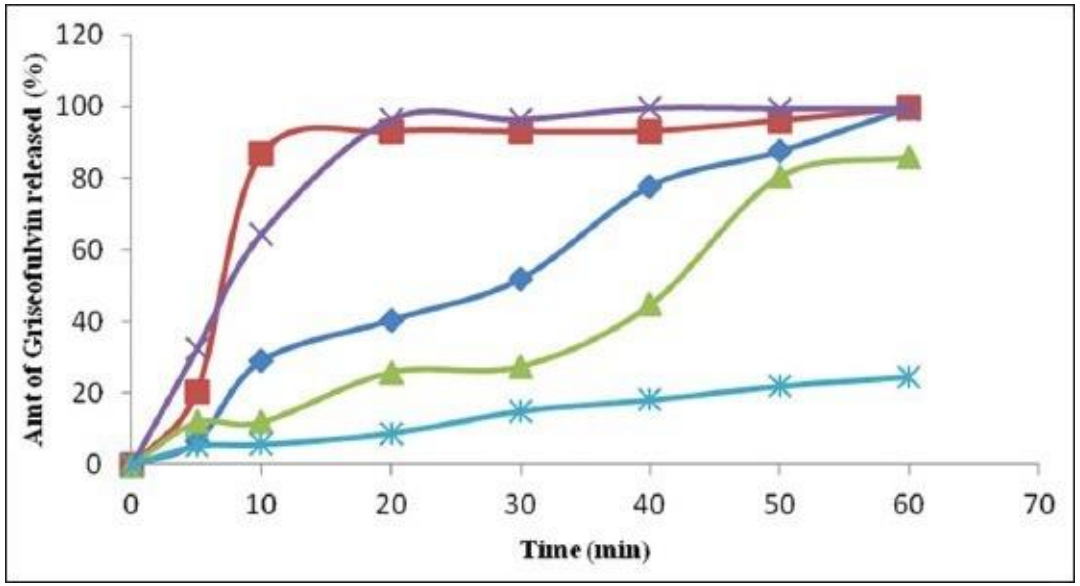
Role of Excipient in Dissolution

Diluents



Release profiles of griseofulvin from the formulated and commercial Samples
lactose (—♦—), sucrose (—■—), mannitol (—▲—) and dextrose (—×—) Fulcin® (—ж—), a commercially available sample.

Effect of Hydrophilic Diluents on the Release Profile of Griseofulvin from Tablet Formulations
O. N. C. Umeh,* J. C. Azegba, and S. I. Ofoefule

FORMULA FOR GRISEOFULVIN TABLETS

Ingredients	Batches			
	I	II	III	IV
Griseofulvin powder (mg)	100	100	100	100
Maize starch (mg)	50	50	50	50
Gelatin (mg)	25	25	25	25
Lactose (mg) q.s.to 500mg	320	·	·	·
Sucrose (mg) q.s to 500mg	·	320	·	·
Mannitol (mg) q.s to 500mg	·	·	320	·
Dextrose (mg) q.s to 500mg	·	·	·	320
Magnesium stearate (mg)	5	5	5	5

Four batches of griseofulvin tablets each containing one of the hydrophilic diluents (lactose, sucrose, mannitol and dextrose) were prepared using the wet granulation method and 60 tablets were produced for each batch

Fulcin: MCC, SLS, Povidone, starch (corn and Potato), Mag stearate

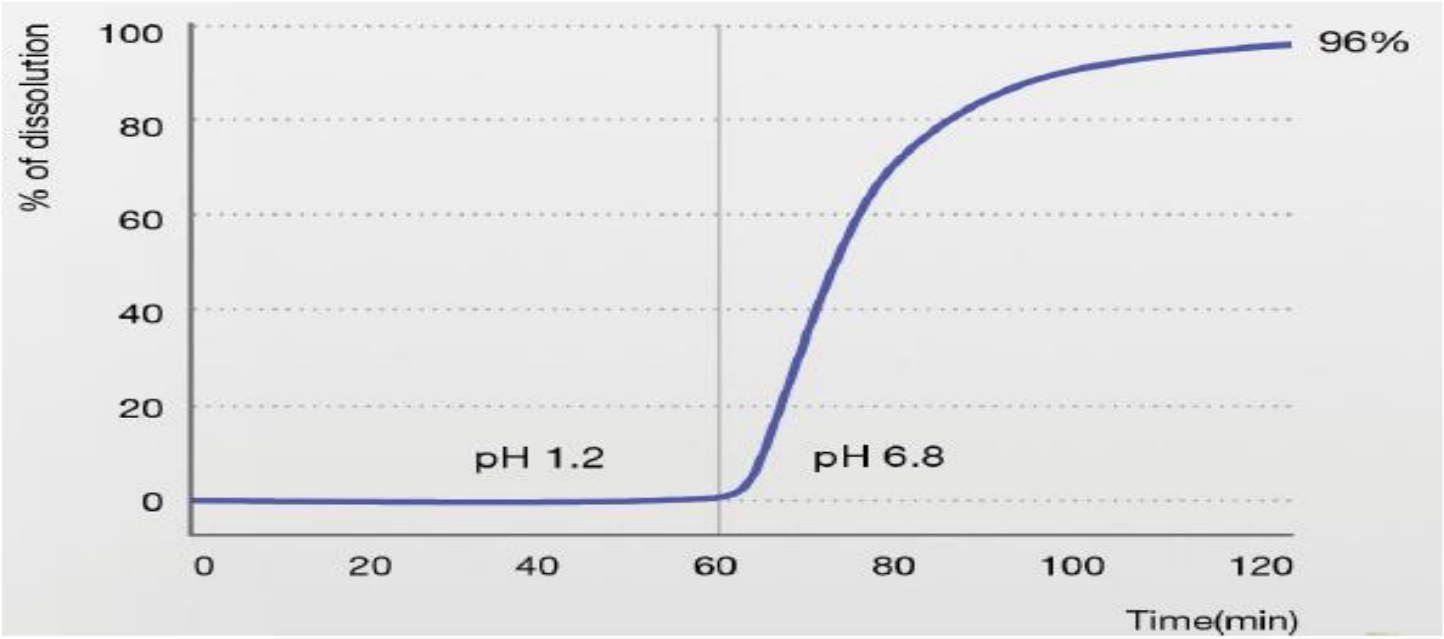
Role of Excipient in Dissolution

Polymers in Modified Release

pH dependent solubility

Dissolution Profile of Lansoprazole Tablet

- Sub-coating : HPMC 2906 type 10%
- Enteric coating : HPMC HP-55 15%



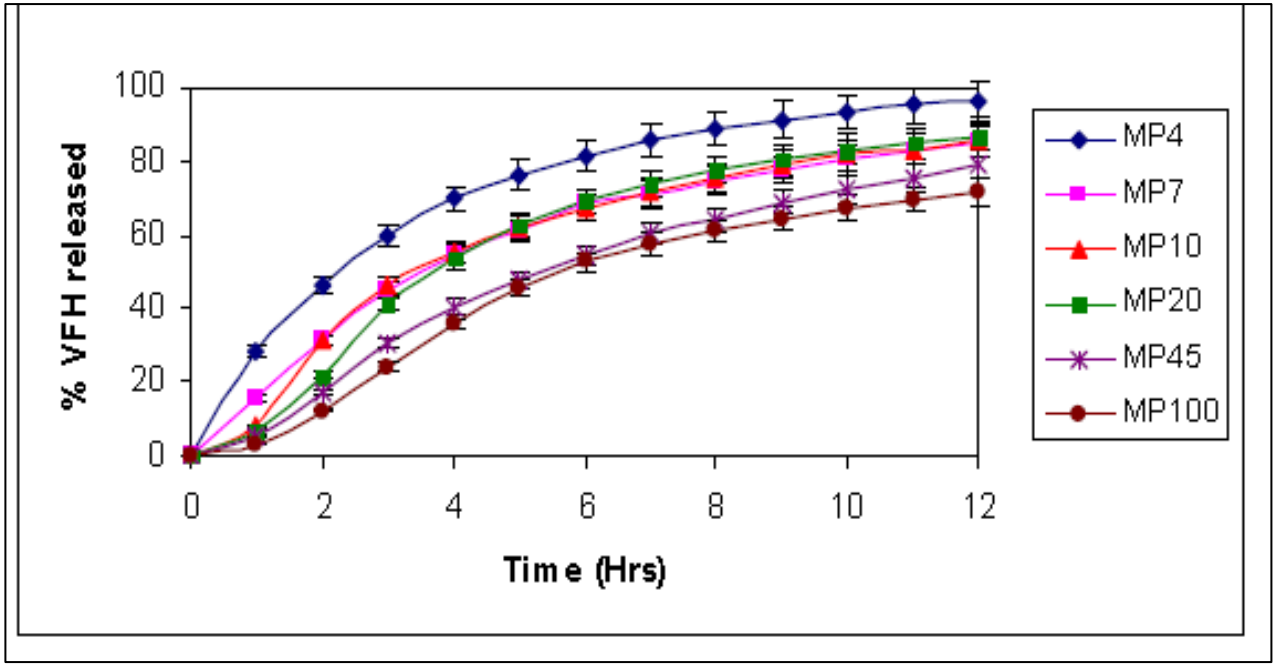
Role of Excipient in Dissolution

Effect of Ethyl Cellulose Viscosity

Venlafexine HCl (VFH) dissolution

Medium : 900 ml of 0.1N HCl; Apparatus: Paddle, Speed 50 rpm

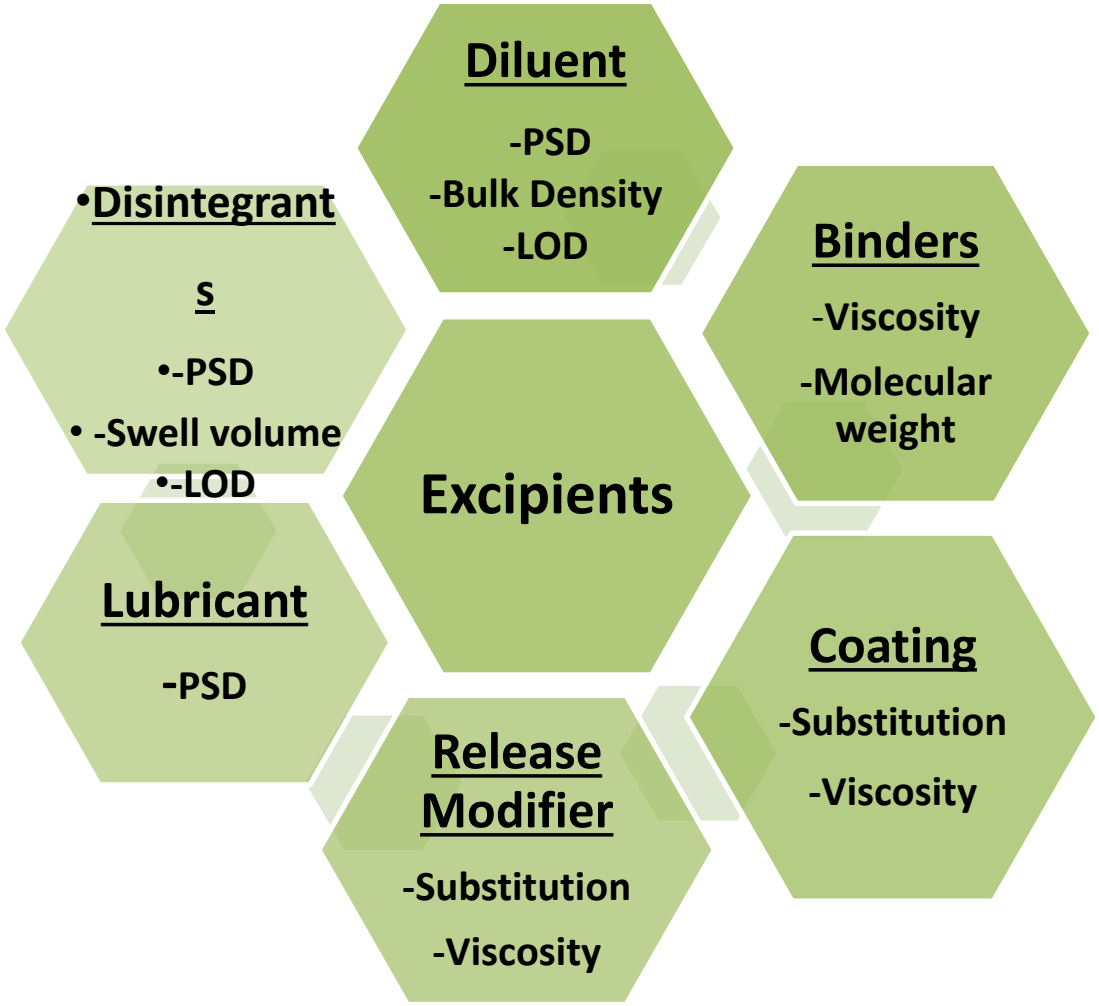
(10% weight gain)



Note: Ethyl Cellulose from Asha Cellulose was used in this study

Critical Quality Attributes

Functionality Tests are critical Quality attributes for Performance



Case Studies

Case Study- I

Microcrystalline Cellulose- Diluent

Problem: Percentage particles passing through 200 mesh was out of specification (OOS) on the higher limit

- **Investigation**
  - Samples were drawn from different boxes by using sampling thief from various points (top, middle and bottom) and mixed
  - Sieve Analysis was carried out using calibrated sieve
  - Vibratory sieve shaker was used
- **Probable cause**
  - Batch representation
  - Sieves were not calibrated
- **Corrective action**
  - Calibrated Sieve to be used
  - Batch representative Sampling

Case Study II

Hydroxy Propyl Methyl Cellulose- Polymer

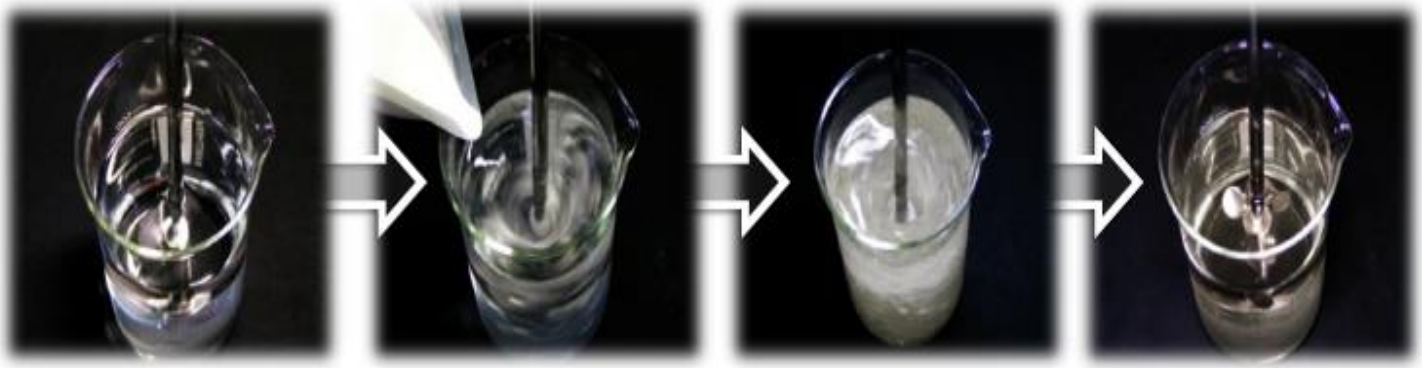
Problem : Out of specification results for Viscosity of Hypromellose 100,000 cps

- **Root Cause**
  - **Solution Preparation**

    Non-uniform solution preparation due to
    - Non uniform dispersion in hot water
    - Immediate cooling
    - Heat transfer in high viscosity solution is very slow and the lower, Middle and upper part in solution can be different
    - The swelled part is not visible, which can contribute to higher viscosity

- **Corrective action:**
  - **Solution Preparation (on next slide)**
    - The dispersed powder should be treated at 20~40 min in ice water
    - After the solution attains 20º C in ice water, transfer it to 20º C bath
    - The viscosity is measured at different positions

Solution Preparation Viscosity



1.Heat water above 90 ° C

2. Add HPMC above 90 ° C under stirring

3. Agitate till wetting and uniform dispersion is obtained

4. Cool to 20ºC transparent solution

Case Study III
Super-Disintegrant

Problem: Moisture Content : Out of specification results were obtained for Moisture Content

- **Root cause**:
  - Crospovidone is a highly hygroscopic material
  - Due to hygroscopicity, the sample had picked up moisture due to
    - Improper packing of sample
    - Time gap between sampling and analysis
- **Corrective Action:**
  - Notification on precautions to be taken during handling of Crospovidone for sampling, analysis and manufacturing accompanies the material
  - The label states that the material is hygroscopic in nature

Conclusion

- ➢Excipients are inert but play a vital role in formulating a stable product with efficacy and safety
- ➢Different grades are available to cater to the specific needs of API
- ➢Selection of excipient is critical to have a bioequivalent/ bioavailable drug product
- Critical quality attributes are functional tests which differentiate between excipient quality
- ➢Analytical Errors in CQA can lead to failure and rejection of the material

Anshul Life Sciences

An Introduction

- Established in 1978.
- Over the years, Anshul from an indenting agency has now become a partner in innovation and value addition to many customers
- Has a strong customer base of over 800
- Has a good track record of being an ethical and reliable company in the Specialty Chemicals, Excipients & Ingredients space.
- Has an application lab of Pharma, Personal care and Food to cater to the needs of customers
- ISO 9001:2015 compliant

Anshul Product Portfolio

MINGTAI CHEMICAL CO., LTD.

- Microcrystalline Cellulose
- Croscarmellose Sodium
- Sodium CMC + MCC

LOTTE FINE CHEMICAL

- Hypromellose
- Hypromellose Phthalates

armor pharma
Technological Lactose Excipients

- Lactoses

JHNH

- Povidones
- Crospovidones
- Copovidone

productos aditivos since 1929

- Saccharins
- Cyclamates

CAFOSA
A subsidiary of Mars, Incorporated

Wei 威尔化工

- Polysorbate 80
- PEG
- Poloxamer

DIVAKAR
Techno Specialities & Chemicals Limited
Innovation just for you.

- Directly Compressible Gum Bases for medicated Chewing Gums

Ingredion

- Mannitol
- Corn Starch

- Capsudx Cool 3
- Cool Strips
- Glowspheres

山东阜丰发酵有限公司
SHANDONG FUFENG FERMENTATION CO.,LTD.

- Xanthan Gum

Techno Food Ingredients

- Sucralose

ASHA CELLULOSE (I) PVT. LTD.

- Ethyl Cellulose

Thank You

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