Bristol-Myers Squibb

# Reactive Impurities in Pharmaceutical Excipients and Their Impact on Drug Stability

## AAPS Chicagoland Pharmaceutical Discussion Group
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# ACKNOWLEDGEMENTS


- Y. Wu
- J. Levons
- K. Raghavan
- A. Narang
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- V. Sadineni
- Y. Quan
- Many other colleagues at BMS

# Agenda

- Background and Context
- Sources, Variability, Speciation and Stability
- Examples of drug incompatibility with excipient impurities
- Mitigation and control strategies

# Reactive Impurities in Excipients

- Excipients are generally multi-component systems
- Some components are added for functionality or processing aid
- These components may be*
  - Necessary
  - Desirable
  - Innocuous
  - Undesirable
- Is the term ‘ excipient impurity’ a misnomer?*
- In this discussion, we define excipient impurities as the components (reactive) that are detrimental to the drug product stability

**Discussions with B. Carlin (FMC)*

# Drug/Excipient Incompatibilities

- From a drug/excipient chemical incompatibility perspective, a good portion of reactions are between drugs and ‘impurities’ in excipients

- Relevant not only to drug stability but also robustness

# A Sample of Drug Degradation Due to Excipient Impurities

| Drug | Impurity | Excipient | Drug Loading (w/w) |
|---|---|---|---|
| BMS-203452 | Formaldehyde | PEG 300 /Polysorbate 80 | 1% |
| Fluoxetine HCl | Reducing sugars | Lactose | 10% |
| Org-30659 | Lactose phosphate | Lactose | 0.10% |
| Compound A | Peroxides | Povidone/Copovidone | 2-3% |
| Compound B | Peroxides | Povidone/Copovidone | 2-3% |
| Raloxifene | Peroxides | Povidone/Copovidone | 12.50% |
| CP448187 | Free Radicals/Peroxides | Microcrystalline Cellulose | 0.50% |
| BMS-A | Free Radicals/Peroxide/Reducing Sugars | Microcrystalline Cellulose | 0.83% |
| Vigabatrin | Reducing Sugars, Aldehydes | Microcrystalline Cellulose | - |
| Irbesartan | Formaldehyde | PEG in Film-coating | Low Strength |
| Haloperidol | Furfuraldehyde | Lactose | 0.575% |
| Varenicline | Formic Acid/Formaldehyde/Acetic Acid | PEG or Acetate | 0.68% |
| Hydralizine | Aldose | Starch | 10% |

**Wu Y., Levons J., Narang A., Raghavan K. and Rao. V., AAPS Pharm. Sci. Tech., Dec 2011**

# Drug Interaction with Excipient Impurities

- Predict/determine “soft spots” on the drug molecule
- Understand the source and variability of reactive impurities in excipients
- Assess the risk and implement a mitigation strategy

# Common Excipient Impurities

- Aldehydes
  - Reducing Sugars
- Hydroperoxides
- Organic Acids and Esters
- Metals
- Nitrates, Nitrites
- Free radicals
- Solvents

•IMPACT

- DRUG STABILITY
  - Chemical
  - Dissolution
- EXCIPIENT PROPERTIES

**Table II.** Profiling of Reactive Impurities in Selected Lots of Pharmaceutical Excipients

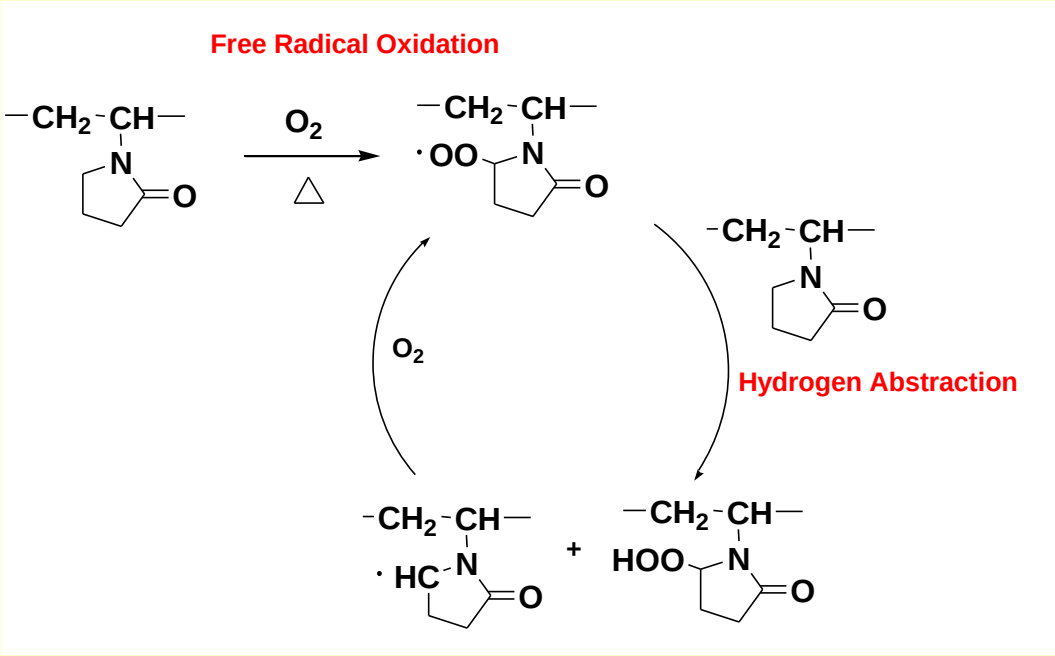
| Excipients | Sources/lot | Impurity (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Glucose | HCHO | Hydrogen peroxide | $NO_2$ | $NO_3$ | Monochloroacetate | Heavy metals | Trace metals |
| Microcrystalline cellulose, PH102 | FMC/1 | 79.6 | 4.8 | <2 | N/A | N/A | N/A | <10 | <5 Mg, Mn; <10 Al, Cr, Cu, Fe, Ni, Zn; 10 Ca |
| | FMC/2 | 59.5 | 5.1 | <2 | 9.4 | 23.0 | 0.9 | N/A | N/A |
| | FMC/3 | 40.7 | 4.1 | ND | N/A | N/A | N/A | N/A | N/A |
| Lactose Fast Flo | Foremost | ND | N/A | <2 | 10.4 | 12.4 | 12.0 | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al; 15 Ca |
| Lactose monohydrate | Foremost/1 | ND | 1.4 | <2 | 5.1 | 9.1 | 1.0 | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al, Ca |
| | Foremost/2 | ND | ND | <2 | 5.5 | 8.0 | 0.9 | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al, Ca |
| Lactose anhydrous | Quest/1 | ND | 7.4 | <2 | 5.4 | 4.3 | 0.6 | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al; 37 Ca |
| | Quest/2 | ND | 3.6 | <2 | 3.7 | 6.0 | 0.6 | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al; 32 Ca |
| Pre-gelatinized starch | Colorcon/1 | ND | 14.7 | <2 | 14.5 | 29.2 | 4.4 | <10 | <10 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <20 Al, Ca |
| | Colorcon/2 | ND | 10.9 | <2 | 11.8 | 22.9 | 2.3 | <10 | <10 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <20 Al, 21 Ca |
| | Colorcon/3 | ND | 11.1 | N/A | N/A | N/A | N/A | N/A | N/A |
| Povidone | ISP/1 | INC | INC | 37 | 2.2 | 13.6 | ND | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al, Ca |
| | ISP/2 | INC | INC | 72 | 1.6 | 13.1 | ND | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al, Ca |
| Crospovidone | ISP/1 | ND | 40.8 | 66 | 17.2 | 52.4 | ND | N/A | <5 Mn; <10 Al, Cr, Cu, Fe, Ni, Zn; 5 Mg; 10 Ca |
| | ISP/2 | ND | 8.5 | 69 | 10.5 | 30.4 | ND | N/A | <5 Mg, Mn; <10 Al, Ca, Cr, Cu, Fe, Ni, Zn |
| Sodium starch glycolate | Roquette/1 | – | 4.6 | <2 | 279.2 | 183.1 | ND | <10 | <5 Cr, Cu, Fe, Mn, Ni, Zn; <10 Al, 79 Ca; 9 Mg |
| | Roquette/2 | – | 1.5 | <2 | 285.6 | 117.3 | 135.8 | <10 | <5 Cr, Cu, Fe, Mn, Ni, Zn; <10 Al, 75 Ca; 8 Mg |
| Croscarmellose Na | FMC/1 | ND | 6.5 | <2 | 2.4 | 23.8 | 52.2 | N/A | N/A |
| | FMC/2 | ND | 6.6 | <2 | 1.4 | 10.3 | 21.6 | <10 | <10 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <20 Al, 42 Ca |
| Magnesium stearate | Mallincrodt/1 | ND | 3.8 | <2 | 2.1 | 6.0 | ND | <10 | <5 Mn; <10 Al, Ca, Cr, Cu, Fe, Ni, Zn; |
| | Mallincrodt/2 | ND | 3.7 | <2 | 5.3 | 12.5 | 0.7 | N/A | N/A |
| Stearic acid | Crompton | ND | 3.1 | <2 | 3.5 | 6.6 | ND | ND | <5 Mn; <10 Al, Ca, Cr, Cu, Fe, Ni, Zn; 30 Mg |
| Hydroxypropyl cellulose | Hercules/1 | ND | 11.4 | 13 | N/A | N/A | N/A | N/A | N/A |
| | Hercules/2 | ND | 9.4 | 13 | 0.9 | 3.5 | ND | <10 | <5 Cr, Cu, Fe, Mg, Mn, Ni, Zn; <10 Al, 23 Ca |
| Silicone dioxide | Degussa/1 | ND | 6.1 | <2 | 5.8 | 12.5 | ND | N/A | 7 Mg; <5 Mn; <10 Al, Ca, Cr, Cu, Fe, Ni, Zn |
| | Degussa/2 | N/A | N/A | <2 | 1.5 | 8.7 | ND | N/A | 200 Al; 480 Ca; 30 Fe; 130 Mg; <5 Mn, <10 Cr, Cu, Ni, Zn |

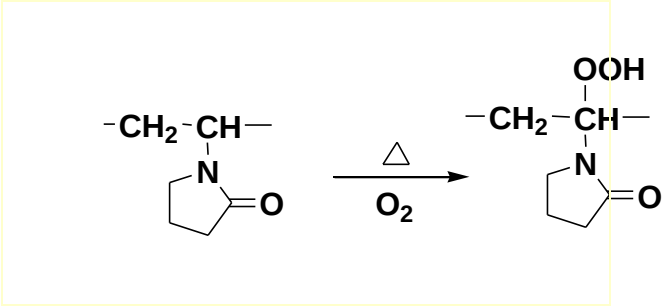
*ND* not detectable, *N/A* not available, *INC* incompatible
Heavy metals and trace metals analysis conducted using Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) - Microwave digestion in acid was used for treatment of insoluble excipients

Wu et al., Reactive impurities in excipients: profiling, identification and mitigation of drug-excipient incompatibility, *AAPS Pharm Sci Tech*, 2011

# Source of Hydroperoxides in PVP

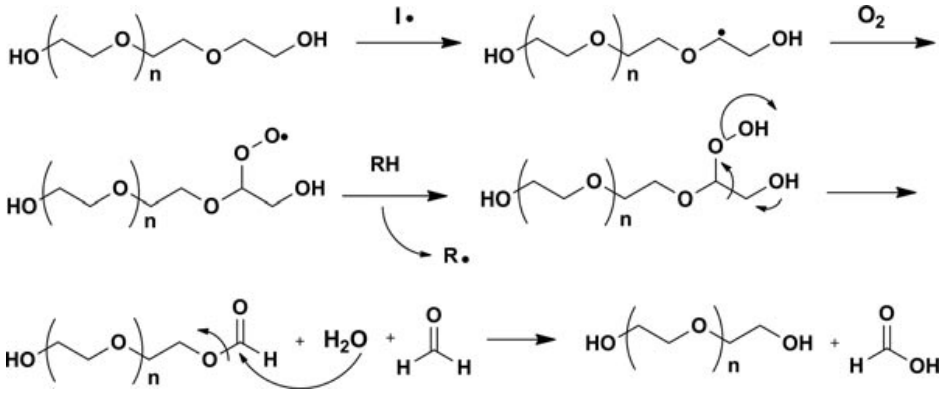
- Hydrogen peroxide may be used in the manufacturing process
- Oxidation of PVP leads to hydroperoxides



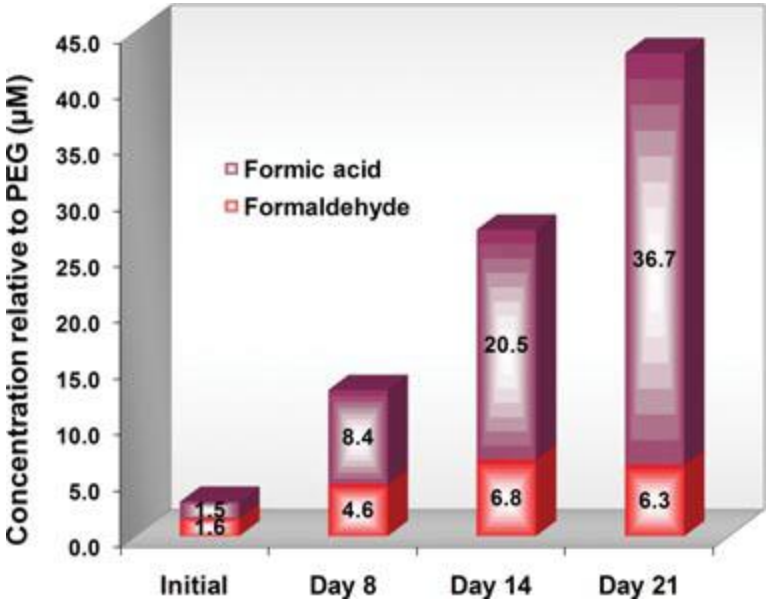




Tallon et al., J. Appl. Polymer Sci., 107, 2008, 2780

# Source of Formaldehyde and Formic Acid in PEGs and/or Pluronics




Waterman et al., J. Pharm. Sci., 97, 2008

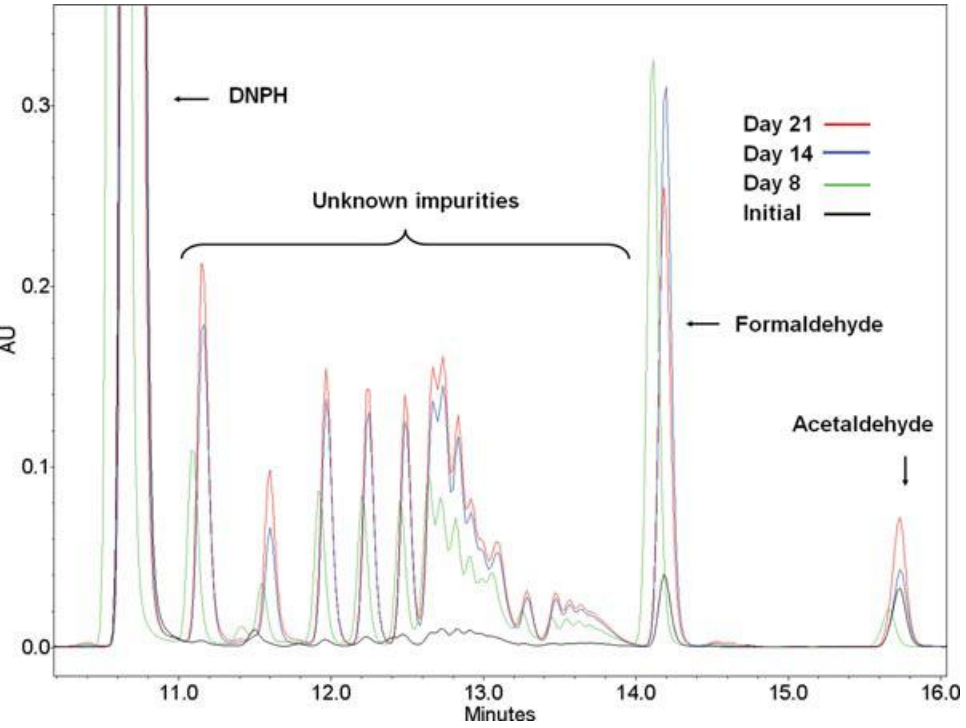



50% PEG 400 in sealed vials at 40 C

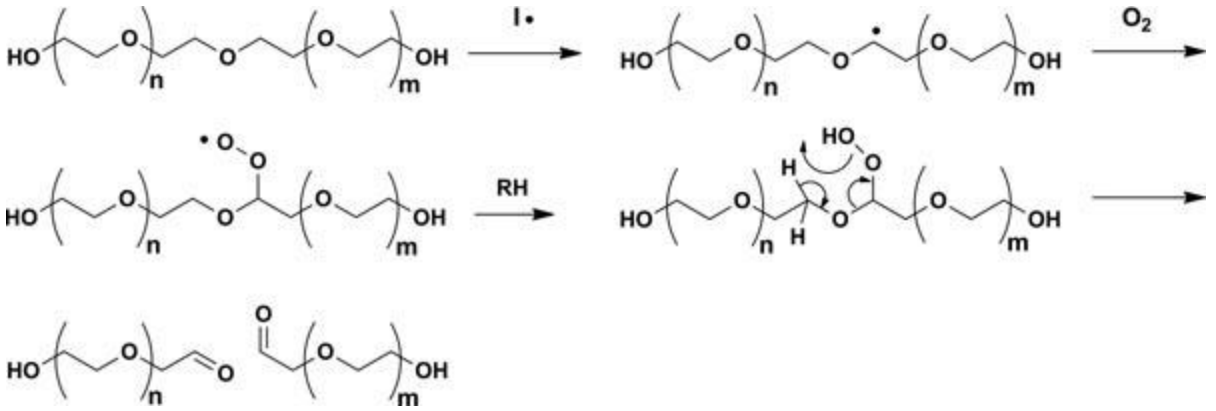
Hemenway et al., J. Pharm. Sci., 101, 2012

- In solid dosage forms, formyl esters of PEG may be greater than formic acid
- Relevant for formylation of certain nucleophiles

# Source of Aldehydes in PEGs and/or Pluronics




Hemenway et al., J. Pharm. Sci., 101, 2012




Waterman et al., Pharm. Dev Tech., 7, 2002

# Impurities in Excipients: Lot Variability

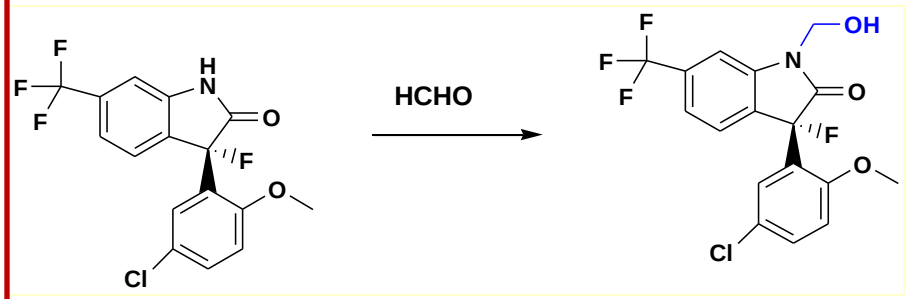



*Table 3.* Formaldehyde content in various lots of ethanol, PEG 300, and polysorbate 80.

| Sample | Lot number | HCHO (μg/g) |
|---|---|---|
| EtOH | C00215 | 0 |
| PEG 300 | IS796632, sublot C98343, Barrel #1 | 165 |
| PEG 300 | IS796632, sublot C98343, Barrel #2 | 15 |
| PEG 300 | IS796632, sublot C98343, Barrel #3 | 9 |
| PEG 300 | IS796632, sublot C99134 | 16 |
| PEG 300 | OB16711 | 2 |
| Polysorbate 80 | 0B16711 | 10 |
| Polysorbate 80 | 0E27309 | 22 |

Nassar et al., Pharm. Dev. And Tech., 2004

8 ppm of HCHO in BMS-203452 Formulation (10 mg/mL) sufficient to generate 1% deg product

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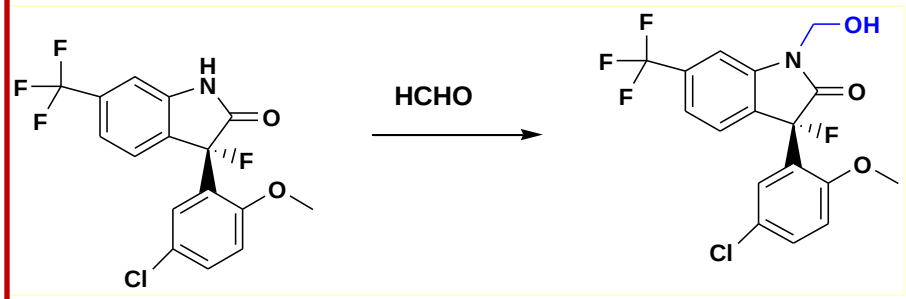


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**Table 4a.** Detailed Study of Hydroperoxides in HPC (LF Grade)

| Lot ID | HPO (nmole/g) | RSD (%) |
|---|---|---|
| 3994 | 890 | 0.2 |
| 4362 | 440 | 4.0 |
| 4360 | 500 | 5.4 |
| 4718 | 750 | 1.3 |
| 5047 | 110 | 1.7 |
| 5825 | 140 | 6.3 |
| 6648 | 200 | 1.2 |
| 6832 | 210 | 3.2 |
| 9137 | 220 | 3.3 |
| 7622 | 270 | 3.9 |
| 9159 | 450 | 1.2 |
| 7616 | 220 | 11.2 |
| 8592 | 150 | 9.9 |
| 8604 | 100 | 17 |
| 8940 | 130 | 9.6 |

*Wasylaschuk et al., 96, J. Pharm Sci., 2007*

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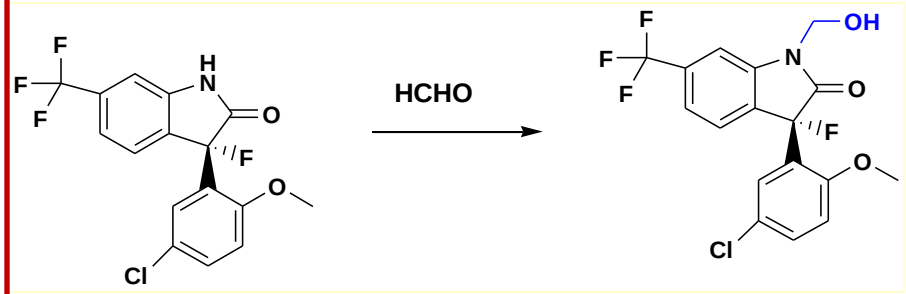
# Impurities in Excipients: Lot Variability

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| 8592 | 150 | 9.9 |
| 8604 | 100 | 17 |
| 8940 | 130 | 9.6 |

*Wasylaschuk et al., 96, J. Pharm Sci., 2007*

## Peroxide in Crospovidone

| Lot # | H2O2 (ppm) |
|---|---|
| 73200 | 197.4 |
| 2C69284 | 88.2 |
| OC 29758 | 109.5 |
| 8K09908 | 118.1 |
| G108G | 68.7 |
| 2F59164 | 54.9 |

# Impurities in Excipients: ‘Speciation’

- Hydroperoxide and Hydrogenperoxide
  - Determination is dependent on the assay method
  - Most methods determine total hydroperoxide

- Formic acid and Formyl Esters
  - Methods involve transesterification with ethanol or methanol and Headspace GC
  - Measuring total formyl content
  - Reactivity (Kinetics) of formic acid and formyl ester will be different

# Impurities in Excipients: 'Speciation'

**Table 7.** Distribution of Hydrogen Peroxide and Organic Hydroperoxides in PEG, PS80, PVP, and HPC

| Excipient | ID of Lot | Distribution of Hydroperoxides | | HPO (nmole/g) |
|---|---|---|---|---|
| | | % ROOH | % $H_2O_2$ | |
| PVP | K12 Acros Lot A0180479[a] | 80 | 20 | 2300 |
| | K17 Acros Lot A0199571[a] | 40 | 60 | 2800 |
| | K29 Acros Lot A0189374[a] | 60 | 40 | 3500 |
| | K29 ISP Lot 05200087543 | 70 | 30 | 3900 |
| | K90 Acros Lot A0159153[a] | 80 | 20 | 13000 |
| | K90 ISP Lot 03400121902 | 80 | 20 | 7000 |
| PEG 400 | Dow RD0755S4D2 | 50 | 50 | 730 |
| | Dow QJ1155S4D5 | 60 | 40 | 1100 |
| | Dow QH2355S4D3 | 80 | 20 | 3200 |
| PS 80 | Croda T4H-1033 | 100 | 0 | 1100 |
| | Croda T4H-1014 | 100 | 0 | 1500 |
| | Croda T4H-1028[b] | 100 | 0 | 3900 |
| HPC LF | Hercules Lot 4360 | 30 | 70 | 500 |
| | Hercules Lot 9899 | 40 | 60 | 440 |
| | Hercules Lot 9159 | 50 | 50 | 450 |
| | Hercules Lot 4718 | 30 | 70 | 750 |
| | Hercules EF Lot 9897 | 80 | 20 | 560 |

[a]Noncompendial grade.
[b]Stored under ambient laboratory conditions for approximately 18 months.

*Wasylaschuk et al., 96, J. Pharm Sci., 2007*

# Impurities in Excipients: Impact of Storage

**Table 1.** Effect of Storage Conditions (Temperature and Humidity) on Peroxide Concentrations in Povidone Powder

| Storage Condition | 2.5 Months | 28 Months |
|---|---|---|
| 25°C/11% RH | 99.3 ± 11.0 | 206.7 ± 18.0* |
| 25°C/32% RH | 87.3 ± 8.3 | 34.0 ± 3.5* |
| 25°C/50% RH | 71.3 ± 9.5 | 7.3 ± 1.2* |
| 25°C/60% RH | 44.0 ± 6.0* | Not detected |
| 40°C/11% RH | 124.7 ± 12.2* | 261.3 ± 40.3* |
| 40°C/32% RH | 93.3 ± 14.2* | 39.3 ± 4.2* |
| 40°C/50% RH | 73.3 ± 12.1 | Not detected |
| 40°C/60% RH | 8.7 ± 4.2* | Not detected |

Results represent the average ± standard deviation of n = 3. Initial peroxide concentration in povidone was 74.7 ± 3.1 ppm. The results marked with an asterisk (*) were statistically significantly ($p < 0.05$) different from the initial peroxide concentration using a two-tailed t-test for comparing two sample means with the assumption of unequal variances.

Narang A.S., Rao V.M., Desai D.S., Effects of antioxidants & silicates on peroxides in povidone, J. Pharm. Sci., 2011

# Impact of Excipient Manufacturing Process on Impurities: Peroxide Growth in PVP

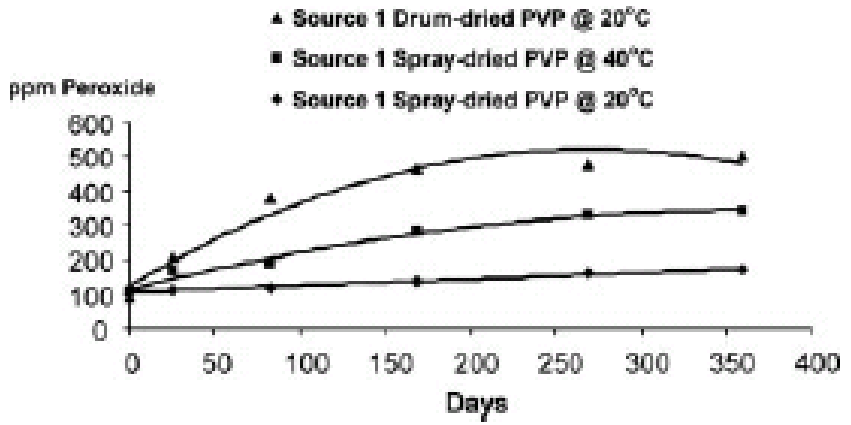



**Figure 2** Peroxide buildup in Source 1 Drum-dried PVP at 20 vs. Spray-dried PVP at 20°C and 40°C.

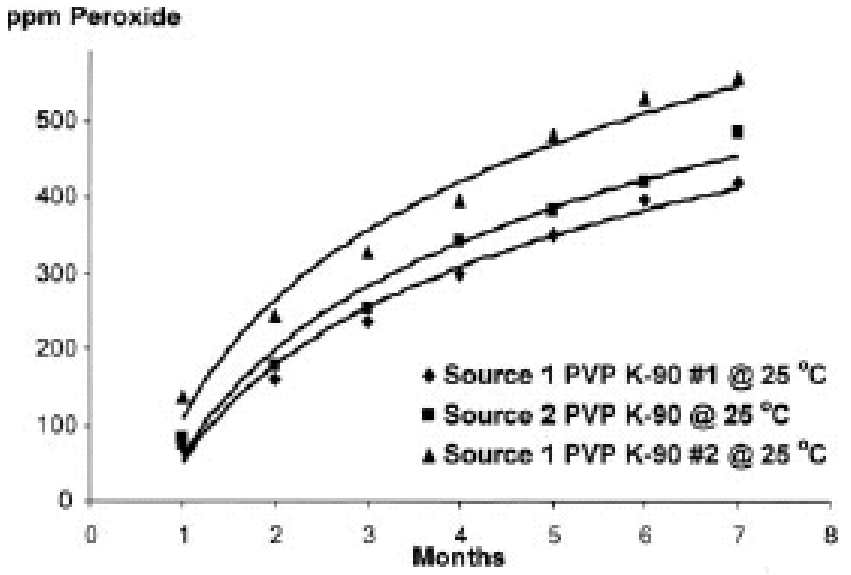
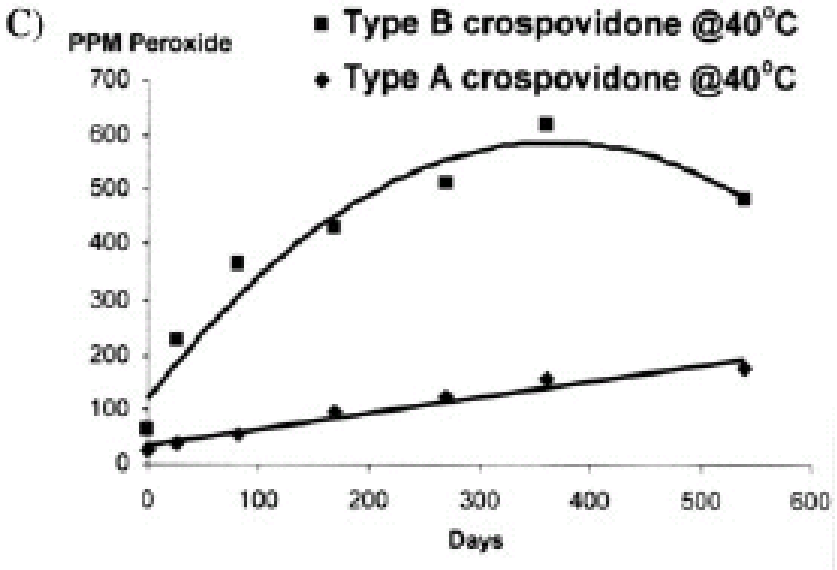


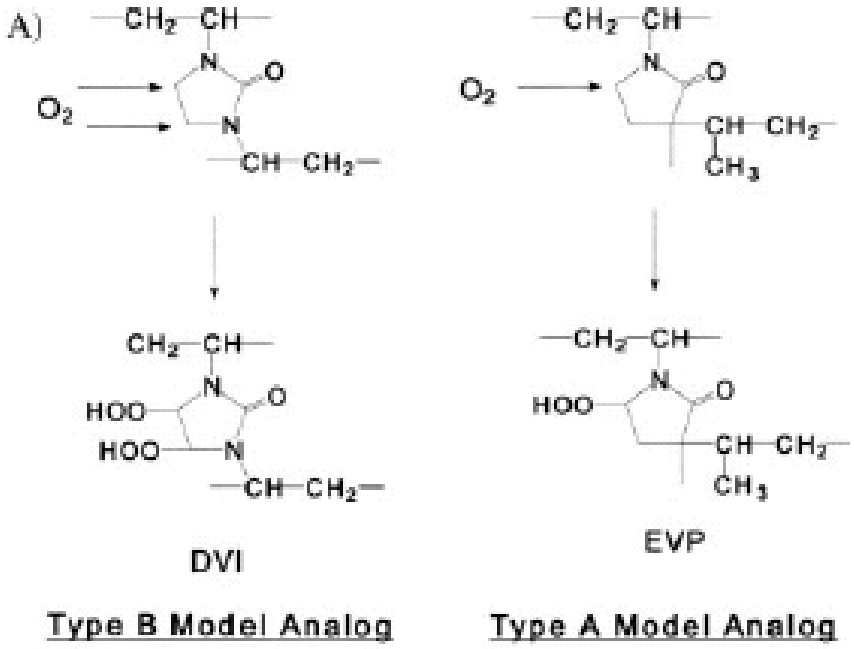

**Figure 1** Peroxide buildup in Source 1 and Source 2 PVP K-90 at 25°C.

- Drum-dried PVP (involves heating) causes mechanical fracture leading to free radical formation that can initiate the peroxide formation in PVP

Tallon et al., J. Appl. Polymer Sci., 107, 2008, 2780

# Impact of Excipient Manufacturing Process on Peroxide Growth in Crospovidone




- Crosslinker Type A: N,N-divinyl imidazolidinone (EVP)
- Crosslinker Type B: Ethylidene vinylpyrrolidinone (DVI)
- The rate at which peroxides is dependent on the crosslinking agent used. Type B has twice the number of oxidation sites.
- Note that some vendors claim that they do not use any crosslinkers

Tallon et al., J. Appl. Polymer Sci., 107, 2008, 2780

# Examples of Drug Incompatibility with Excipient Impurities

# Example 1:Try in Fab Protein Oxidized by Autocatalytic Rxn of Polysorbate 20 in Formulation

a

```
          10         20         30         40         50
EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWIN
          60         70         80         90        100
TYTGEPTYAADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYP
         110        120        130        140        150
YYYGTSHWYFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD
         160        170        180        190        200
YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
         210        220        230
TQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
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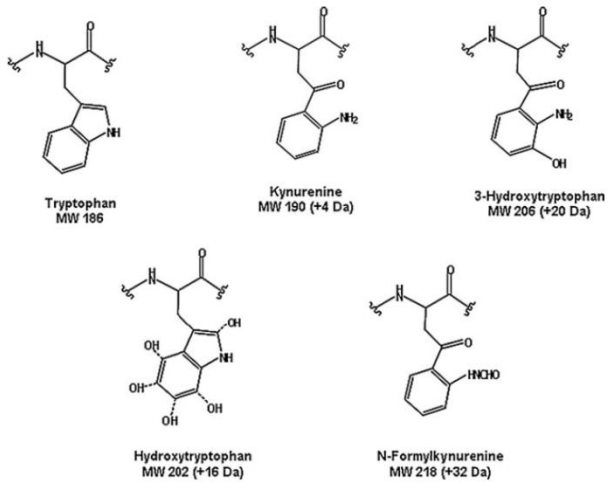


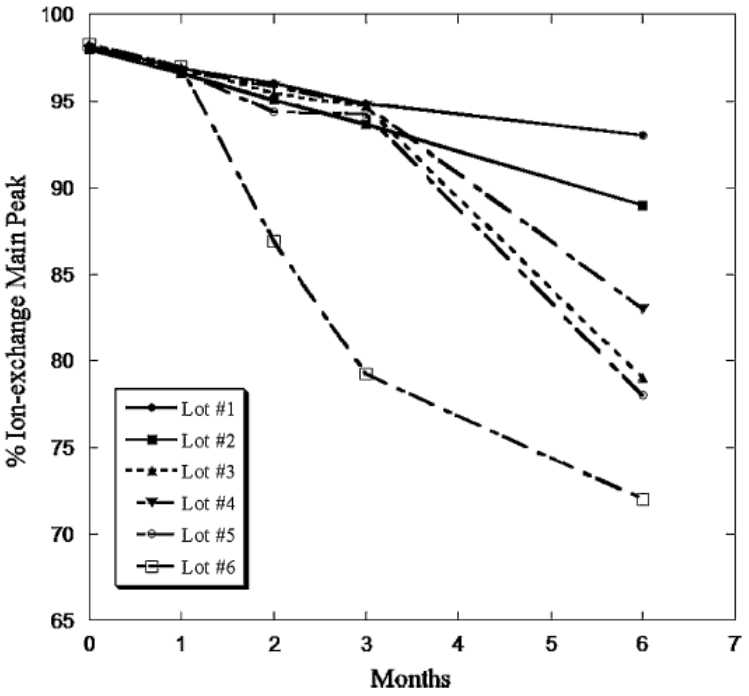




**Fig. 2** The degradation of Fab drug product stored for 6 months at 30°C as determined by IEC. Fab typically degrades in a linear fashion as shown by Lot 1. In Lot 6, a significant increase in degradation was observed between 1 and 2 months of storage. In other lots (Lot 2–5), a significant increase in main peak degradation was observed between 3 and 6 months of storage.

Lam et al., Site-Specific Tryptophan Oxidation Induced by Autocatalytic Reaction of Polysorbate 20 in Protein, Pharm Res. (2011), 28:2543-2555

# Example 1:Try in Fab Protein Oxidized by Autocatalytic Rxn of Polysorbate 20 in Formulation

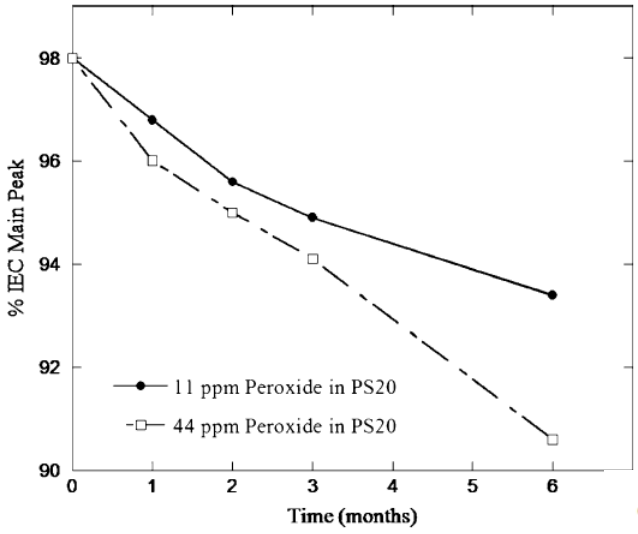



**Table II** Methods to Inhibit Tryptophan Oxidation in Fab at 30°C

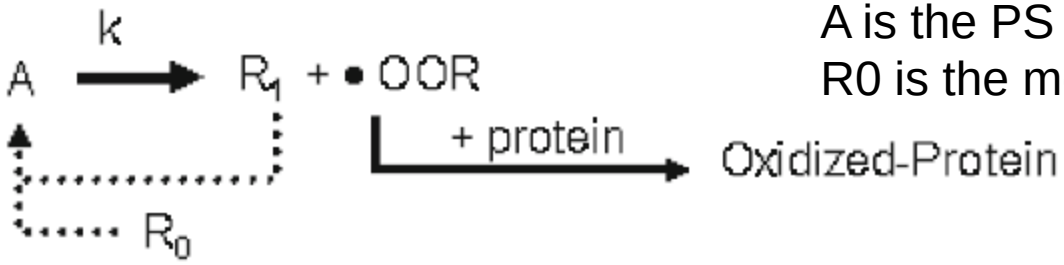
| Time point (months) | % IEC basic peaks in lot 6 with oxidation inhibitory agents[1] | | | | |
|---|---|---|---|---|---|
| | No oxidation inhibitor | 1 mM EDTA | 1 μM catalase | Vial purged with $N_2$ | 10 mM L-tryptophan |
| 0 | 1.6 | 1.1 | 1.4 | 1.6 | 2.0 |
| 1 | 1.9 | 1.7 | 2.0 | 2.0 | 3.5 |
| 2 | 9.9 | 3.1 | 4.1 | 2.3 | 4.1 |
| 3 | 15.7 | 3.0 | 3.1 | 2.8 | 4.4 |

[1] % IEC basic peaks was used as an indicator for Trp oxidation.

Lam et al., Site-Specific Tryptophan Oxidation Induced by Autocatalytic Reaction of Polysorbate 20 in Protein, Pharm Res. (2011), 28:2543-2555

# Example 1:Try in Fab Protein Oxidized by Autocatalytic Rxn of Polysorbate 20 in Formulation

- Reaction profile shows autocatalytic in nature
- Reaction with hydrogen peroxide alone or in combination with Ferric Chloride was also not significant
- EPR results detected free radicals in the formulation
- The authors suggest a mechanism involving free radicals
  - Initial rates are slow
  - As more radicals are generated, the reaction rate is increased
  - Subsequent slow down due to consumption of oxidant/free radicals

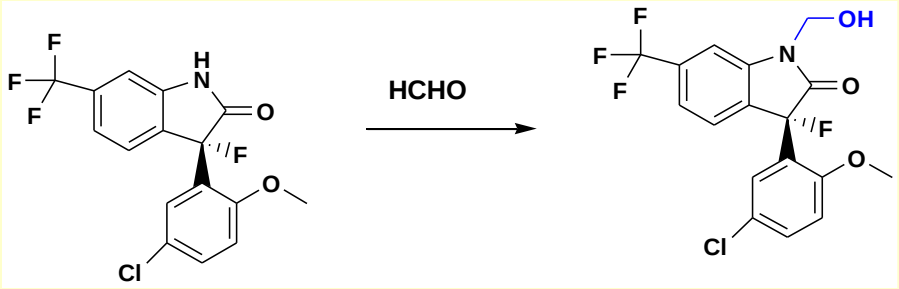



A is the PS 20 oxidant
R0 is the metal

Lam et al., Site-Specific Tryptophan Oxidation Induced by Autocatalytic Reaction of Polysorbate 20 in Protein, Pharm Res. (2011), 28:2543-2555

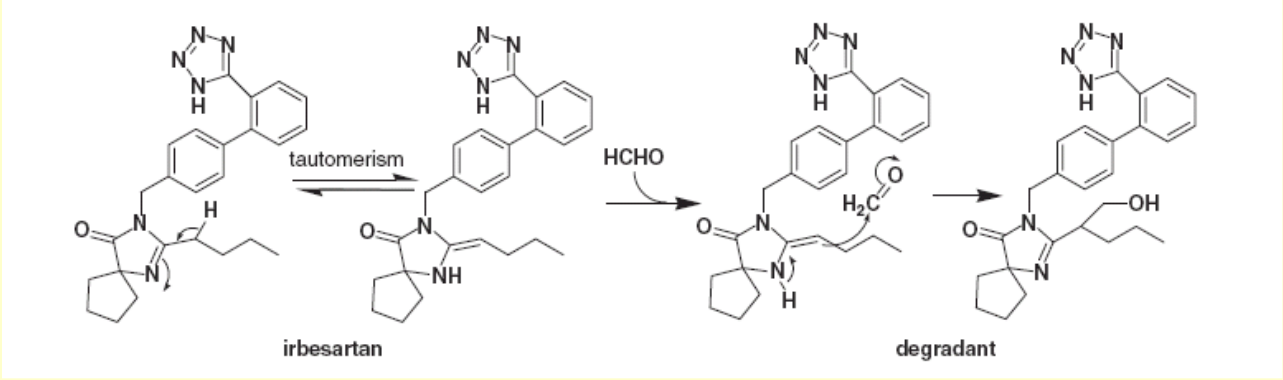
# Addition Reactions with Aldehydes

- Example 2: Maxipost Inhibitor-Formaldehyde (in polysorbate)
  - Formaldehyde impurity in polysorbate (Solubilizer in lyo product)




Nassar et al., Pharm. Dev. & Techn., 13, 2008, 393-399

- Example 3: Irbesartan-Formaldehyde (in Film-Coating containing PEG)
  - Formaldehyde impurity in PEG (Plasticizer in Film-Coating Opadry™ II )
  -

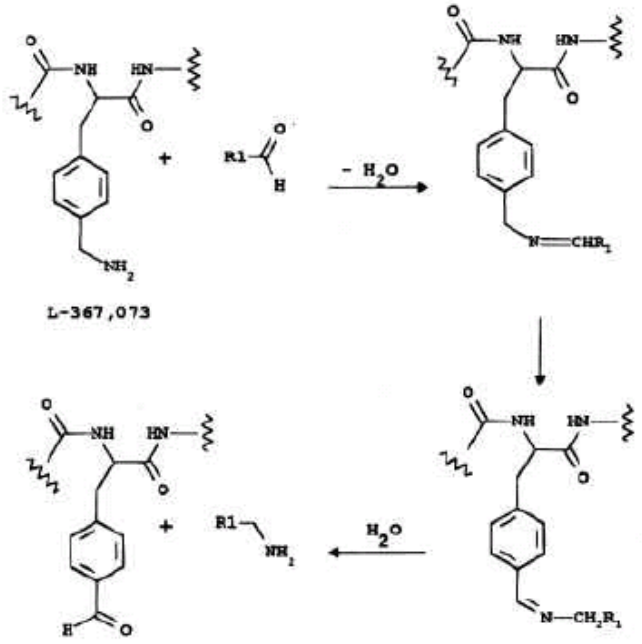



Wang et al., Pharm. Dev. & Techn., 13, 2008, 393-399

# Amine Drug Interaction with Reducing Sugar Impurities

Example 4: Mannitol, being a non-reducing sugar, was deliberately chosen to avoid Schiff-base formation with an Amine Drug.

- Trace level reducing sugar/aldehyde are present in non-reducing sugars!

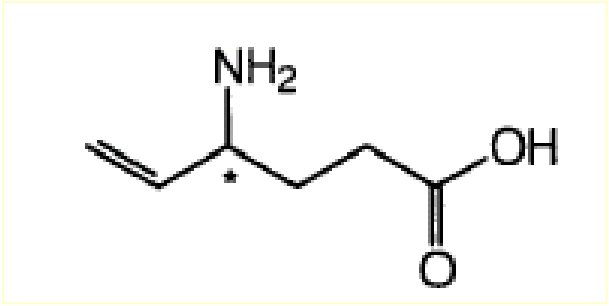



Dubost et al., Pharm. Res., 13, 1996, 1811

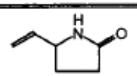
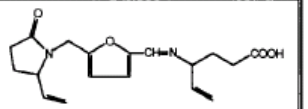
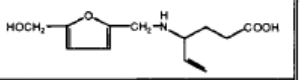
# Amine Drug Interaction with Reducing Sugar Impurities/Aldehydes

Example 5: Interaction with reducing sugar impurities (free or end-chain of MCC)

- Maillard products with Microcrystalline Cellulose Impurities (e.g. Furfuraldehyde)




Vigabatrin

| Compd. | Protonated Molecular Ion/ Elemental Formula* | CI Daughter Ions MS/MS | Proposed Structure |
|---|---|---|---|
| I | 112 | --- |  |
| II | 331 $C_{18}H_{23}N_2O_4$ | 313, 285, 220 219, 152, 124 |  |
| III | 328 $C_{18}H_{22}N_3O_3$ | 310, 292, 282 268, 216 | None |
| IV | 440 $C_{24}H_{30}N_3O_5$ | --- | None |
| V | 240 $C_{12}H_{18}NO_4$ | --- |  |
| VI | 553 | --- | None |

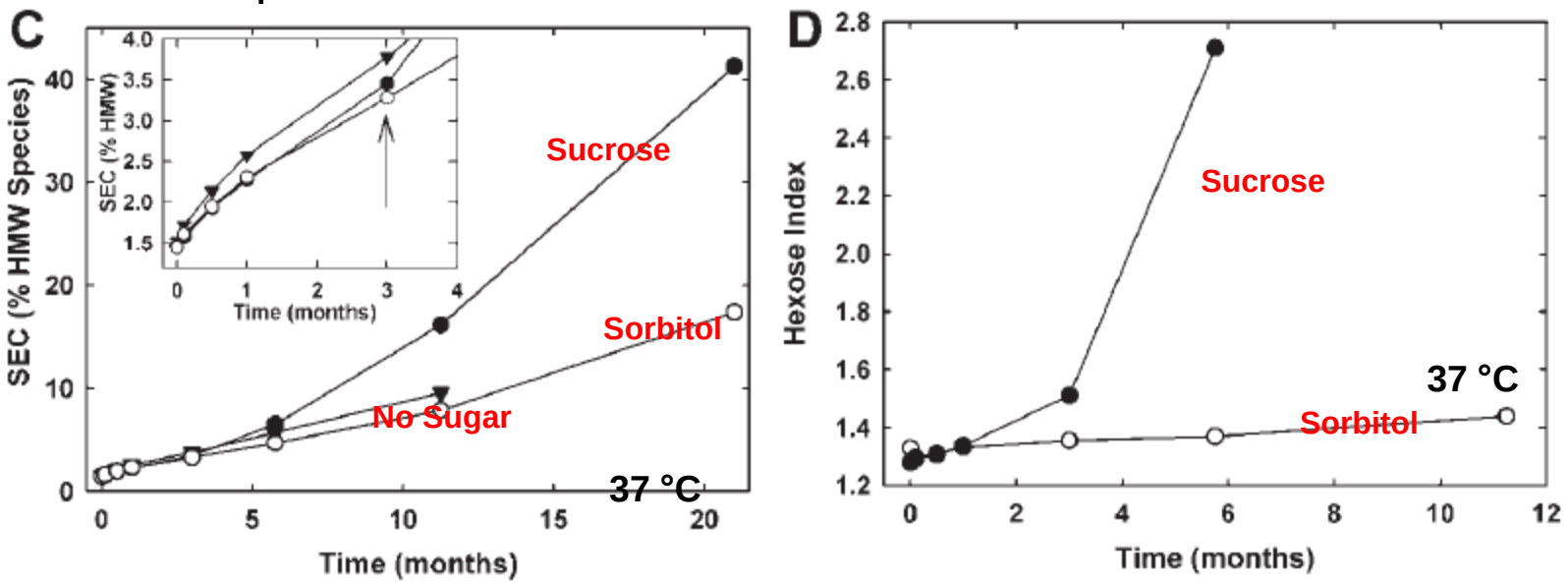
*Obtained from molecular ion data and HRMS, respectively.

George et al., Drug. Dev. & Ind. Pharm., 20, 1994, 3023-3032

# Example 6: Degradation of Excipient under Accelerated Conditions Confounds Drug Stability Interpretation

## The Effect of Sucrose Hydrolysis of Protein (mAB) Stability at Accelerated Conditions

- Sucrose hydrolysed at 37 °C and the 'impurities' (glucose and fructose) reacted with protein (glycation)
- Glycated protein has higher aggregation rate--hypothesis: change in surface charge
- No impact at 2-8 °C




Banks D.D.., J. Pharm Sci, 98 (12), 2009, 4501-4510

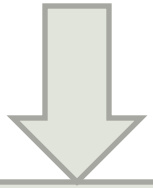
# Additional factors to consider during RAs

- Drug Properties (e.g. reactivity, crystal from, solubility, particle size)
- Low drug to excipient ratio
- Moisture
- pH or micropH
- Temperature
- Oxygen

# Early Prediction & Prevention is the Best Mitigation Strategy!

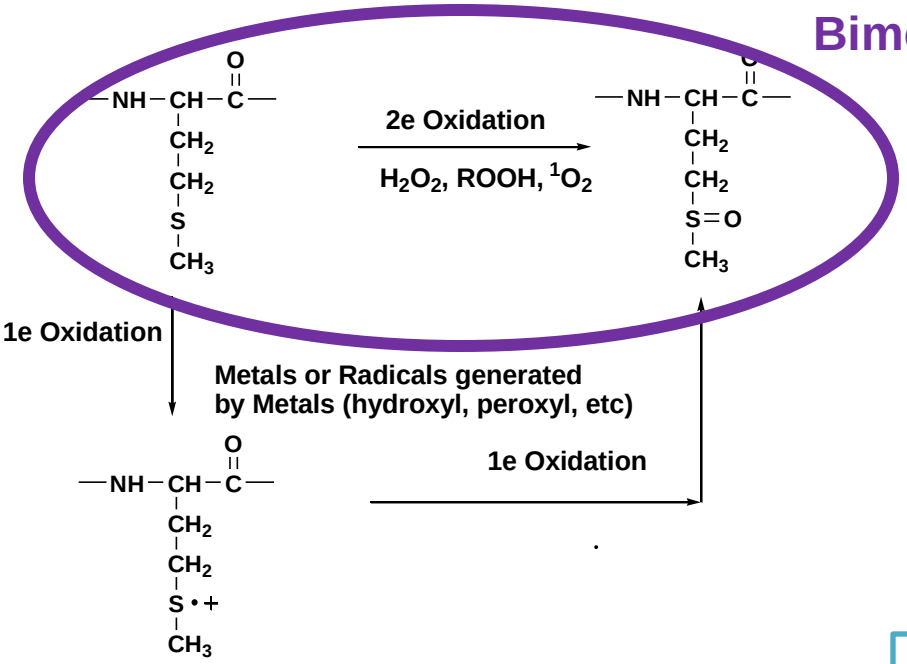
Risk Assessment of Chemical Incompatibilities:

- Degradation ‘soft spots’ of the drug
- Proactive excipient compatibility studies
- Knowledge of potential reactive impurities in excipients (e.g. nature & source of impurities, type of drug incompatibilities)



Mitigation Strategies

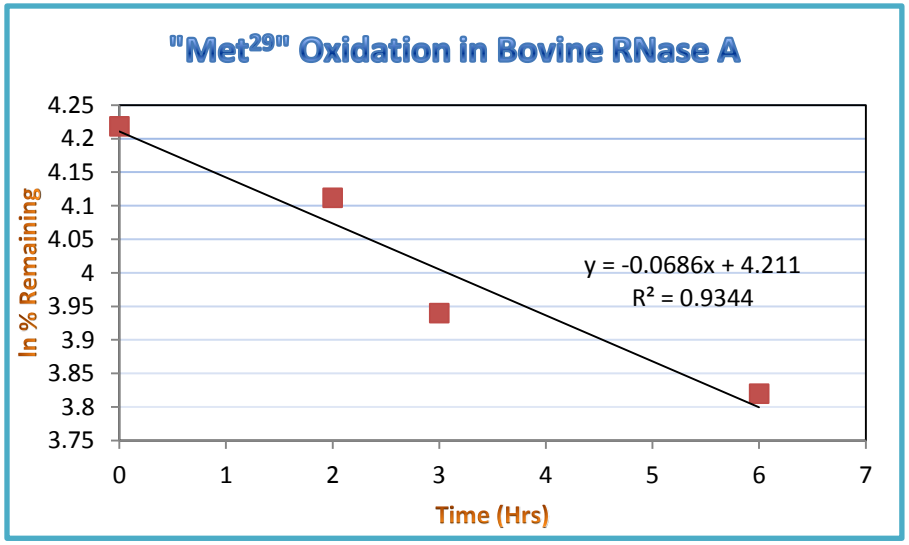
# Risk Assessment to Predict Impact of Methionine Oxidation due to Polysorbate 80: Kinetics of degradation and impurities level




## Bimolecular Reaction (protein and peroxide)

| Tryptic Peptide | Oxidation Prone AA in Model Protein (Bovine Rnase A) |
|---|---|
| T4 | QHMDSSTSAASSSNYCNQMMK |
| T8 | CKPVNTFVHESLADVQAVCSQK |
| T10 | NGQTNCYQSYSTMSITDCR |
| T12 | YPNCAYK |
| T14 | HIIVACEGNPYVPVHFDASV |

| Residue | + $H_2O_2$ (1:10) |
|---|---|
| **T4** | **-37.3** |
| **T8** | 1.1 |
| **T10** | -4.7 |
| **T12** | -3.5 |
| **T14** | 0.2 |




Quan, Sadineni et al., (2011)

# Typical Levels of Polysorbates and Pluronics in Biologics:

| Marketed name (Generic name) | Manufacturer | Formulation type / Route of Admin | Surfactant (% w/v) |
|---|---|---|---|
| Orthoclone® | Ortho Biotech | Liquid/ IV | 0.02% - PS 80 |
| Reopro® | Lilly | Liquid/ IV | 0.001%- PS 80 |
| Rituxan® | Biogen Idec | Liquid/ IV | 0.07%- PS 80 |
| Herceptin® | Genentech | Lyophile/IV | 0.01%- PS 20 |
| Remicade® | Centocor | Lyophile/IV | 0.005%- PS 80 |
| Humira® | Abbott | Liquid/SC | 0.1% - PS 80 |
| Avastin® | Genentech | Liquid/IV | 0.04%- PS 20 |
| Yervoy™ | BMS | Liquid/IV | 0.01%- PS 80 |
| Orencia® | BMS | Lyophile/IV | No Surfactant |
| Orencia® | BMS | Liquid/SC | 0.8%-Polox 188 |
| Nulojix® | BMS | Lyophile/IV | No Surfactant |

PS: Polysorbate

Polox: Poloxamer (Pluronic)

Sadineni et al., (2012)

# Risk of “Met” Oxidation based on Stressed Studies:

- Two electron oxidation of “Met” due to peroxide contamination from excipients can be reasonably predicted from stressed studies
- A risk based strategy can then be implemented to take appropriate mitigation steps

| “Met” Sulfoxide Growth: %/year | Risk Category |
|---|---|
| 0.00 – 1.5 | Low |
| 1.51 – 2.0 | Medium |
| 2.0 and above | High |

Sadineni et al., (2012)

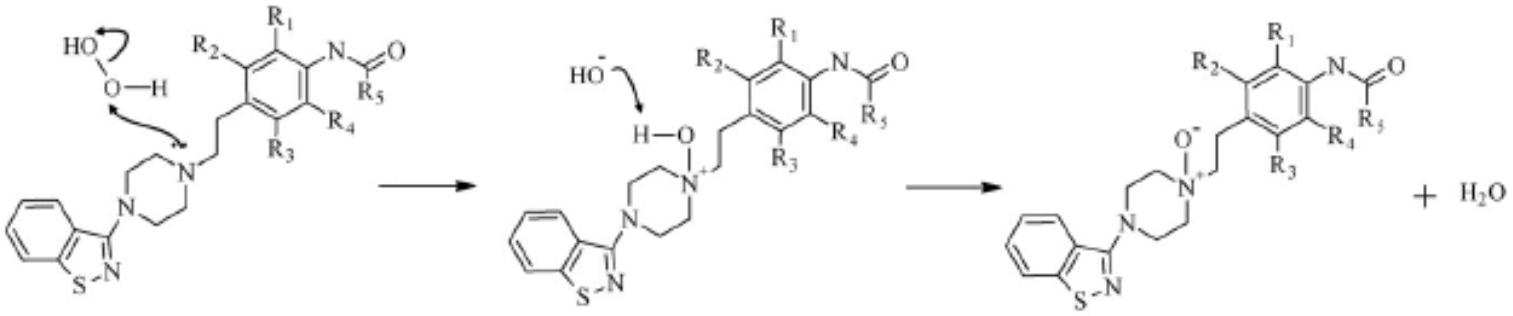
# MITIGATION STRATEGIES

- Modify API Properties, formulation or manufacturing process
  - API (salt versus base)
  - Stabilizers (e.g. pH-modifiers, anti-oxidants)
    - Excipients
    - Formulations
  - Processing
- Use protective packaging (moisture, light or oxygen)
- Set controls on the raw materials i.e. excipients

V. Rao, Jan 31, 2013

6asd

# Mitigation Strategies
# Use of Stabilizing Excipients



| Formulation | % N-Oxide (Initial) | % N-Oxide 6-weeks at 40C/75%RH |
|---|---|---|
| Form.1/H2O2 | 0.05 | 0.21 |
| Form.2/H2O2 | 0.05 | 0.17 |
| Form.3/H2O2 | 0.05 | 0.50 |
| Form.4/H2O2 | 0.05 | 0.27 |
| Form.1/H2O2/ Citric Acid | - | - |
| Form.2/H2O2/ Citric Acid | - | - |
| Form.3/H2O2/ Citric Acid | 0.02 | 0.01 |

Lowering of pH (protonation of Piperazine Nitrogen reduces the reactivity

*Freed et al., Int. J. Pharm., 2008*

# Mitigation Strategies
# Impact of Manufacturing Process

- Fluid bed processing of HPC led to increase in peroxide levels and formation of oxidative degradation product*
  - Level of peroxides in HPC increased with time until plateau was reached (irrespective of initial levels)
  - Oxidative degradation product dependent on the processing time

- High shear mixing of oxidation-prone drug with Avicel/Lactose based formulation**
  - Higher mixing time leads to greater degradation
  - Hypothesis: Mechanoradical formation during high shear mixing

***Harmon *et al*., AAPS 2004 Annual Meeting**

****Polizzi et al., 2008, 14 (2008)**

# Mitigation Strategies
# Raw Material Specifications

- Not reasonable to expect compendial limits to address the product-specific requirements
- Requires good communication & collaboration with excipient supplier
  - Proper mechanistic understanding necessary to link impurity levels to stability
  - Obtaining excipients with a range on impurities is not feasible
    - Typical batches have smaller range of impurities than the vendor (or compendial) limits
    - 'Spiking' (introducing) of volatile impurities during drug product manufacture is not trivial
- Analytical methods of trace level impurities is challenging
- Cost of implementation

# Summary

- Many of the reported drug-excipient incompatibilities are due to impurities in excipients
- Understanding of sources of generation, speciation, analytical methods and stability of these impurities is needed
- Knowledge of excipient impurities along with understanding of drug stability ‘soft spots’ and dosage form characteristics are essential for building product robustness
- Mitigation strategies can involve:
  - Product design approaches (formulation, processing and packaging)
  - Setting acceptance criteria for impurities in the excipients require strong collaboration between product manufacturers and excipient suppliers