Workshop IV
Understanding Drug-Excipient Interactions

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- Excipients are more complex than well-characterized active pharmaceutical ingredients (“APIs”). Often, it is the multi-component nature of the excipient that drives many of the interactions with APIs. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential API interactions with trace components. This workshop will illustrate the contrasting nature of excipients, and help identify reaction mechanisms. This session is recommended for industry professionals in manufacturing, formulation, quality, and technical service functions dealing with drug degradations.

Drug (API)

- Predominantly single synthetic small molecule chemical entities (excluding biologics)
- Batch manufacture
- Well characterised impurity profiles
- Impurities are unintended or unavoidable constituents which differ from the labelled chemical entity
  - Process (by-products & residuals)
  - Degradation
  - Contamination

API/Drug Product Impurities

- *Impurity*: Any component of the new drug substance that is not the chemical entity defined as the new drug substance. ICH Q3A
- *Impurity*: Any component of the intermediate or API that is not the desired entity. ICH Q7A
- *Impurity*: Any component of the new drug product that is not the drug substance or an excipient in the drug product. ICH Q3B

- Drug = Labelled entity + impurities

Impurity

- The quality or condition of being impure, especially:
  - Contamination or pollution.
  - Lack of consistency or homogeneity; adulteration.
  - A state of immorality; sin.
- Something that renders something else impure
- Inferior component or additive.

Excipient

- Inert(?) substances used as a diluent or vehicle for a drug
  - Chemically inert?
  - Biologically inert?
- Enablers of medicinal products

- Majority of Pharmaceutical Suppliers are Chemical Industry subsidiaries
- Small fraction of Parent Production
- Varying degrees of dedicated R&D
- Specifications-driven
- Global Market and Manufacturing Base

Excipients are from a Diverse Materials Base

- Chemical synthesis*
- Mining of minerals
- Harvesting of vegetation
- Formulated Products
- Biotechnology
- Genetic Modification
- Animal by-products

* often less defined than single low mol wt entities, multicomponent &/or polymeric

Excipient vs Drug (API)

- Rarely single synthetic small molecule chemical entities
- Often polymeric (synthetic, semi-synthetic & natural)
- Inorganics
- Continuous Production
- Less well defined composition and “impurity” profiles
- Composition & impurities may be process/source dependent
- Excipient = Labelled entity + other components + impurities
  - concomitant components
  - additives
  - processing aids

Humpty Dumpty language

- *n*. An idiosyncratic or eccentric use of language in which the meaning of particular words is determined by the speaker.

"When *I* use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less."

"The question is, " said Alice, "whether you *can* make words mean so many different things."

"The question is," said Humpty Dumpty. "which is to be master—that's all."

"Pure" Excipients that don't work

- Pure DiCalcium Phosphate doesn't compact well
  - Absence of impurity related crystal defects
  - Crystal 'strength' depends on dislocations in the crystal lattice
- Pure Magnesium Stearate doesn't lubricate
  - Absence of water (only hydrates lubricate)

What might be contained in an Excipient?

- The ‘nominal’ chemical component
- Impurities (Raw material, process & degradation)
  - Organic
  - Inorganic
- Processing aids
- Additives
- Residual solvents/water
- Other (concomitant) components
- Some may be essential for performance/functionality

What are ‘concomitant’ components?

- Related substances
- Unrelated substances
- Organic or inorganic
- By-products from the manufacturing process
- Residues from starting materials
- Residual solvent and/or water
- May be quantitatively significant (tens of %)
- May be:-
  - Necessary (≠ Impurities)
  - Desirable (≠ Impurities)
  - Innocuous (= Impurities?)
  - Undesirable (= Impurities)

Excipient Impurities

- The term ‘impurity’ is a misnomer when applied to excipients in the same manner as used for APIs
- There may be some components that must be controlled for safety or functionality
- **An excipient impurity is any undesirable component**
- This definition requires full understanding of manufacturing and sourcing history!
- The presence of multiple components in an excipient may be beneficial and should not be construed as undesirable
- Coprocessed excipients multicomponent by definition
  - Focus on new impurities (or absence)

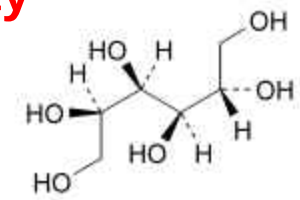
International Pharmaceutical Excipient Council

- IPEC Composition Committee developing guidelines on excipient composition which will address concomitant components, additives, processing aids, impurities and related issues
- Working with PDG (USP, PhEur, JP) to develop policy on additives, processing aids and co-processed excipients.

SORBITOL

Sorbitolum

97% purity



$C_6H_{14}O_6$ M_r 182.2

DEFINITION

Sorbitol contains not less than 97.0 per cent and not more than the equivalent of 102.0 per cent of D-glucitol (D-sorbitol), calculated with reference to the anhydrous substance.

SORBITOL, LIQUID (NON-CRYSTALLISING)

Sorbitolum liquidum non cristallisabile

DEFINITION 72% purity

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content:

- anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,
- D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 72.0 per cent to 92.0 per cent (anhydrous substance).

SORBITOL, LIQUID (CRYSTALLISING)

Sorbitolum liquidum cristallisabile

DEFINITION 95% purity

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content:

- anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,
- D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 92.0 per cent to 101.0 per cent (anhydrous substance).

SORBITOL, LIQUID, PARTIALLY DEHYDRATED

Sorbitolum liquidum partim deshydricum

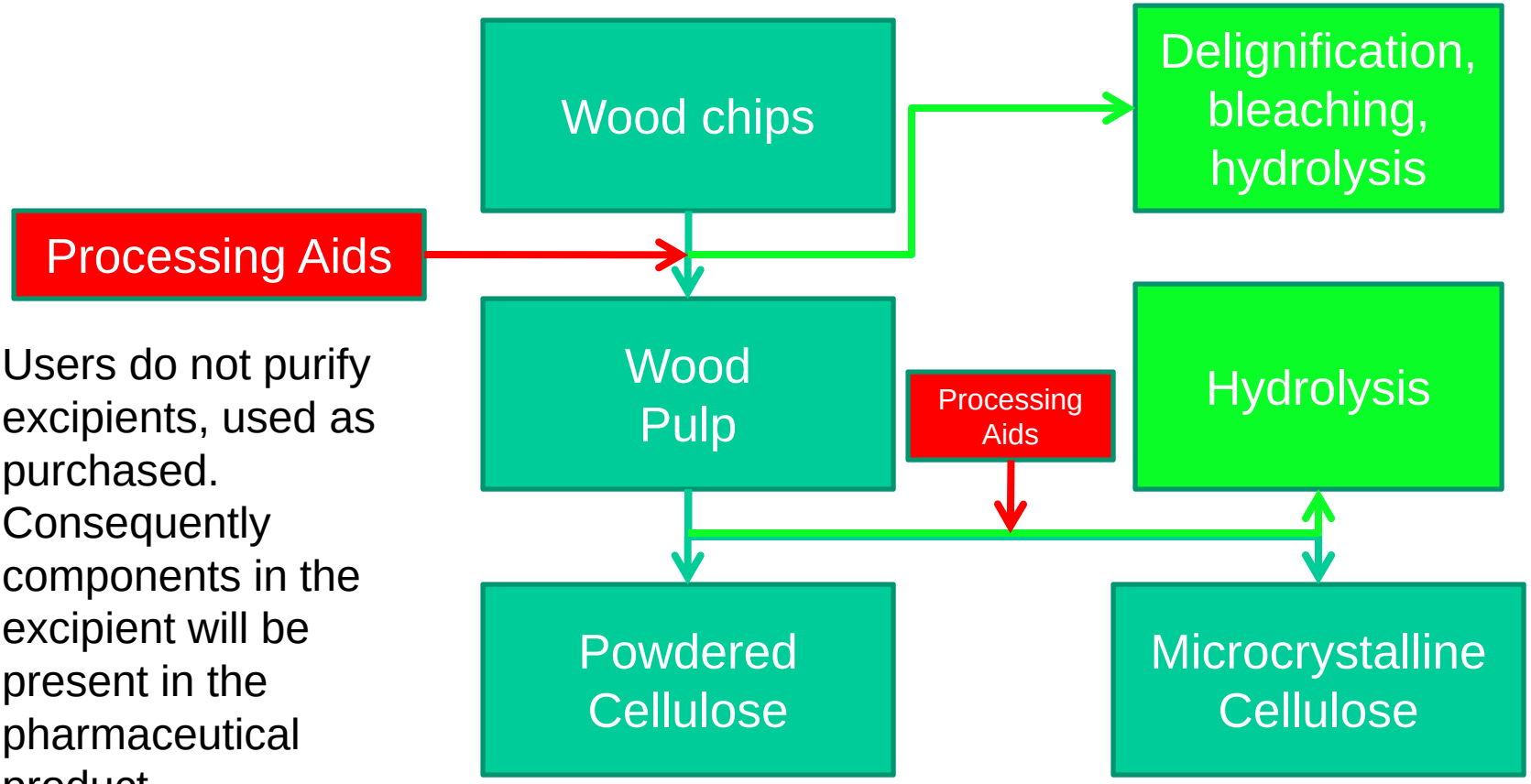
DEFINITION 25% purity + degradants

Liquid sorbitol, partially dehydrated is obtained by acid-catalysed partial internal dehydration of liquid sorbitol. It contains not less than 68.0 per cent *m/m* and not more than 85.0 per cent *m/m* of anhydrous substances, composed of a mixture of mainly D-sorbitol and 1,4-sorbitan with mannitol, hydrogenated oligo- and disaccharides, and sorbitans.

Content (nominal value):

- 1,4-sorbitan ($C_6H_{12}O_5$): minimum 15.0 per cent (anhydrous substance),
- D-sorbitol ($C_6H_{14}O_6$): minimum 25.0 per cent (anhydrous substance).

Difficult to purify non crystallised or non-precipitated excipients Eg MCC

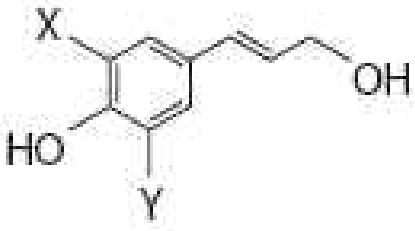


Users do not purify excipients, used as purchased. Consequently components in the excipient will be present in the pharmaceutical product.

MCC Hydrolysates (Ether & Water Solubles)

Lignin (%):	Emcocel 6132 0.70 (0.09)	Emcocel 5114 0.82 (0.05)	Emcocel 6001 0.55 (0.08)
Hemicelluloses (TFA)			
Xylose (%)	0.32 (0.06)	0.19 (0.02)	0.39 (0.06)
Mannose (%)	0.12 (0.02)	0.08 (0.01)	0.17 (0.01)
Glucose (%)	1.68 (0.25)	1.00 (0.02)	1.46 (0.11)
Total sugars (H_2SO_4)			
Xylose (%)	3.9	3.7	4.1
Mannose (%)	7.1	4.9	5.3
Arabinose (%)	1.4	0.5	0.5
Galactose (%)	1.7	1.2	1.8
Glucose (%)	86.0	89.8	88.3

Landin et al Int J Pharm 91 133-41 1993



X and Y = H: *p*-coumaryl alcohol
X = OMe, Y = H: coniferyl alcohol
X and Y = OMe: sinapyl alcohol

Lignin derived MCC components (ether solubles)
Crowley PJ Martini LG, Pharmaceutical Technology Oct 2001

Pharmacopoeial compliance insufficient

- Safety/toxicology focus on identified components
- May not be comprehensive wrt to all components (esp if undisclosed)
- Inconsistent approach to additives and process aids
- Qualitative limits (pass/fail) rather than quantitative results.
- Non-specific assays or limits

Drug Excipient Interaction

- Biological
  - Pgp and CYP3A4 inhibition
- Physical
  - API adsorption onto suspended insoluble excipient
- Ionic
  - Basic drugs with acidic excipients
  - pH microenvironment vs drug pH-stability profile
- Chemical

Major Routes of Drug Degradation

Table I Modes of degradation of medicinal agents.

Hydrolysis	Oxidation	Isomerization	Photolysis	Polymerization
Methyl dopa	Calcitonin	Tetracycline	Riboflavin	Ceftazidime
Procaine	Ascorbic acid	Vitamin A	Folic acid	Ampicillin
Penicillins	Isoprenaline	Adrenaline	Nifedipine	

Crowley PJ Martini LG, Pharmaceutical Technology Oct 2001

- Solid-state vs Liquid
- Water activity more important than water content
- Water effects on mobility of reactants outweighs direct hydrolysis

Excipient or Impurities?

- Few drugs react directly with excipients, except amines with reducing carbohydrates (Maillard reaction)
- In many cases drugs react with excipient impurities, including reducing carbohydrates
- Major Reactive Excipient Impurities (Waterman K)
  - Water
  - Hydrogen peroxide (other oxidised species)
  - Formaldehyde (other aldehydes)
  - Formic Acid (other acids)
- Low drug excipient ratio = higher reaction risk
- Low reactant mol wt = higher risk (mobile or even volatile)

Common Impurities in Excipients

Table II Impurities found in common excipients.

Excipient	Residue
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Polyethylene glycol	Aldehydes, peroxides, organic acids
Microcrystalline cellulose	Lignin, hemicelluloses, water
Starch	Formaldehyde
Talc	Heavy metals
Dibasic calcium phosphate dihydrate	Alkaline residues
Stearate lubricants	Alkaline residues
Hydroxypropylmethyl/ethyl celluloses	Glyoxal

Crowley PJ Martini LG, Pharmaceutical Technology Oct 2001

Profiling of Reactive Impurities in Pharmaceutical Excipients

Excipient	Impurities	Level ppm
MCC	Glucose	40-80
Pregelatinised Starch	Formaldehyde	11-41
Crospovidone		
HPC		
Povidone	Peroxide	37-72
Crospovidone		
SSG	Nitrate	117-286
	Nitrite	
	Monochloroacetate	

Y. Wu, J. Levons, W. Fu, V. Rao AAPS2007-002404

Reactive Aldehydes

Excipient	ppm formaldehyde
Corn starch	72
Pregelatinized starch	100
MCC	71
PVP	208
PEO MW 600K	66
PEO MW 2000K	65
HPC	63

Waterman K, 2nd Annual Drug-Excipient Compatibility Conference, Princeton 2006

Trace Formic Acid and Formaldehyde in Film Coatings

Raw material description	Number of lots	Average formic acid concentration & (standard deviation) ppm	Average formaldehyde concentration & (standard deviation) ppm
Polyvinyl alcohol	12	34.2 (6.0)	5.6 (2.6)
Hypromellose 2906 (3 cps)	6	57.7 (10.7)	9.0 (0.6)
Hypromellose 2906 (6 cps)	6	97.5 (27.5)	14.7 (3.3)
Hypromellose 2906 (15 cps)	6	67.7 (25.9)	12.8 (5.7)
Polyethylene glycol 400 (no BHT)	3	14.7 (7.6)	7.7 (2.3)
Polyethylene glycol 3350 (no BHT)	3	10.3 (2.1)	< 5
Polyethylene glycol 3350 (w/ BHT)	3	ND	ND
Triacetin	3	16.3 (5.5)	ND
Starch 1500® partially pregelatinized maize starch	3	< 5	ND
StarCap 1500® co-processed starch excipient	6	10.2 (1.3)	ND

Ferrizzi & Farrell
AAPS 2008

Packaging Impurities

- Na_2O, SiO_2, MgO, CaO from glass
- Styrene from polystyrene
- Diethylhexylphthalate plasticiser from PVC
- Dioctyltin isooctylmercaptoacetate stabiliser from PVC
- 2 mercaptobenzothiazole accelerator from rubber
- Furfural from rayon

Water

- Excipient moisture increases water activity and reactant mobility
- Reactivity increases exponentially
- Mobility usually more of a problem than hydrolysis
- If water is also a reaction product:- autocatalysis

- Acetylsalicylic acid + water $\rightarrow$
  Salicylic acid + Acetic Acid + water

- Control of free water can enable stable combination of otherwise incompatible reactants

Excipients Containing Peroxides

- Polyvinyl pyrrolidones
  - povidone
  - crospovidone
- Polyethers
  - PEG's, PEO's
  - polysorbates
- Oils

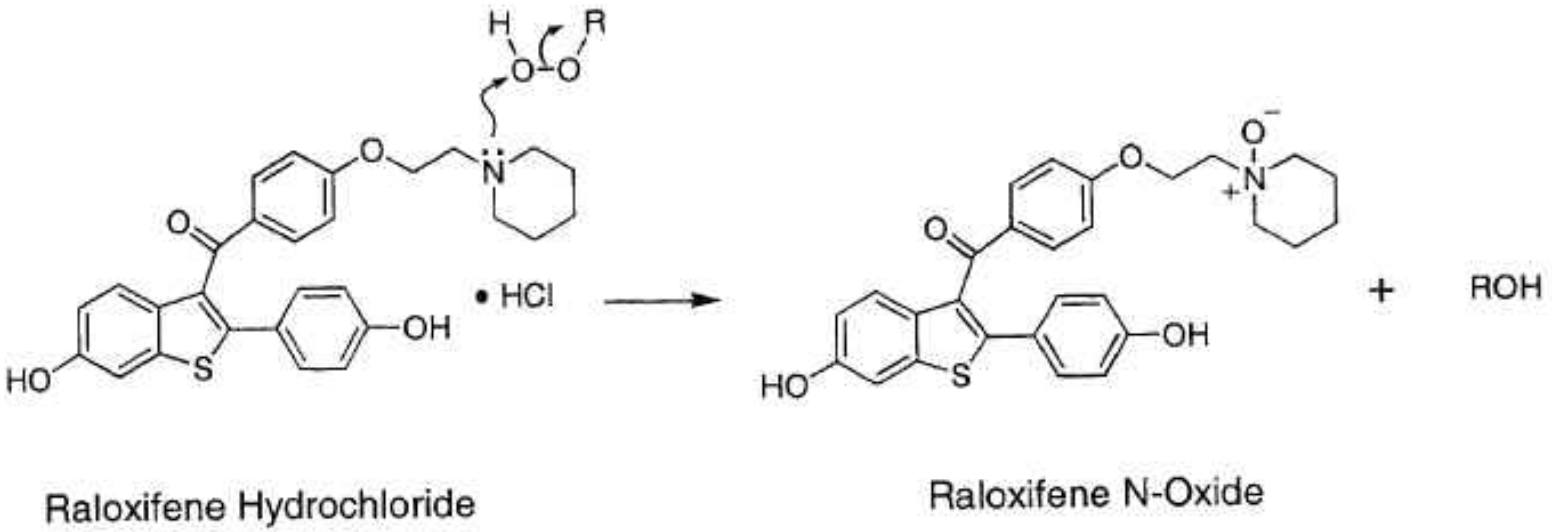
Polyvinylpyrrolidones

- Peroxide initiated polymerisation, ppb heavy metal catalysis
- Peroxides formed during spray drying
- Peroxide content increases with age
- Drying excluding air, low temp storage, packaging under vacuum/inert gas slows but does not stop peroxide
- Higher levels of heavy metals (ppm) inhibit peroxide
- Peroxide-cleaving enzymes stabilise PVP

Amount of copper added (based on the povidone powder)	Peroxide content after storage [ppm]			
	After drying	After 6 months	After 12 months	After 24 months
2 ppm	58	253	276	322
4 ppm	69	184	184	253
6 ppm	69	69	69	<50
8 ppm	69	58	<50	<50

US Patent 6592900

Oxidation from PVP/PVP-XL peroxide impurities



Raloxifene Hydrochloride

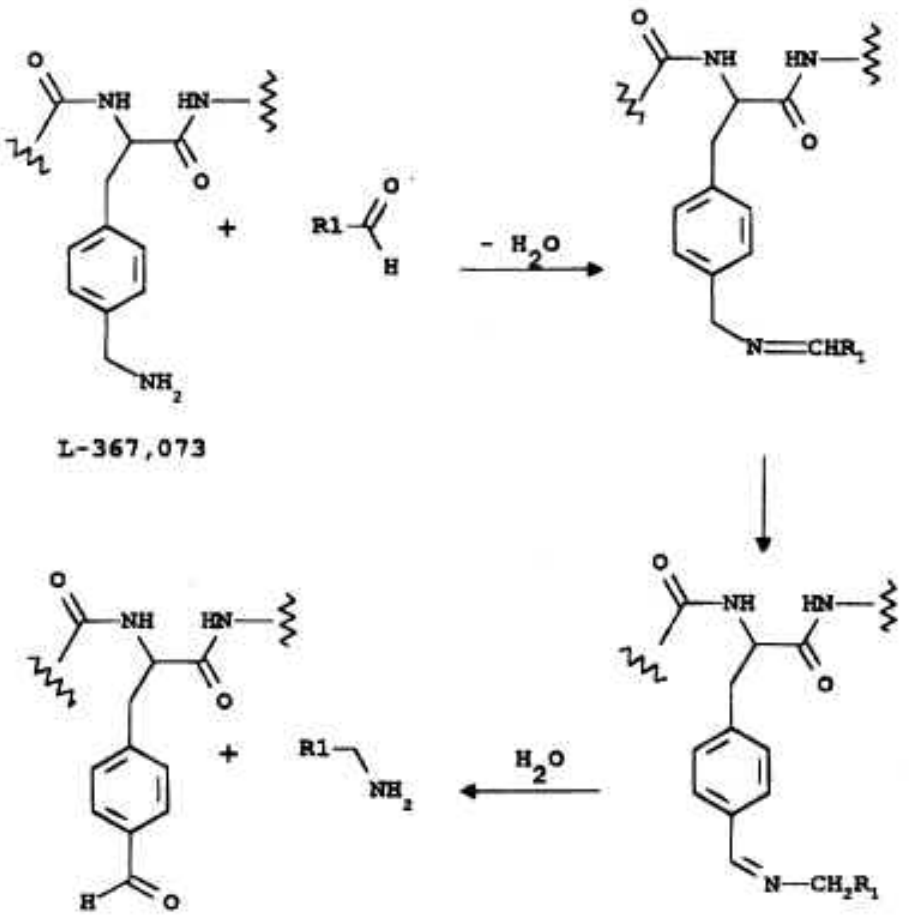
Raloxifene N-Oxide

Hartauer et al Pharm Dev & Technol 5(3) 301-10 2000

Polyether oxidation

- Ethers react with oxygen to form peroxides, esp with light
- Hydrogen peroxide and other oxides formed, up to 0.2%
- Concentrations may increase with raw material age
- Concentrations may stabilise due to reaction with other polyether molecules forming carbonyl compounds
  - HCHO, HCOOH, CH_3COOH and other aldehydes & acids
  - hence carbonyl content test for non-carbonyl polyethers
- Chain-breaking antioxidants but not metal-chelators block peroxide accumulation eg BHA, BHT, Pr Gallate
- Anti-oxidants interfere with peroxide assays
- If anti-oxidant also stabilises drug don't switch to anti-oxidant-free grades of surfactant!

Oxidation due to reducing sugar impurities in Mannitol USP



Reducing sugar impurities in mannitol responsible for oxidative degradation of cyclic heptapeptide by mechanism involving Schiffs base intermediates.

Potential route of degradation for other arylmethylamines in mannitol based formulations.

Dubost et al, Pharm Res 13 1811 1996

Formaldehyde from drug attacking excipient

- HCTZ + $H_2O \rightarrow$ 5 Cl-2,4-disulfamoylanaline + HCHO
- HCHO + 2RCOOH $\rightarrow$ $RCOCH_2OCR + H_2O$
- Acetal crosslinking of SSG, reducing disintegration
- Formaldehyde from drug attacked disintegrant, reducing dissolution

Desai et al Int J Pharm 107 141-7 1994

Excipient Induced Formaldehyde from one drug attacking another drug

- Irbesartan/HCTZ combination tablets
- Hydroxymethyl-Irbesartan adduct formed from HCHO from HCTZ
- Povidone and poloxamer destabilised HCTZ

US Patent 5994348

Glyoxal in Hydroxyethyl Cellulose

- Dialdehyde surface treatment additive
- Ph Eur limit of NMT 20ppm (defined impurity)
- Can react with amine groups on API

Other Impurities

- Acids
  - Oxidation of aldehydes, residual reactant or process aid
  - Formic, Acetic from HCHO, CH_3CHO respectively
  - React with alcohol to form esters
  - Eg Glycolic acid from carboxymethylation processes
- Esters
  - Formate, acetate, glycolate (hydroxyacetate)
  - May form amides by reacting with amines.
- Alcohols
  - Residual process aid
  - MeOH, EtOH, PrOH
  - Risk of trans-esterfication
  - Eg Processing of disintegrants and carrageenans

How to control excipient impurities

- Chemical Modification
  - Practically impossible without Pharmaceutical sponsor
- Minimise impurities
  - Technically or economically within supplier process capability?
  - Lot selection (frequency, process capability)
  - User purification
- Additives to suppress undesirable reactants
  - Transparency vs trade secret
  - Need for common pharmacopoeial approach (IPEC)
- Formulate
- Talk to your suppliers to understand context of specific excipient manufacture and process capability.

Increased Data from Supplier to User

- User needs more information than in past.
  - Confidential information via DMF?
  - Does FDA really need such information unrelated to safety or performance risk?

- Paradigm shift as FDA gets more focused on risk management.

- FDA only wants to review key data to assess safety and risk.

- FDA doesn't want DMF to become entire dossier about excipient.

- Non-confidential details should be provided to users during product development and potentially in their filing if really needed by FDA.

Change Control Risk Assessment

- Functionality data key to assessing significance of change
- Communication between users and pharmaceutically oriented suppliers
- User notification essential but avoiding unnecessary qualifications
- User Preapproval and qualification of all supplier changes counterproductive:-
  - Diverts resources with no added safety
  - Inconsistent with PAT risk assessment approach

B Carlin USP Ann Sci Mtg 2005

In conclusion

- The labelled or nominal entity may not be the cause of excipient-related API degradation
- Understand your excipient manufacture and chemistry
- Use supplier excipient expertise
- Provide feedback to your suppliers:-
  - They cannot ensure fitness for use if user doesn't provide criteria
- Seek win-win to minimise cost-in-use