Drug Dissolution:Excipient vs Excipient

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Agenda

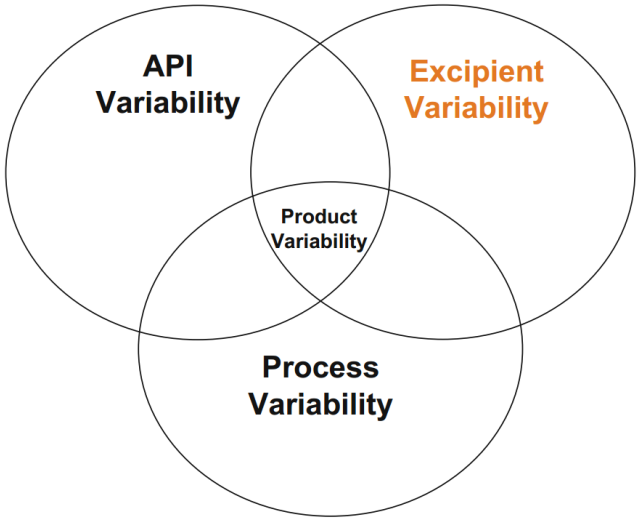
- Definition
- Understanding excipients
- Role of dissolution
- Super-disintegrants
- Capsule shells
- Case studies

Definition

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

Understanding Excipients

- Excipients enable API's
- Major source of variability
- QbD
- Impacts CQA
- Source of impurity?
- Patient safety
- Speed to market

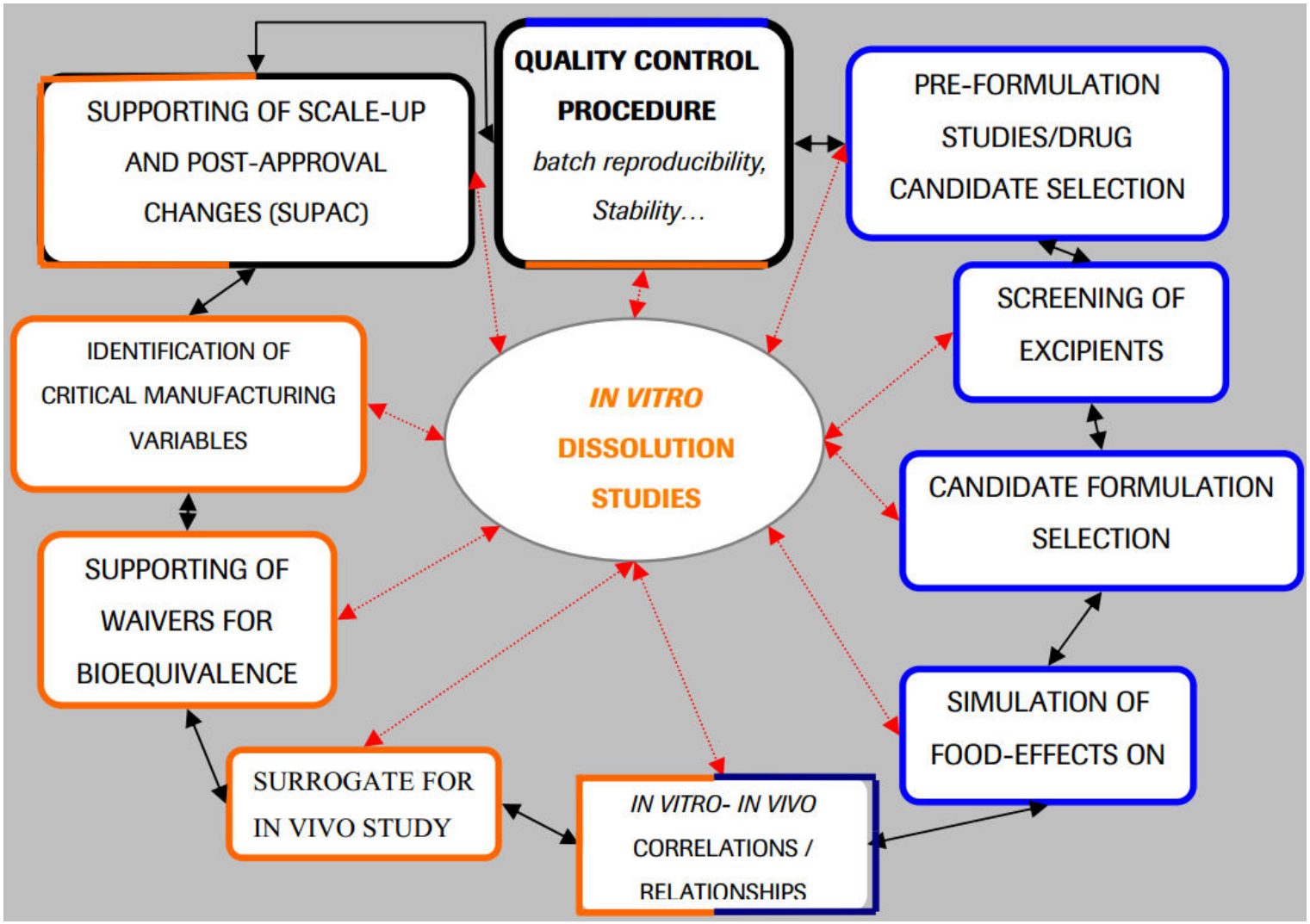


Understanding variability & tolerating it = Robustness

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

Ref: C. Moreton

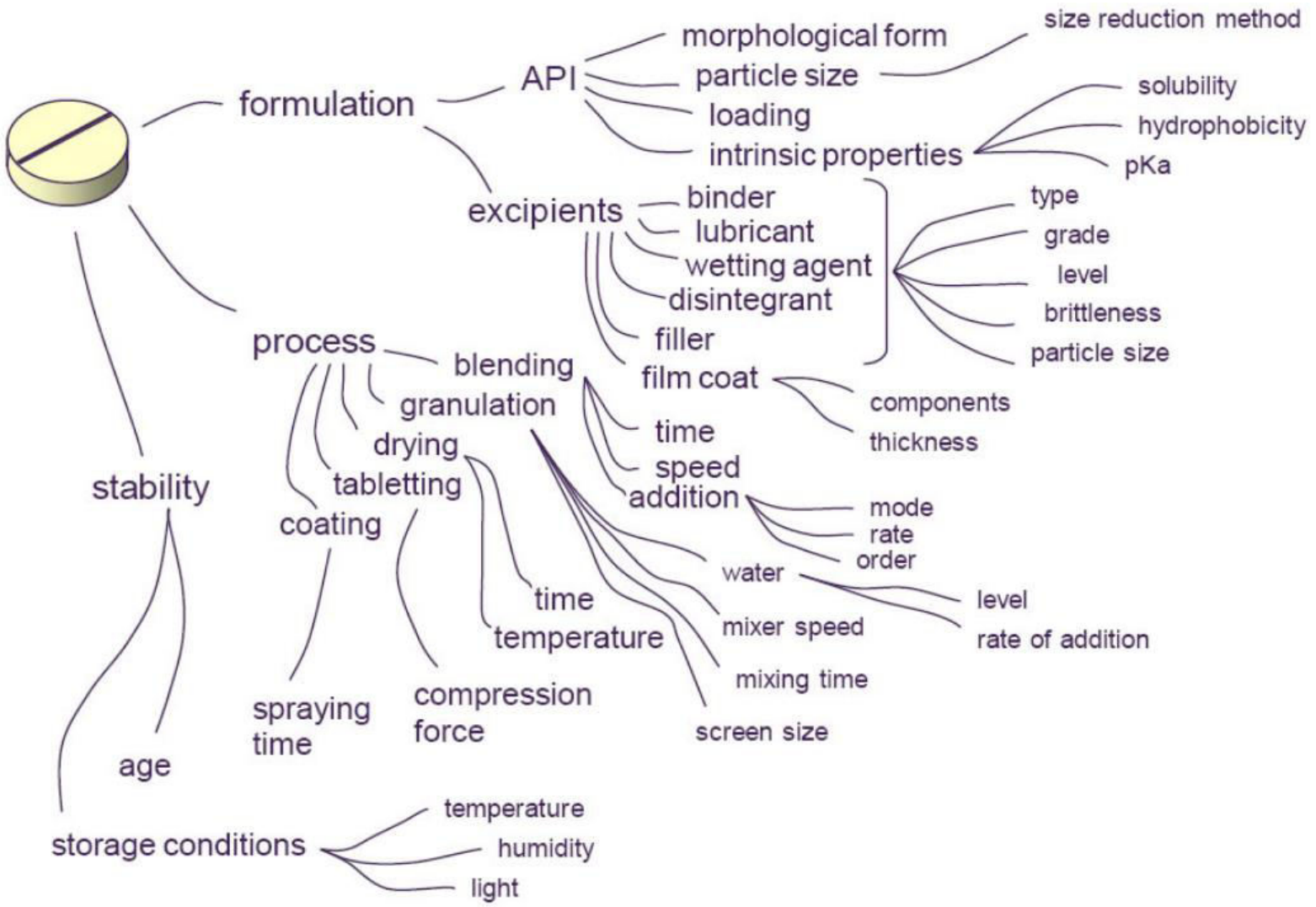
Central Role of Dissolution



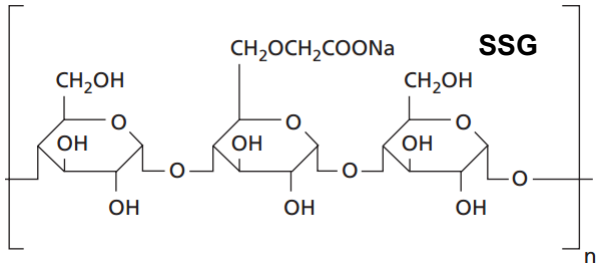
Ref: Emmanuel Scheubel

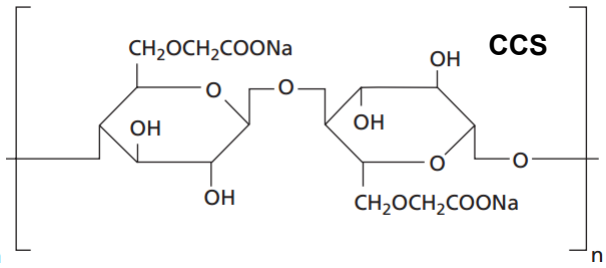
Early phase of development — Late phase — Market

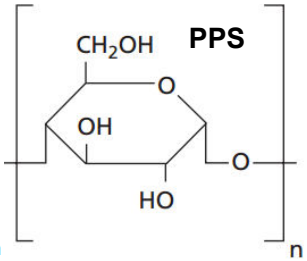
Factors affecting in-vitro dissolution

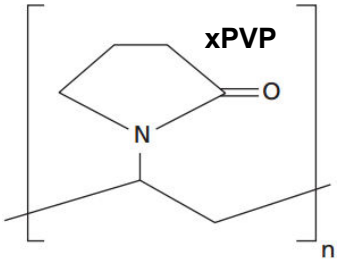


Dr Donald Murphy, Astra Zeneca UK, IRR Conference, May 07, Budapest









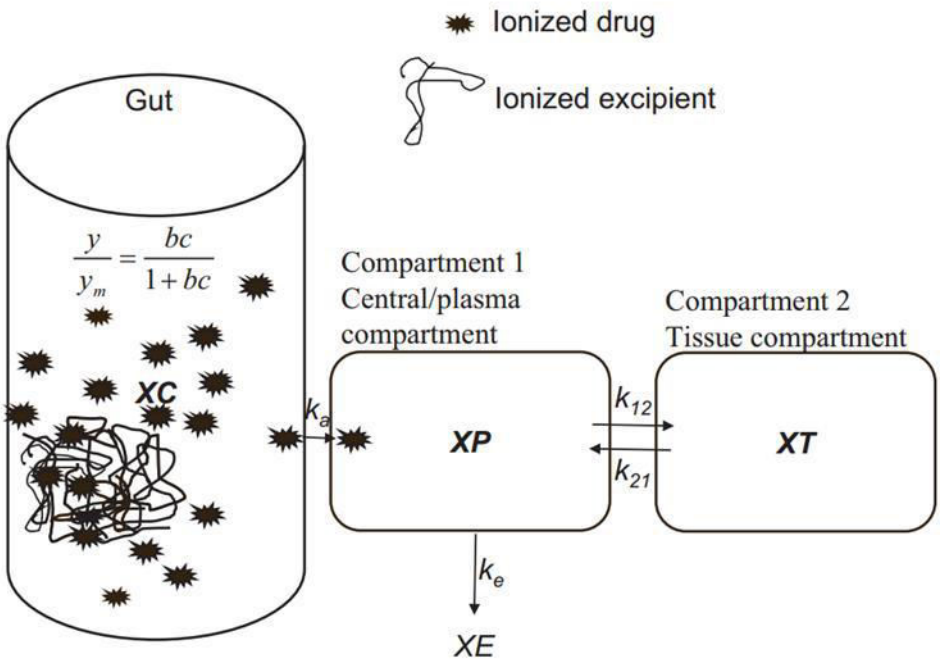
Chemical class	Common name	Chemical nature
Cellulose derivatives	Low hydroxypropyl cellulose	Hydroxyl groups of cellulose in the repeating glucose units are hydroxypropylated
	Microcrystalline cellulose	Derived from a special grade of alpha cellulose
	Crosscarmellose sodium	Cross-linked form of sodium carboxymethyl cellulose
	Crosscarmellose calcium	Cross-linked form of calcium carboxymethyl cellulose
Acrylic acid derivatives	Poly(acrylic acid)	Acrylic acid crosslinked with an allyl ether of pentaerythritol, allyl ether of sucrose, or allyl ether of propylene
Alginates	Sodium alginate	Sodium salts of alginic acid
Polyvinyl- -pyrrolidone	Crospovidone	Synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone
Starch derivatives	Sodium Starch Glycolate	Sodium salt of carboxymethyl ether of starch
	Pregelatinized starch	
Polysaccharides	Natural polysaccharide	Soy polysaccharides
Resins	Ion exchange resins	Weakly acidic cation exchange resin
Gas evolving disintegrants	Citric acid, tartaric acid, sodium bicarbonate	

Super-disintegrants

Super-disintegrants

Drug Excipient binding interaction

- Unintended physicochemical interaction of excipient with drug
- Ionic in nature
- Results in slow and/or incomplete drug release
- Can impact BA if complex is not disrupted by physiological salt concentrations

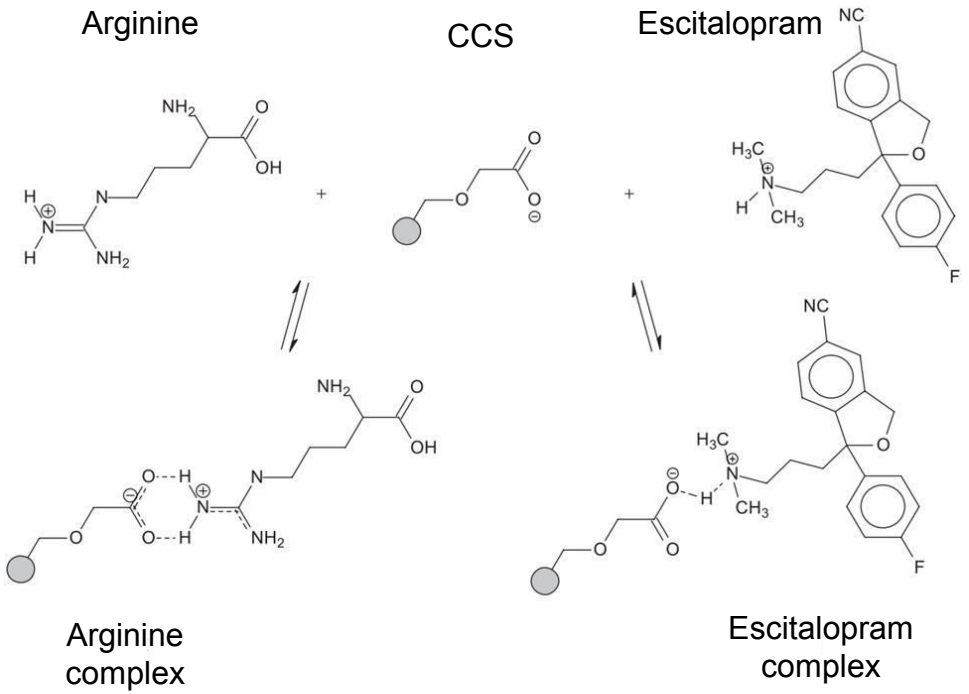


Schematic of model for assessing the effect of drug-excipient binding interaction on oral absorption and plasma PK with Langmuir isotherm equation

Narang et al, JPP; 2012(64), 553-565

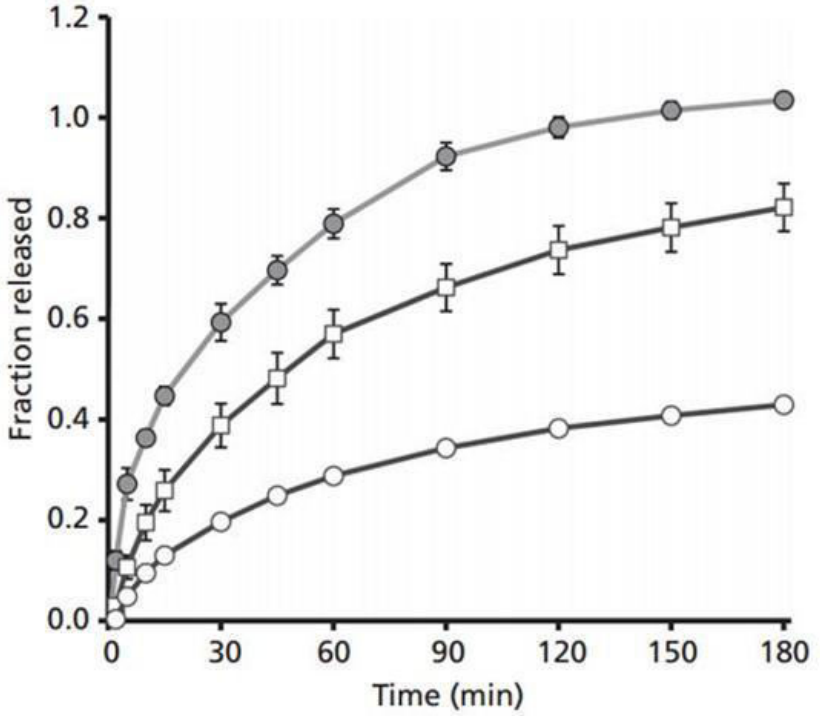
Super-disintegrants: CCS & SSG

Interaction of croscarmellose with arginine and escitalopram in solution



Larsen et al, DDIP,2012; 38(10):1195-1199

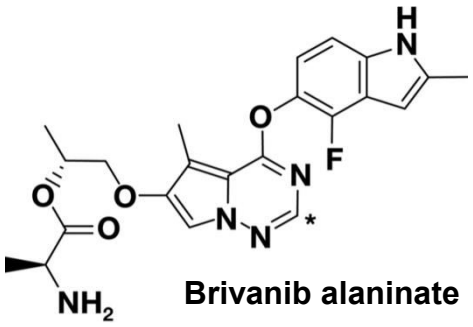
Interaction of sodium starch glycollate



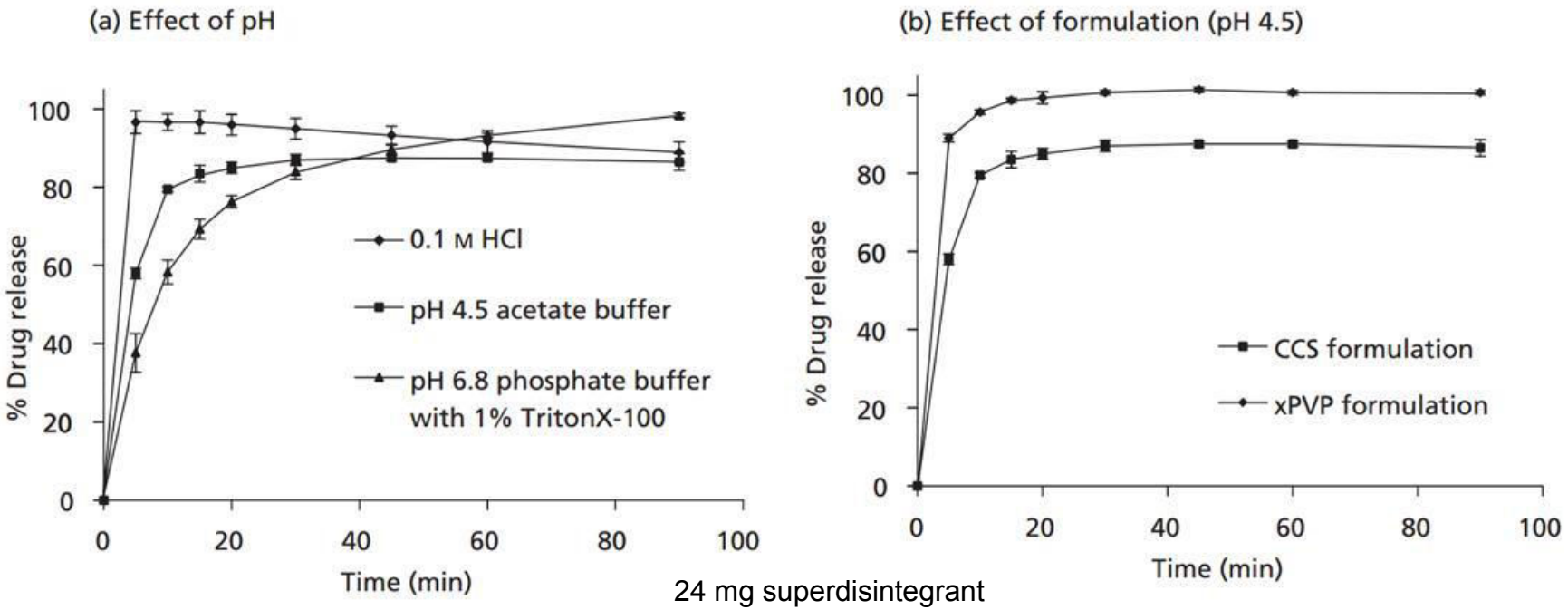
The cumulative release of naproxen (●) or diphenhydramine (○□) to 5 mM Tris buffer (●○) or 5 mM Tris buffer supplemented with 145 mM NaCl (□) from SSG gels. Mean values ± s.d., n = 3.

Fransen et al; JPP 2008, 60:1583-1589

Drug Dissolution: CCS vs xPVP



Brivanib alaninate Hydrophobic (log P = 2.5), weakly basic (pKa = 6.9), amine drug, Dose = 400 mg



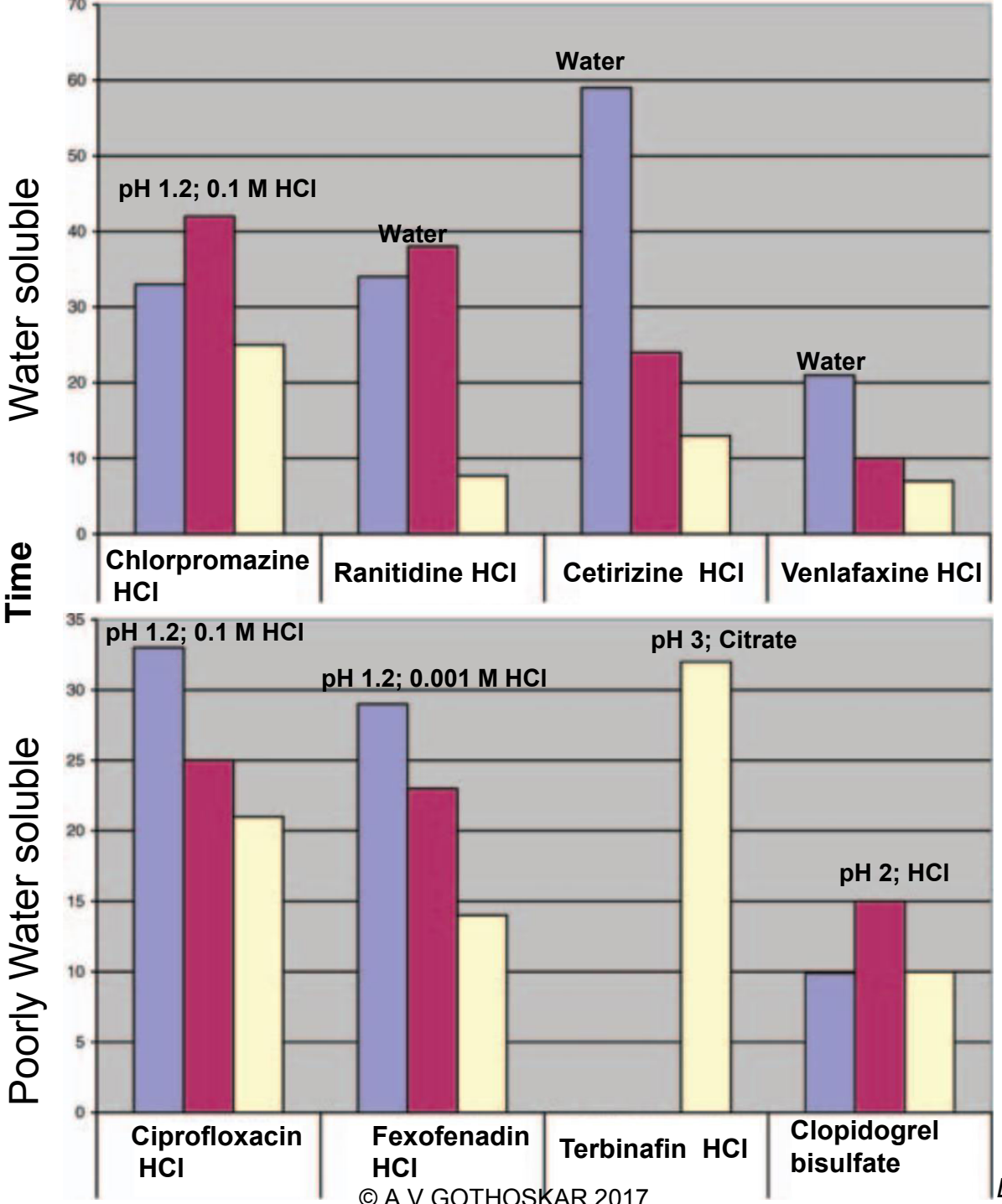
24 mg superdisintegrant

Comparison of drug release from a brivanib alaninate formulation containing croscarmellose sodium in different pH media (a) and with a formulation not containing croscarmellose sodium in pH 4.5 acetate buffer (b).

Narang et al, JPP; 2012(64), 553-565

Cationic Drugs Dissolution

Effect of Super-disintegrant on $T_{80\%}$



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

CCS

SSG

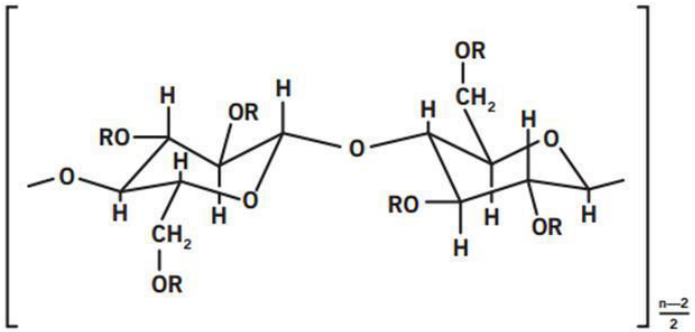
xPVP

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

HPMC Capsules

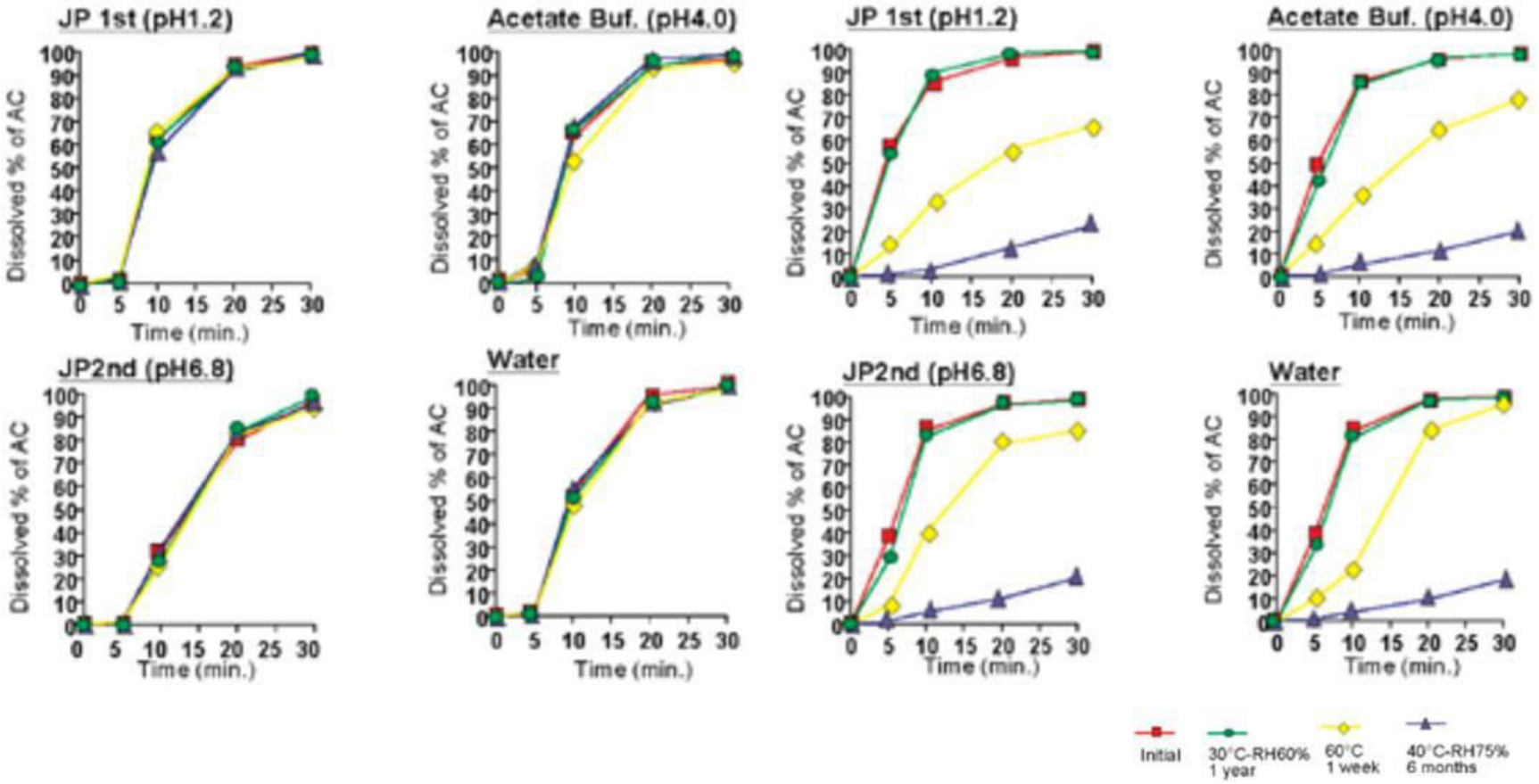
Substitution Type	Methoxy %	Hydroxypropoxy %	Anycoat grade
2208	19.0-24.0	4.0-12.0	C
2906	27.0-30.0	4.0-7.5	B
2910	28.0-30.0	7.0-12.0	A

- Inert
- Low moisture content
- Low water vapour permeability
- Less brittle even at low humidity
- High tolerance to temperature (80^0C vs 60^0C)
- No cross linking upon storage
- Contains co-gelling agent and gel promoter ion



Drug Release: HPMC vs Gelatin Capsules

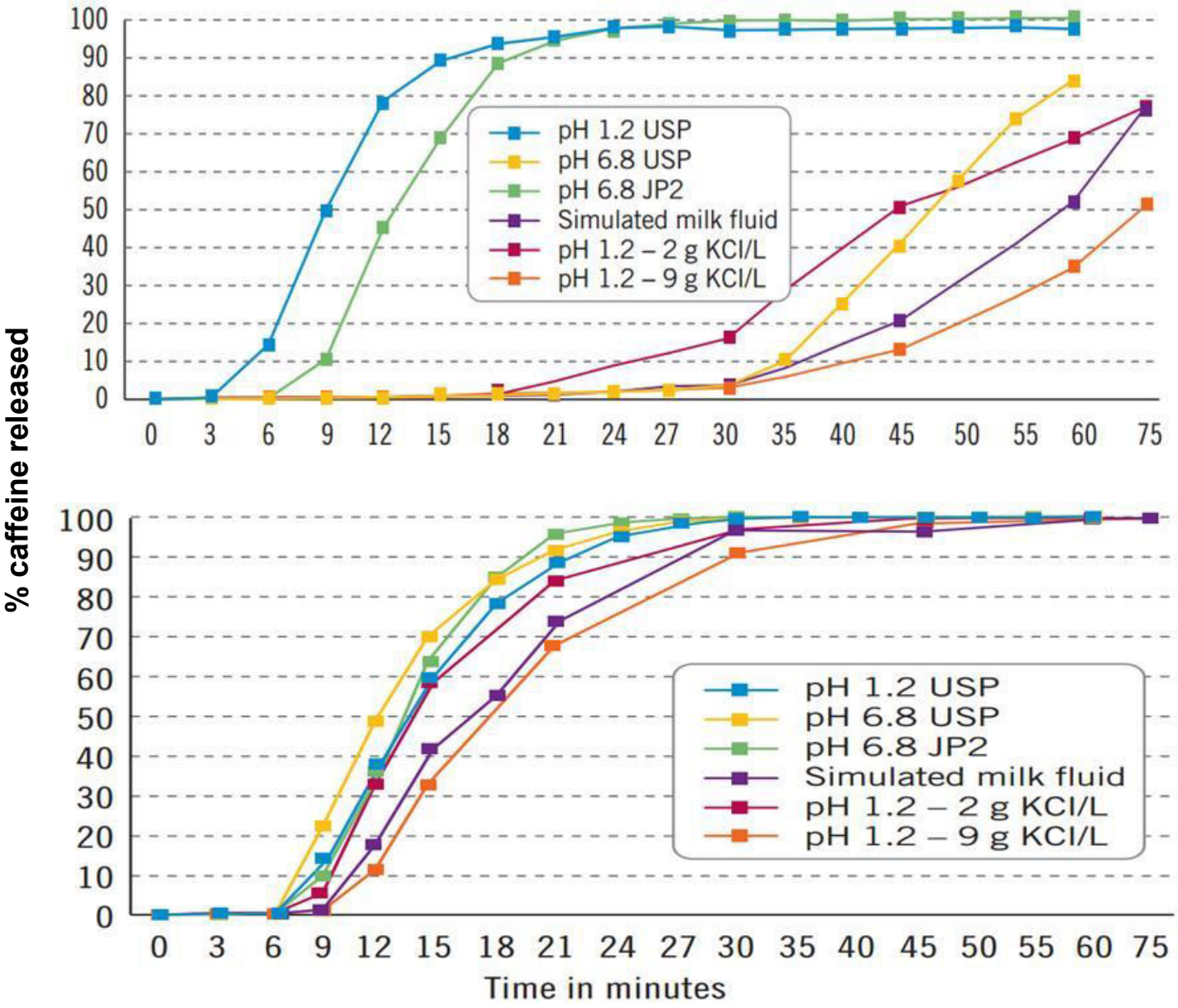
Paracetamol dissolution



Drug Dev & Delivery, 2 (2), 2002

Drug release: HPMC capsules

Effect of gelling agents



Caspugel brochure

Summary

- Excipients are ACTIVE!
- Excipients determine the drug release
- Right selection of excipients = successful formulation
- Understanding excipients is key to bio-behaviour.

Thank you