The Good, The Bad & The Ugly: Formulation Tips for Traditional Preservatives

Personal Care Products Council Microbiology Seminar

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The Dow Chemical Company

Lest You Think Preservative Consideration Is Not Important ----- The “UGLY”

Too often chemists prepare a formulation, check it’s stability, and then send it to the microbiologists to ‘simply’ add the preservative system and confirm the formulation microbial stability.

The results can be surprising, if not devastating......

This was a ‘stable’ water-in-oil sunscreen, with a non-traditional preservative added during cool-down.

Bottom Line: Preservative consideration can be critical during formulation!
PPE for Handling of Preservatives

Formulating with “Traditional” Preservatives

- Formaldehyde releasers
- Isothiazolinones
- Organic acids (benzoic, sorbic, etc.)
- Parabens
- Phenoxyethanol
Formaldehyde Releasers

In 2010, about 15% of the 36,811 PC product formulations submitted to the FDA’s Voluntary Cosmetic Registration Program were reported to contain formaldehyde donors.*

- DMDM Hydantoin (DMDMH)
- Imidazolidinyl Urea (IU)
- Diazolidinyl Urea (DU)
- Quaternium-15
- Sodium Hydroxymethyl Glycinate


Formaldehyde Releasers – The Good

- Formaldehyde is effective against bacteria.

- Also, because of the chemistry (donor molecule), formaldehyde donor preservatives release small amounts of formaldehyde over time, rather than all at once.

\[
\text{NaO-CH2-NH2} + \text{CHOH} \rightarrow \text{NaO-C-CH2-NH2} \quad \text{Sodium glycinate} \quad \text{Formaldehyde}
\]

- Generally most are easy to formulate into cosmetic products.
Formaldehyde Releasers – Limitations

- In general, formaldehyde releasers (FR) are not very effective against fungi.
- In general, formaldehyde releasers are not stable at high temperatures.
- In general, formaldehyde releasers are not stable over a pH of 9.

Formaldehyde Releasers – Challenges

- Published reports indicate a reaction with DHA (dihydroxyacetone), which is used in self-tanning products.
- Also, formaldehyde releasers react with avobenzone, which may make them unstable in sunscreen and daily wear products.
Formaldehyde Releasers – Solutions

- Since formaldehyde releasers are not very effective against fungi, use in combination with an antifungal preservative if the formulation is susceptible to fungi.

- Add formaldehyde releasers lower temperatures, such as during cool down of emulsions. This could be an issue in water-in-oil emulsions.

- Seek an alternate preservative for formulations that are highly alkaline since formaldehyde releasers are not stable over a pH of 9. (Or if pH adjustment is during formulation, add formaldehyde releasers after pH adjustment or close to the end of the process.)

- If avobenzone or DHA is in the formulation, choose an alternate preservative system.

Isothiazolinones

- Methylchloroisothiazolinone / Methylisothizolinone (MCI / MI)
  - Also referred to as CMIT / MIT
- Methylisothizolinone (MIT)
- Benzisothiazolinone (BIT)
**Isothiazolinones – The “Good”**

- Broad spectrum preservatives with excellent activity against many microorganisms

- Isothiazolinones are typically effective over a pH range that is relevant to cosmetics.

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Bacteria</th>
<th>Fungi</th>
<th>Optimal pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI / MI</td>
<td>++</td>
<td>++</td>
<td>2 - 8</td>
</tr>
<tr>
<td>MIT</td>
<td>++</td>
<td>-</td>
<td>2 -12</td>
</tr>
<tr>
<td>BIT</td>
<td>+*</td>
<td>-</td>
<td>2 -12</td>
</tr>
</tbody>
</table>

*Pseudomonas gap*

- Generally easy to formulate into cosmetics (water and propylene glycol-miscible)

**Isothiazolinones – Limitations**

- In general, these preservatives react with bisulfite (residual in some surfactants), strong nucleophiles and secondary amines, even as trace contaminants. BIT is more tolerant of amines than other isothiazolones.

- Isothiazolinones typically should be added at as low a temperature (< 50°C) as possible and after pH adjustments have been made. MIT and BIT may tolerate higher temperature and pH exposure.

- Incorporation during cool down in water-in-oil emulsions could be an issue for aqueous-based isothiazolinones.

- Some isothiazolinones are inactivated by proteins that have sulphydryl groups in the active site.
Isothiazolinones – Challenges

- Some isothiazolinone products are sold as aqueous solutions with salt stabilizers. The stabilizers can cause formulation issues. Some divalent salts may react with a stearic acid emulsifier system to form a precipitate.

- Hair Gel – INCI: Water, PVP, Glycerin, Carbomer, TEA.

<table>
<thead>
<tr>
<th>Sample</th>
<th>6 rpm</th>
<th>Viscosity (cps) 10 rpm</th>
<th>20 rpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control – no preservative</td>
<td>16,033 ± 400</td>
<td>11,140 ± 200</td>
<td>6,860 ± 100</td>
</tr>
<tr>
<td>CMIT/MIT* Salt Stabilized</td>
<td>91</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>CMIT/MIT Low Salt</td>
<td>5333</td>
<td>3840</td>
<td>2460</td>
</tr>
<tr>
<td>CMIT/MIT No Salt</td>
<td>18,000</td>
<td>12,360</td>
<td>7,520</td>
</tr>
</tbody>
</table>

*CMIT/MIT = Methylchloroisothiazolinone/Methylisothiazolinone

Isothiazolinones – Solutions

- Request surfactants with low residual bisulfite from your supplier.

- Add isothiazolinones at as low a temperature (< 50°C) as possible and after pH adjustments have been made.

- If by proteins having sulfhydryl groups in the active site are in the formulation, one may have to chose an alternative preservative system.
**Isothiazolinones – Solutions**

- For those formulations which may be sensitive to salt, an associative thickener can be used with salt stabilized CMIT/MIT as they are more tolerant of salt.

- Hair Gel – INCI: Water, PVP, Glycerin, Acrylates / Beheneth-25 Methacrylate Copolymer, TEA.

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</tr>
<tr>
<td>CMIT/MIT* Salt Stabilized, Acrylates / Beheneth-25 Methacrylate Copolymer</td>
<td>23,833</td>
<td>16,200</td>
<td>9,400</td>
</tr>
<tr>
<td>CMIT/MIT No Salt</td>
<td>18,000</td>
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<td>7,520</td>
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**Organic Acids**

- Benzoic Acid
- Formic Acid
- Propionic Acid
- Salicylic Acid
- Sorbic Acid
- And the salts, to name a few………

[Image of Benzoic Acid and Sodium Benzoate structures]
Organic Aids – The “Good”

- Products are solubilized as the salts in water, and then the pH is lowered. The salts are generally very soluble.
- Very compatible with other ingredients
- Generally considered safe, even as food additives. Also, they are obtaining a reputation as being ‘green’ or ‘natural’ (Whole Foods).

Organic Acids – Limitations

- Although the salts of the acids are very soluble, the acids themselves are not particularly soluble.
- Generally the acids are active against fungi, but the organic acids are not particularly effective against bacteria.
Organic Acids – Challenges

- The acid form is the active form, so pH is critical. Must use these acids at the appropriate pH range.

- Sodium Benzoate - Solubility in water: 556 g/L (vs. 2.9 g/l for Benzoic acid).

<table>
<thead>
<tr>
<th>Benzoic acid</th>
<th>pH = 3</th>
<th>pH = 4</th>
<th>pH = 5</th>
<th>pH = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>% RCOOH</td>
<td>94%</td>
<td>61%</td>
<td>13%</td>
<td>1.5%</td>
</tr>
<tr>
<td>5900 ppm Na benzoate</td>
<td>4700 ppm</td>
<td>3050 ppm</td>
<td>650 ppm</td>
<td>75 ppm</td>
</tr>
<tr>
<td>3000 ppm Na benzoate</td>
<td>2390 ppm</td>
<td>1550 ppm</td>
<td>330 ppm</td>
<td>38 ppm</td>
</tr>
<tr>
<td>4500 ppm Na benzoate</td>
<td>3585 ppm</td>
<td>2325 ppm</td>
<td>495 ppm</td>
<td>55 ppm</td>
</tr>
</tbody>
</table>

- Next slide shows data that demonstrates the activity versus pH.

Organic Acids – Challenges

- Evaluation in a shampoo (difficult to preserve) at pH 4, 5, and 6

- 4-cycle challenge test –Challenged at day 0, 7, 14, 21

- Bacterial and Fungal pools evaluated separately

- Microorganism enumeration / estimation
  - Streak plate method
  - Enumerations on day 7, 14, 21 and 28
  - Rating Scale:

<table>
<thead>
<tr>
<th>Growth Rating</th>
<th>Approximate cfu/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>1</td>
<td>10^2 to 10^3</td>
</tr>
<tr>
<td>2</td>
<td>10^3 to 10^4</td>
</tr>
<tr>
<td>3</td>
<td>10^4 to 10^5</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 10^5</td>
</tr>
</tbody>
</table>

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Organic Acids – Challenges

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Bacterial Rating</th>
<th>Fungal Rating at Day</th>
<th>ppm</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpreserved</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Na benzoate</td>
<td>3000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Na benzoate</td>
<td>4500</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

**pH 4**

**pH 5**

**pH 6**

**Bottom line:** pH is a critical parameter when the preservation system includes organic acids.

Organic Acids – Solutions

- Use salt form for best solubility. Adjust the pH to acidic after solubilization of the salt.
- If the formulation is susceptible to bacteria, use with other preservatives for broad spectrum activity.
Parabens

- Methylparaben
- Ethylparaben
- Propylparaben
- Butylparaben
- Benzylparaben
- Isopropyl-, Isobutyl, and Na⁺, K⁺ salts

Parabens – The “Good”

- Very effective versus fungi.
- There are quite a few global suppliers of various parabens, so availability should not be an issue.
Parabens – Limitations

- Some activity against Gram-positive bacteria; weak against Gram-negative bacteria.

- Inactivated by strong hydrogen bonders (polysorbates), cellulose derivatives, proteins and lecithin. They can be absorbed by clays.

- pH limitations; most effective at or below pH 6. Between 6 and 7 there is some antimicrobial activity, but it is reduced. Typically, parabens are not recommended above pH 8.

Parabens – Challenges

- Although the salts are very soluble, the esters themselves are not particularly soluble.

- They function only in the water phase.

- Order and/or method of addition is critical. Not a simple drop in preservative. Formulation expertise is necessary, such as solubilizers (propylene glycol), or use of salts and pH adjustment to cosmetic range.
Parabens – Solutions

- Because parabens are weak against Gram-negative bacteria, use in combination if the formulation is susceptible to bacteria.

- If the formulation contains polysorbates, cellulose derivatives, proteins, lecithin or clays, one may have to choose an alternate preservative.

- Be aware of the pH of the formulation. Some pH adjustment may have to be made to a lower formulation pH (<6) for optimal preservation.

Phenoxyethanol – The “Good”

- Phenoxyethanol is generally widely accepted.

- In general, phenoxyethanol is a stable compound to heat up to 85°C, and is useful from pH 3 to 10.

- It is a free-flowing liquid, soluble in water (up to ~2.5%), and miscible with propylene glycol and glycerin.
**Phenoxyethanol – Limitations**

- Phenoxyethanol can be deactivated by highly ethoxylated compounds.
- It is a weak preservative, and most active against Gram-negative bacteria.
- Actual cosmetic grades vary in purity (92 – 99%). The trace contaminants can affect odor and color of the formulation.

**Phenoxyethanol – Challenges**

- Phenoxyethanol can act like a ‘hydrophobic’ surfactant in some formulations. (HLB = 6.4 by Griffin Method)
- As a low HLB surfactant, it can combine with associative rheology modifiers (thickeners) to raise the viscosity.
- Hair Gel – INCI: Water, PVP, Glycerin, Acrylates/Beheneth-25 Methacrylate Copolymer, TEA.

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<td>38,666</td>
<td>16,200</td>
<td>9,400</td>
</tr>
<tr>
<td>0.6% Phenoxyethanol</td>
<td>54,000</td>
<td>21,600</td>
<td>12,585</td>
</tr>
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</table>
Phenoxyethanol – Solutions

- Avoid using phenoxyethanol in formulations with ethoxylated compounds such as alkyl ethoxylated surfactants.

- Phenoxyethanol should always be used in combination with other preservatives.

- Be well aware of the purity of your cosmetic grade of phenoxyethanol if the formulation is susceptible to trace contaminants that can affect odor and color of the finished product.

Phenoxyethanol – Solutions

- Instead of using an associative rheology modifier in a formulation that needs to be preserved with phenoxyethanol, use a carbomer instead to achieve the viscosity.

- Hair Gel – INCI: Water, PVP, Glycerin, Carbomer, TEA.

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<td></td>
</tr>
<tr>
<td>0.6% Phenoxyethanol with associative RM</td>
<td>54,000</td>
<td>21,600</td>
<td>12,585</td>
<td></td>
</tr>
<tr>
<td>0.6% Phenoxyethanol with carbomer</td>
<td>39,333</td>
<td>17,333</td>
<td>9,560</td>
<td></td>
</tr>
</tbody>
</table>
Blends / Combinations

- Most preservatives are used in combination today
  - Examples:
    - DMDMH / IPBC
    - IU / parabens
    - Sodium benzoate / potassium sorbate / phenoxyethanol
    - MIT with phenoxyethanol, caprylyl glycol, parabens, etc.
    - Phenoxyethanol with parabens, caprylyl glycol, ethylhexylglycerin, etc.

- Formulation effects of each component should be considered; combining certain preservatives may exacerbate the effect
  - Examples:
    - Phenoxyethanol / caprylyl glycol – viscosity
    - Phenoxyethanol / benzyl alcohol - odor

Summary

- Five traditional preservatives were included in this review of formulation tips
- When formulating, it is REALLY IMPORTANT that the chemist consider the preservative package as part of the formulation.
- All preservatives, both traditional and non-traditional, have their “Achilles Heel”.
Acknowledgements


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