Considerations in Using Alternative Preservatives in Personal Care Products

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What is a Preservative?

A chemical agent that will either kill or inhibit the growth of microorganisms.
Why do we need to preserve product formulations?
Regulatory Status of Traditional Preservatives - Europe

  - Maximum Authorized Concentration.
  - Limitation and Requirements.
    - Rinse-off products only.
    - Prohibited in aerosols.
  - Conditions of Use and Warnings which must be printed on the product label.
    - Not to be used for children under 3 years of age.
    - Contains XYZ.
Regulatory Status of Traditional Preservatives - Japan

- Ministry of Health and Welfare Positive Preservative List – 2 Parts
  - Preservatives that can be used in all cosmetic products.

- Preservatives that are restricted depending upon the type of cosmetic product that they are going to be used in:
  - Rinse-off products not applied to a mucous membrane.
  - Leave-on products not applied to a mucous membrane.
  - Cosmetics applied to a mucous membrane.
Regulatory Status of Traditional Preservatives - USA

- **No Positive Preservative List.**
  - Food and Drug Administration has the ability to restrict or prohibit the use of a preservative due to safety reasons.

- **Prohibited or Restricted Preservatives:**
  - **Hexachlorophene (21 CFR 250.250)**
    - Has neurotoxic effects and ability to penetrate human skin
    - May be used only when an alternative preservative has not shown to be effective.
    - Level cannot exceed 0.1% and may not be applied to a mucous membrane
  - **Mercury Compounds (21 CFR 700.13)**
    - Readily absorbed through the skin on topical application and is able to accumulate in the skin.
    - Limited use to the eye-area only at a concentration of 65 ppm provided no other effective and safe preservative can be used.
  - **Bithionol (21 CFR 700.11)** – causes photo-contact sensitization.
  - **Halogenated Salicylanilides (21 CFR 700.15)** – causes photo-contact sensitization.
The Usage of Traditional Preservatives Under Fire from:

- Regulatory
  - Bans
  - Usage Restrictions
- Consumer/Market Demands
Examples of Traditional Preservatives with Current Regulatory Bans


- **Chloracetamide** - July 2012 – French regulatory ban for usage in cosmetics.

- **Iso-alkyl Parabens** – October 2014 – EC disallowed used due to the lack of safety data.


- **Methylisothiazolinone & Methylchloroisothiazolinone mixture** – April 2016 – EC disallows use in leave-on products.
Examples of Traditional Preservatives with Regulatory Usage Restrictions

- **Propyl and Butylparaben**
  - Maximum Usage Concentration is 0.14% when used individually or together.

- **Iodopropynyl Butylcarbamate (IPBC)**
  - Maximum Usage Concentration in Leave-on Products is 0.01%.
  - Maximum Usage Concentration in Rinse-Off Products is 0.02%.

- **Phenoxyethanol**
  - SCCS Opinion of October 2016 – Safe as used, Maximum Usage Concentration is 1.0%.

- **Poly(hexamethylen) Biguanide hydrochloride (PHMB)**
  - Before 2014, PHMB could be used up to a 0.03% concentration.
  - SCCS Opinion of October 2014 - Not safe when used up to a concentration of 0.03%.
  - SCCS Opinion of April 7, 2017 - Now considered to be safe up to a concentration of 0.01%.
Consumer/Market Claims and Demands

- Claims and demands such as
  - Preservative Free
  - Paraben Free
  - Formaldehyde Free
  - Naturally Preserved
Replacement of Traditional Preservatives with Non-Traditional or Alternative Preservative Systems

- Not as easy as people think it is.
  - Replacement is not a one to one replacement.
  - Cost of the formulation may increase by using a non-traditional or alternative preservative system in place of the traditional preservative system.

- Will need to repeat the following types of testing on a product formulation containing an alternative preservative system:
  - Microbial challenge testing.
  - Allergy testing.
  - Claims testing.
Alternative Preservatives

- Will generally have:
  - Antimicrobial activity by itself.
  - Can be an ingredient marketed for some other function in combination with a traditional preservative.
  - Can be used to boost or enhance the antimicrobial activity of a traditional preservative by which:
    - A lower concentration of the traditional preservative can be used in a formulation.
    - Allows for a switch to a less powerful or potent preservative that does not have a marketing issue to guarantee preservative adequacy of a formulation.
Alternative Preservatives – Regulatory Aspects

- Alternative preservatives can have antimicrobial activity, but are generally not on an approved preservative list such as:
  
  
  - The Japan Ministry of Health and Welfare Positive Preservative List.
Alternative Preservatives Can be Marketed for Some Other Functions

- Besides having antimicrobial activity, they can serve in a product formulations as multi-functional ingredients such as:
  - Antioxidant
  - Emollient
  - Fragrance
  - Fragrance Additives
  - Humectant
  - Moisturizer
  - Skin and Hair Conditioner
  - Viscosity Regulator
Types of Alternative Preservatives
Types of Alternative Preservative Systems

- Glycols
- Glycerin Esters
- Essential Oils
- Other Phytochemicals
- Plant Extracts
- Peptides
- Organic Acids
- Fragrance Additives/Fragrances
- Ketones
- Phospholipids
- Monoterpenoid Phenol
Glycols

- Propylene Glycol
- Butylene Glycol
- Pentylene Glycol
- 1,2-Hexanediol
- Caprylyl Glycol
- Decylene Glycol
Glycol Preservative Potentiators

- Propylene Glycol and Butylene Glycol (1,2 – Butanediol).

- Multi-functional Ingredients:
  - Solvent
  - Are known preservative potentiatiors and has some antimicrobial activity (e.g. 10-20% Propylene Glycol and 5 to 20% Butylene Glycol).
  - Are also able to function as a humectant by lowering the water activity of the formulation to aid in preservation of the formulation.

- Water Solubility: Propylene Glycol - Miscible in water; Butylene Glycol - Insoluble in water, but soluble in alcohol. Each of these glycols are normally added to the water phase of a product formulation.

- Normal usage concentration in product formulations is between 3 to 6%.
  - At high concentrations, Propylene Glycol (e.g. >20%) and Butylene Glycol (e.g. >10%) have antimicrobial activity and will self-preserve a product formulation.
Pentylene Glycol (1,2-Pentanediol)

- Multi-functional Ingredient
  - Skin moisturizer  Emulsion stabilizer  Antimicrobial  Solvent
- Soluble in water and oil.
- Incorporation: Add to the water phase of a product formulation.
- Recommended usage concentration: 1 to 5%.
- Has a broad spectrum of antimicrobial activity.
  - Example of % Minimum Inhibitory Concentration (MIC) Data for Pentylene Glycol
    
    \[
    \begin{array}{cccccc}
    E. coli & Ps. aeruginosa & S. aureus & C. albicans & A. brasiliensis \\
    3.2 & 1.6 & 3.2 & 1.6 & 1.6 \\
    \end{array}
    \]
1,2-Hexanediol

- Multi-functional Ingredient: Antimicrobial and Humectant
- Soluble in water.
- Stable at high/low pH and high temperatures.
- Recommended usage concentration: up to 3%
- Has a broad spectrum of antimicrobial activity
  - Example of % Minimum Inhibitory Concentration (MIC) Data for 1,2-Hexanediol
    
    E. coli  Ps. aeruginosa  S. aureus  C. albicans  A. brasiliensis
    1.25  0.63  2.5  1.25  0.63

- Will also enhance the antimicrobial activity of Parabens, Phenoxyethanol and formaldehyde donating preservatives.
- Often used in preservative blends such as:
  - 1,2-Hexanediol/Caprylyl Glycol/Methylbenzyl Alcohol
  - 1,2-Hexanediol/1,2-Octanediol/Troplone
  - 1,2-Hexanediol/Caprylyl Glycol
  - 1,2-Phenoxyethanol/Decylene Glycol/1,2-Hexanediol
Caprylyl Glycol (1,2-Octanediol)

- Multi-functional Ingredient:
  - Antimicrobial
  - Moisturizer
  - Humectant

- Use concentration is 0.5 to 1.0% in leave-on and rinse-off products.

- Recommended formulation pH range: 2 to 10.

- Antimicrobial activity: Good against bacteria and yeasts, but weak against mold. Besides being used by itself, it is commonly used in combination with traditional or alternative preservative blends and EDTA.

- Water Solubility: 0.5% and should be introduced directly into the water phase before emulsification.

- Potential Issues:
  - May cause the de-stabilization of emulsions. To prevent it, need to increase the concentration of the emulsifier or use a mixture of different emulsifiers (especially non-ionic or anionic emulsifiers).
  - Concentration of usage: High levels can cause eye-area stinging issues or numbing in the lip-area.
Decylene Glycol (1,2-Decanediol)

- Multi-functional Ingredient:
  - Preservative booster
  - Antimicrobial activity
  - Moisturizer
  - Deodorant
  - Foam and viscosity booster for shampoos and shower gel product formulations.

- Antimicrobial Activity
  - Has synergism with alpha hydroxyl acids against *P. acnes* and has activity against body odor causing Gram-positive microorganisms.
  - Known to enhance the antimicrobial activity of other preservatives.
  - Has a broad spectrum of antimicrobial activity, but the potency is lower in comparison to other diols. With this low potency, Decylene Glycol has to be used in combination with other compounds that has activity:
    - Example of % Minimum Inhibitory Concentration (MIC) Data for Decylene Glycol
      
      | E. coli | Ps. aeruginosa | S. aureus | C. albicans | A. brasiliensis |
      |--------|--------------|-----------|-------------|----------------|
      | 0.090  | 0.045        | 0.23      | 0.011       | 0.006          |
  
- Recommended usage concentration: 0.1 to 2%.
- Solubility: Water insoluble, but soluble in cosmetic esters.
Glycerin Esters

- Ethylhexylglycerin
- Glyceryl caprate
- Glyceryl caprylate
- Glyceryl undecylenate
Ethylhexyglycerin

- Known antimicrobial preservative booster or enhancer for Phenoxyethanol and Methylparaben. Also is known to improve the antimicrobial activity of glycols (e.g. Pentylene glycol or Caprylyl glycol).

- Use concentration; 0.1 to 1.0%.

- Recommended formulation pH: 2 to 12.

- Solubility:
  - In water - <0.2%
  - Good solubility in organic solvents such as alcohol, glycols and glycol ethers.

- Incompatibilities:
  - Ethoxylated surfactants will neutralize the preservative boosting effects of ethylhexylglycerin. Not evident in products containing cationic or amphoteric surfactants.

- Multi-functional Ingredient
  - Preservative Booster  Deodorizing Agent  Emollient  Mild Humectant
Glyceryl caprate

- Has good antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and yeasts. Can serve as an antimicrobial boosting agent of other preservatives in oil-in-water emulsions.
- Recommended usage concentration: 1 to 2%.
- Recommended pH range: 4.5 to 7.0.
- Incorporation: Add to water or oil phase at < 80°C and a pH of less than 7 to prevent hydrolysis.
- Can have an impact on emulsion viscosity and stability.
- Multi-functional Ingredient: Deodorant activity, antimicrobial activity, and moisturizer.
Glyceryl caprylate

- Has very good antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria. Due to the lack of antimicrobial activity against fungi, it needs to be used in conjunction with p-Anisic acid in product formulations.

- Solubility: Water Insoluble.

- Recommended Usage Concentration: 0.3 to 0.7%

- Recommended pH range: 4.0 to 7.0; After a pH of 7.0, hydrolysis could occur.

- Method of incorporation: Add to the water or oil phase before emulsification.

- Temperature tolerance: <60°C.

- Incompatibilities:
  - Has limited antimicrobial activity in surfactant based product formulations.

- Multi-functional Ingredient: Antimicrobial and wetting agent
Glyceryl undecylenate

- Used in a blend of Glyceryl undecylenate and Glyceryl caprylate.
  - Avoid use of the above blend in products with pH’s above 7 due to the hydrolysis of the Glyceryl caprylate component.
  - Blend is water insoluble.
  - Blend has a broad spectrum of antimicrobial activity
  - Blend use concentration: 1 to 1.5%.
  - Blend is effect in formulations with a pH of 4.0 to 7.0, but has optimum activity at a pH of less than 5.5.
  - Recommended for use in water/oil or oil/water emulsions and should be added to the formulation during the emulsification process.
Essential Oils

- Essentials oils are the most common antimicrobial compounds that can be extracted from plants.

- Examples of known essential oil extracts with antimicrobial activity:
  - Cinnamon Oil
  - Lemon Grass Oil
  - Clove Oil
  - Rosemary Oil
  - Eucalyptus Oil
  - Thyme Oil
  - Lavender Oil
  - Tea Tree Oil
Antimicrobial Activity of Essential Oils

- In the published literature, the antimicrobial activity of essential oils will vary. For example:
  - Lemongrass, Oregano and Bay essential oils are known to inhibit the growth of 10 different test microorganisms at a concentration of \( \leq 2.0\% \text{ (v/v)} \).
  - Rosewood, Coriander, Palmarosa, Tea Tree, Niaouli, Peppermint, Spearmint, Sage and Marjoram essential oils are known to inhibited the growth of 9 different test microorganisms at \(<2\% \text{ (v/v)} \) with the only exception of \textit{Ps. aeruginosa}.
  - Pumpkin, Macadamia, Evening Primrose, Apricot Kernal, Sweet Almond, and Calary Sage essential oils failed to inhibit any of the 10 different test organisms.
  - Myrrh and Cypress essential oils had activity only against Gram-positive test microorganisms.
  - Carrot, Patchouli, Sandalwood and Vetiver inhibited Gram-positive bacteria and \textit{Candida albicans} only.
  - Mandarin oil inhibited \textit{Candida albicans} at 2.0\% (v/v), while bacteria were found not to be inhibited.
Tea Tree Oil – Essential Oil

- Composition of this essential oil is complex. The dominant antimicrobial ingredient is Terpinen-4-ol.

- Solubility: Water Insoluble.

- Formula Incorporation: Pre-dissolve in Polysorbate 20.

- Use concentration: 1 to 5%.

- Problem Issues with Tea Tree Oil:
  - Has the distinctive odor that is similar to turpentine.
  - Has week antimicrobial activity.
  - Is a known skin sensitizer.
  - Regulatory: 2008 EU SCCP opinion had indicated that there is no clear cosmetic function for this ingredient.
Formulation Problem Issues with Essential Oils

- Will often provide a mild to a strong odor to the formulation.
- Generally not soluble in water.
- May impart more of a yellow color to a product formulation.
- May cause a high level of irritation or sensitization at product use levels.
- Some essential oils contain ingredients that are listed on the EU Allergens List.
Examples of Essential Oil Blends Used as Natural Preservatives

- **Salinaturals CCL**
  - Consists of a mixture of Curry Leaf and Cinnamon Leaf Essential Oils
  - Recommended usage concentration: 0.75 to 1.2%
  - Optimum pH range for usage is <6.0

- **Salinaturals OLG**
  - Consists of a mixture of Orange, Lemon Grass and Sesame Essential Oils
  - Recommended usage concentration: 1 to 2%
  - Optimum pH range for usage is <6.0

- **Salinaturals BCLS**
  - Consists of Basil Extract, Clove Bud, Lemon Grass and Sesame Essential Oils
  - Recommended usage concentration: 1 to 2%
  - Optimum pH range for usage is 3 to 7

- **Salinaturals TCLS**
  - Consists of Turmeric, Clove Bud, Lemon Grass, and Sesame Essential Oils
  - Recommended usage concentration: 1 to 2%
  - Optimum pH range for usage is <6.0
Other Types of Phytochemicals with Antimicrobial Activity

- **Terpenoids**
  - Capsaicin
  - Menthol
  - Caffeic Acid

- **Flavonoids**
  - Catechin
  - Kaempferol
  - Quercetin

- **Phenolic Compounds**
  - Catechol
  - Pyrogallol
  - Eugenol
Aspen Bark Extract Powder

- Water soluble and can be added to aqueous systems and aqueous phase of emulsions.
- Recommended usage concentration: 0.2 to 3.0%.
- Heat stable to 60°C (140°F).
- Recommended formulation pH: 3 to 8.
- Contains 54 to 60% Salicylates.
- Multi-functional Ingredient: Antimicrobial and Skin Conditioning Agent.
Plant Extracts - Natural Preservatives (2)

- Black Currant (Ribes nigrum) Powder
  - Water Soluble
  - Recommended usage concentration: 1 to 3%.
  - Heat stable to 75°C.
  - Recommended formulation pH: 3 to 8.
  - Multi-functional Ingredient: Antimicrobial and Skin Conditioning Agent.
Honeysuckle (Lonicera caprifolium/Lonicera japonica) Flower Extract/Aq. Blend.

- Water Soluble.
- Has a broad spectrum of antimicrobial activity.
- Recommended usage concentration: Up to 1%.
- Recommended formulation pH: 3 to 8.
- Heat stable.

**Compositional Issue – the antimicrobial active ingredient(s) is unknown:**

- Supplier says that it is a natural paraben (parahydroxybenzoic acid), but no parabens or parahydroxybenzoic acid has ever been detected.
- A small amount of Benzoic Acid (less than 5 ppm) has been detected.
- Loncierin, a flavonoid, is present in this blend.
Plant Extracts – Natural Preservatives (4)

- **Elderberry OS**
  - Insoluble in water.
    - Has to be added to the oil phase of a product formulation or in anhydrous and oil-based product formulations.
  - Multi-functional Ingredient:
    - Antioxidant, Anti-Conditioning, Antimicrobial
  - Known to contain the following phytochemicals:
    - Caffeic Acid (Terpenoid with antimicrobial activity).
    - Chlorogenic Acid (Antioxidant).
    - Ferulic Acid (Antioxidant).
    - Quercetin (Flavonoid with antimicrobial activity).
  - Recommended usage concentration: 1 to 5%.
  - Recommended formulation pH: 3 to 8.
  - Temperature Stability: <75°C.
Other Available Plant Extracts (1)

- **Citrus Seed Extracts**
  - Depending upon the species, the extract should contain the essential oils of either Naringenin or Hesperidin that are anti-bacterial.

![Chemical structure of Citrus Seed Extracts](image)

- Supposed to be 100% natural, but the presence of traditional preservatives have been found to be present in these extracts (e.g. Grapefruit Seed Extract).

- **Tree Lichen Extract**
  - Not widely used.
  - Contains Usnic acid that has antimicrobial activity against Gram-positive bacteria and some fungi.
    - Usnic acid is normally extracted from lichen and can be used as a preservative at a concentration of 1 to 5%.
Other Available Plant Extracts (2)

- **Suprapein™**
  - **Composition:**
    - Mixture of Oregano Leaf Extract, Thyme Extract, Cinnamon Bark Extract, Olive Leaf Extract, Rosemary Leaf Extract, Peppermint Leaf Extract, Lavender Flower Extract, Goldenseal Root Extract and Lemon Peel Extract
  - **Solubility:** Non-soluble in water, but it is oil soluble.
  - **Has antimicrobial activity against bacterial and fungi.**
  - **Recommended Usage Concentration:** 0.45%
  - **Temperature Tolerance:** 68 to 80°F.
  - **Problem Issue:** Due to its composition, it may contain the following EU fragrance allergens (i.e. Cinnamal, Citral, Linonene and Linalool).
Neopein®

Composition:
- Mixture of plant extracts and essential oils such as Oregano Leaf Extract, Rosemary Leaf Extract, Thymol, Lavender Oil, Goldenseal Extract and Olive Leaf Extract.
- Oil Soluble Only
- Recommended Usage Concentration: 0.55%
- Has a broad spectrum of antimicrobial activity (e.g. bacterial and fungi).
- Temperature Tolerance: 68 to 80°F.
- Problem issue: Due to its composition, it may contain the following EU fragrance allergens (i.e. Eugenol, Limonene, and Linalool).
Peptides as a Preservative (1)

- **Leuconostoc/Radish Root Ferment Filtrate**
  - Derived from *Leuconostoc kimchi* that consists of an antimicrobial peptide that is secreted from the bacteria during the fermentation process.
  - Recommended usage concentration: 2.0 to 4.0%.
  - Peptide is:
    - Water soluble
    - Odorless
    - Has a broad spectrum of antibacterial activity
    - Recommended formulation pH: 3 to 8.
    - Heat stable to at least 70°C
    - Not compatible with Poly (Hexamethylene biquanide) Hydrochloride (PMHB) [Preservative].
    - Due to its cationic nature, it is incompatible with anionic ingredients, such as thickeners (e.g. Carbopol, Xanthan Gum, Carragennan and Hyaluronic Acid).
Peptides as a Preservative (2)

- **e-polylysine**
  - Polypeptide of 25 to 30 L-Lysine residues.
  - Produced by a fermentation process using *Streptomyces albulus*.
  - Heat stable.
  - pH range: 5 to 8.
  - Multi-functional Ingredient:
    - Antimicrobial
    - Hair Conditioning Agent
    - Skin Conditioning Agent
  - Has a broad spectrum of antimicrobial activity.
  - Cationic
  - Approved for use as a preservative in foods (e.g. up to 0.025%)
Organic Acids Used as Preservatives

- **Traditional**
  - Benzoic Acid
  - Dehydroacetic Acid
  - Sorbic Acid
  - Salicylic Acid

- **Alternative**
  - $p$-Anisic Acid
  - Caprylhydroxamic Acid
  - Caprylic Acid
  - Levulinic Acid
  - Undecylenic Acid
p-Anisic Acid

- Also known as 4-Methoxybenzoic acid.
- Has only fungicidal activity and needs to be used with a compound that has bactericidal activity such as Levulinic acid.

- Solubility:
  - Needs to be added to the aqueous phase at 80.0°C and stirred until dissolved.
  - Soluble in glycerin.

- Usage Concentration: 0.05 to 0.5%.
- Can be used in leave-on and rinse-off products, but do not use in AHA formulations.

- Heat stable to 80.0°C.
- Optimum pH for Activity: 4.5 to 5.5.

- Multi-functional Ingredient: Anti-fungal Agent, Anti-Inflammatory Agent and Odor Masking Agent
Caprylhydroxamic Acid

- Is an amino acid derived from coconut oil.
- Water Soluble.
- Only has anti-fungal activity:
  - Used in combination with either Capryl glycol and Glycerin (Spectrastat) or Glyceryl caprylate and Methylpropanediol (Spectrastat G) or Propandediol (Zeastat) to form a preservative blend that has a broad spectrum of antimicrobial activity.
- Can be used in leave-on and rinse-off products.
- Effective antimicrobial activity at neutral pH’s.
- Besides having antimicrobial activity, it can serve as a chelating agent for iron ions. It may also react with residual iron in some clay type compounds (e.g. bentonite, silicates, etc.) in which a mild orange color or color shift is produced.
Caprylic Acid

- Found in coconut oil.
- Has very good anti-fungal activity.
- Solubility by itself:
  - Soluble in ethanol, ether and most organic solvents.
  - Has a very low water solubility.
- Multi-functional Ingredient:
  - Anti-fungal agent  Flavor  Fragrance.
- Used as a component in an alternative preservative blend called MicroCurb™ OC.
  - Combination of Caprylic Acid and Origanurn vulgare Leaf Extract.
  - Can be used in leave-on and rinse-off products.
  - Optimum pH: <5.5.
  - Usage Concentration: Up to 1%. 
Levulinic Acid

- Derived from the degradation of cellulose.
- Water Soluble.
- Has good antibacterial activity.
  - Recommended to be used in conjunction with p-Anisic acid due to its antifungal activity as a preservative system in product formulations.
- Recommended usage concentration: 0.3 to 1.0%.
- Optimum pH for activity: 4.5 to 5.5.
- Component of Dermosoft 690 (Levulinic Acid/Sodium levulinate/Phenylpropanol) and Dermosoft 700B (Levulinic Acid/Sodium levulinate/Glycerin).
- Multi-functional Ingredient:
  - Antibacterial Compound
  - Odor Masking Agent
Undecylenic Acid

- Unsaturated fatty acid derived from Castor Oil.

- **Solubility:**
  - Insoluble in cold/hot water.
  - Soluble in alcohol and Diethyl ether.

- Has its own USP monograph.

- Has anti-fungal activity.

- Allowed in the EU (Annex V) and Brazil up to 0.2% as the acid or salt.

- **Multi-functional Ingredient:**
  - Anti-fungal Agent
  - Skin Conditioning Agent
Fragrance Additives/Fragrances

- Fragrance Additives
  - Phenethyl Alcohol
  - Phenylpropanol
- Fragrances
  - Romacil™ V
  - Naticide®
Phenethyl Alcohol

- Active against bacteria, but weak against fungi.
- Can be used in leave-on and rinse-off product formulations.
- Use concentration by itself: up to 0.5%.

Solubility:
- Slightly soluble in water up to 2%.
- Mostly soluble in organic solvents.

Incompatibility: Inactivated by nonionics and reacts with oxidizers.

Multi-functional Ingredient:
- Antimicrobial Agent
- Flavor
- Fragrance

Mostly used in alternate preservative blends such as:
- Caprylyl Glycol/Phenethyl Alcohol.
- Caprylyl Glycol/Phenethyl Alcohol/Trideceth-8.
- Phenethyl Alcohol/Glycerin/Benzoic Acid.
- Phenethyl Alcohol/Pentylene Glycol/Propanediol.
Phenylpropanol

- Natural.
- Fragrance with antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungi.
- Usage concentration by itself: 0.05 to 0.2%.
- Recommended pH range: Unlimited.
- Multi-functional Ingredient: Antimicrobial agent and fragrance.
- Most commonly used as an ingredient in alternative preservative blends:
  - Caprylyl Glycol/Phenylpropanol.
  - Methylpropanediol/Caprylyl Glycol/Phenylpropanol.
  - 1,2-Hexanediol/Phenylpropanol.
Romacil™ V

- Blend of the following ingredients: 1,5 Pentanediol, Polyglyceryl-10 oleate, Vanilla and Caprylic Acid.
- Has a broad spectrum of antimicrobial activity.
- Solubility: Water soluble
- Recommended pH range: 4 to 7.
- Recommended usage concentration: 1 to 2%.
- Multi-functional Ingredient: Antimicrobial agent and fragrance
- Concerns with usage:
  - Product discoloration.
    - Use of this ingredient may cause the formulation to discolor.
    - To prevent discoloration, the addition of a chelator such as Citric acid or an antioxidant is recommended prior to the addition of Romacil™ V to the batch.
    - Certain emollients may cause more discoloration of the formulation with Romacil™ V.
Naticide®

- Fragrance with an odor of almond and vanilla.
- Is known to contain Heliotropin and Phenylpropanol that has antimicrobial activity.
  - Heliotropin is an aromatic aldehyde that is extracted from essential oils.
- Has a broad spectrum of antimicrobial activity.
- Solubility:
  - Soluble in water up to 0.6%
  - Completely soluble is glycol and alcohol.
- Recommended pH range: 4 to 9.0.
- Usage concentration:
  - 0.3 to 1% when used alone.
  - 0.2 to 0.5% when used with other preservatives.
- Multi-functional Ingredient:
  - Antimicrobial Fragrance
Ketone

- Hydroacetphenone
Hydroacetophenone

- Multi-functional Ingredient:
  - Anti-oxidant
  - Anti-irritant
  - Preservative Booster

- Can boost the antimicrobial activity of the following preservatives:
  - Phenoxyethanol
  - Formaldehyde-donating preservatives (e.g. DMDM Hydantoin, Imidazolidinyl urea, etc)
  - Chlorophenesin
  - Organic acids

- Usage concentration: up to 1%.
- Temperature tolerance: <60°C.
- Solubility: Soluble in Water, Phenoxyethanol, Glycerin, Ethanol and glycols like Pentylene glycol and Propylene glycol.
Phospholipids
Phospholipids

- Multi-functional Ingredients:
  - Conditioning Agent
  - Foaming Agent
  - Moisturizing Agent
  - Emollient

- Antimicrobial Activity:
  - Some can boost or enhance the antimicrobial activity of traditional preservatives.
  - Some have antimicrobial activity by themselves (e.g. Coco phosphatidyl PG-dimonium chloride).

- Solubility: Partially water soluble.

- Usage concentration: 0.5 to 1.0%.

- Can be used in leave-on and rinse-off product formulations.

- Examples of phospholipids with either antimicrobial activity or are able to boost or enhance the antimicrobial activity of preservatives:
  - Sodium Coco PG-dimonium Chloride Phosphate.
  - Cococamidopropyl PG-dimonium Chloride Phosphate.
  - Myristamidopropyl PG-dimonium Chloride Phosphate.
Monoterpenoid Phenol

- o-Cymen-5-ol (p-Thymol, 4-Isopropyl-n-cresol)
O-Cymen-5-ol (p-Thymol)

- Multi-functional ingredient
  - Antioxidant
  - Antibacterial
  - Mild Astringent
- Listed in EU Annex V – List of Approved Preservatives
- Solubility:
  - Insoluble in water, glycerin and mineral oil.
  - Soluble in Propylene glycol, Butylene Glycol, Phenoxyethanol and Benzyl alcohol.
- Recommended usage concentration: up to 0.1%
- Antimicrobial activity: More effective against bacteria and less effective against fungi.. Needs to be used synergistically with either organic acids or Hydroxacetophenone.
- Potential Formulation Issues:
  - Crystals of it may precipitate out in the formulation after a period of time.
  - Incompatible with nonionic surfactants and Carboxymethylcellulose.
- Incorporation into formula: Needs to be dissolved in a pre-mix and added.
Considerations
Considerations for Selecting Alternative Preservative Systems

- Formulation Factors
- Spectrum of Antimicrobial Activity
- Processing Conditions
- Irritation/Sensitivity Factors
- Cost Implications
Formulation Factor Considerations in Using Alternative Preservatives

- pH
- Water Activity
- Solubility of Alternative Preservatives
- Compatibility with Other Cosmetic Raw Ingredients
pH and Microbial Growth

- **Bacteria:**
  Optimum pH for growth is between 5.5 and 8.5.

- **Fungi (Yeasts and Mold):**
  Optimum pH for growth is between 4.0 and 6.0.
pH Affects - Microbiological

- For those product formulations with a pH less than 4.0 or greater than 10.0, the extreme pH of the formulation prevents microorganisms from proliferating or surviving by causing:
  - metabolic injury to the microbial cells.
  - cellular stress by which microorganisms expend a greater amount of energy to maintain intracellular pH. After the energy is used up, the cells die.
  - the function of many microbial cellular enzymes is dependent on the maintenance of proper intracellular pH.

- Examples of Extreme pH Product Formulations without Preservatives
  - **Acidic Product Formulations** (e.g. pH of 3.0 – 5.0):
    - Salicylic acid-containing product formulations.
    - Antiperspirants containing aluminum chlorohydrate.
    - Hair conditioners.
  - **Alkaline Product Formulations** (e.g. pH of 10.0 – 14.0)
    - Hair relaxers.
    - Depilatory creams.
Optimum pH Range for Antimicrobial Activity in a Formulation.

- p-Anisic Acid: < 5.5
- Glyceryl Caprate: 4.0 - 7.0.
- Glyceryl Caprylate: 4.0 - 7.0.
- Sodium levulinate and phenylpropanol: <5.5.
- Caprylyl glycol: Has a broad pH range.
- Phenoxyethanol and Caprylyl glycol: Optimum pH range is 4.0 to 7.0.
- 1,2-Decanediol (Decylene glycol): Optimum pH range is 3.0 to 8.0.
Water Activity

- Water Activity is defined as the ratio of vapor pressure of a substance to that of pure water at a specified temperature.

- Water Activity can be expressed mathematically as a function of Raoult’s Law:
  \[ A_w = \frac{P}{P_0} = \frac{n_1}{n_1 + n_2} \]
  where \( P \) = vapor pressure of a solution, \( P_0 = \) vapor pressure of pure water, \( n_1 \) is the number of moles of solvent, and \( n_2 \) is the number of moles of solute.

- Relationship between \( A_w \) and Equilibrium Relative Humidity (ERH) can be expressed as follows:
  \[ A_w = \frac{P}{P_0} \text{ and } \text{ERH (\%)} = A_w \times 100 \]
# General Water Activity Values Required for Microbial Growth

<table>
<thead>
<tr>
<th>Water Activity Value</th>
<th>Microorganism Types Capable of Proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.96 to 0.99</td>
<td>Gram-positive and Gram-negative bacteria (e.g. <em>Pseudomonas</em> species), mold and yeasts</td>
</tr>
<tr>
<td>0.90 to 0.95</td>
<td>Several Gram-negative and most Gram-positive bacteria (e.g. <em>Enterobacter aerogenes</em>, <em>Escherichia coli</em>, <em>Bacillus</em> species), mold and yeasts</td>
</tr>
<tr>
<td>0.80 to 0.89</td>
<td>Gram-positive bacteria (e.g. <em>S. aureus</em>), mold and yeasts</td>
</tr>
<tr>
<td>0.70 to 0.79</td>
<td>Halophilic bacteria, mold and yeasts</td>
</tr>
<tr>
<td>0.65 to 0.69</td>
<td>Osmotolerant yeasts</td>
</tr>
<tr>
<td>Below 0.6</td>
<td>None</td>
</tr>
</tbody>
</table>
# Formulation Water Activity and Antimicrobial Spectrum of Activity

<table>
<thead>
<tr>
<th>Formulation Water Activity Level</th>
<th>Antimicrobial Spectrum of a Non-Traditional or Alternative Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 0.6</td>
<td>Inclusion may not be necessary.</td>
</tr>
<tr>
<td>0.70 – 0.79</td>
<td>Needs to be active against yeast and mold.</td>
</tr>
<tr>
<td>0.80 - 0.89</td>
<td>Needs to be active against Gram-positive bacteria, yeast and mold.</td>
</tr>
<tr>
<td>0.90 – 0.99</td>
<td>Needs to have a broad spectrum of antimicrobial activity (e.g. Gram-negative and Gram-positive bacteria, yeasts and mold).</td>
</tr>
</tbody>
</table>
Formulation Factors - Solubility

- Water is necessary for microbial growth to occur.

- Microorganisms will only proliferate in the water phase.
  - In emulsions, microorganisms will grow in the aqueous phase, but will also collect at the interface between the oil and water phases of the formulation.

- To prevent microorganisms from growing, the non-traditional or alternative preservative has to be present in the aqueous phase.
Solubility of Alternative Preservatives

Examples of Water Soluble Blends
- Phenoxyethanol/Caprylyl Glycol/Hexylene Glycol
- Phenethyl Alcohol/Caprylyl Glycol/Trideceth-8
- Propanediol/Pentylene Glycol/Phenethyl Alcohol
- Levulinic acid/Sodium levulinate/Glycerin/Aq.

Examples of Limited Water Solubility
- Caprylyl Glycol (1,2-Octanediol) - up to 0.5%.
- Phenoxyethanol and Caprylyl Glycol - up to 1.2%.
- Phenethyl Alcohol and Caprylyl Glycol - up to 0.6%.
- Ethylhexylglycerin - up to 0.2%.
- 1,2-Decanediol (Decylene Glycol) - water immiscible.
- 1,2-Hexanediol and 1,2-Octanediol - up to 1%.
Incorporation of a Limited Water Soluble Alternative Preservative into a Product Formulation

- Use a water miscible solvent to dissolve a limited water soluble alternative preservative.
  - Ethanol
  - Propylene glycol
  - Glycerin
  - Glycerol
Compatibility with Other Cosmetic Raw Ingredients

- Alternative preservatives should be compatible with other raw ingredients in a product formulation.

- Examples of known incompatibilities:
  - Caprylyl Glycol
    - Nonionic surfactants will form micelles containing Caprylyl Glycol and making it unavailable for preserving the formulation.
  - Ethylhexylglycerin
    - Ethoxylated surfactants can neutralize the preservative boosting effects of ethylhexylglycerin.
  - Myristamidopropyl PG – Dimonium Chloride (Phospholipid)
    - Anionic based product formulations will inhibit the preservative boosting effect of phospholipids.
    - Incompatible with Carbopol.
  - Phenethyl Alcohol/Caprylyl Glycol/Trideceth-8 Blend
    - Strong oxidants and strong alkalis causes decomposition.
    - Nonionic surfactants may cause deactivation of antimicrobial activity.
Antimicrobial Spectrum and Potency

- Spectrum of activity and potency of an alternative preservative can be determined by performing Minimum Inhibitory Concentration (MIC) and Minimum Lethal Concentration (MLC) testing:
  - **MIC** – is the lowest concentration needed of a compound to inhibit the growth of microorganisms.
  - **MLC** – is the lowest concentration of a compound to have cidal activity against microorganisms.
Examples of MIC/MLC Test Data for Caprylyl Glycol and a Botanical Extract

<table>
<thead>
<tr>
<th>Alternative</th>
<th>MIC/MLC (%) vs. Bacteria</th>
<th>MIC/MLC (%) vs. Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preservative</td>
<td>S. aureus</td>
<td>S. epidermidis</td>
</tr>
<tr>
<td>Caprylyl glycol</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Botanical Extract</td>
<td>0.125</td>
<td>0.25</td>
</tr>
</tbody>
</table>

MIC/MLC(%) vs. Fungi

C. albicans | A. brasiliensis | P. chrysogenum

0.6 | 0.6 | <0.015 | <0.015 | <0.015 | <0.015

MIC/MLC (%) vs. Bacteria

S. aureus | S. epidermidis | E. coli | E. gergoviae | Ps. aeruginosa | B. cepacia

Botanical Extract

0.125 | 0.25 | 0.25 | 0.25 | 0.06 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25

MIC/MLC (%) vs. Fungi

C. albicans | A. brasiliensis | P. chrysogenum

>1.0 | >1.0 | >1.0 | >1.0 | >1.0 | >1.0
Examples of MIC/MLC Test Data for Methylpropanediol/Capryl Glycol/Phenylpropanol and Glyceryl caprylate/Glyceryl Undecylenate Blends

<table>
<thead>
<tr>
<th>Alternative Preservative</th>
<th>MIC/MLC (%) vs. Bacteria</th>
<th>MIC/MLC (%) vs. Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylpropanediol/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caprylyl Glycol/Phenylpropanol</td>
<td>S. aureus 1.0 S. epidermidis 0.5</td>
<td>E. coli 0.5 E. gergoviae 1.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Glyceryl caprylate/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyceryl undecylenate</td>
<td>S. aureus 0.06</td>
<td>S. epidermidis 0.06</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ps. aeruginosa 0.5</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>
Chelating Agents

- Chelating agents should be included in a product formulation because it increases the permeability of cell membranes and makes them more sensitive to antimicrobial agents.

- Types of chelating agents used in product formulations with alternative preservatives.
  - EDTA
  - Lactic Acid
  - Citric Acid
  - Phytic Acid
Antioxidants

- Inclusion of antioxidants in a product formulation will further aid in the preservation of a product formulation by preventing degradation of ingredients by oxidation.

- Types of Antioxidants that are Commonly Used in Product Formulations:
  - Ascorbic acid [Vitamin C] (up to 3%).
  - BHA (0.02%)
  - BHT (0.02%)
  - Propyl Gallate (0.1%)
  - P-Butyl Hydroquinone (0.1%)
  - Tocopherol
Processing Conditions

- Order of Addition
- pH
- Temperature
Order of Addition During Manufacturing

- Water-soluble alternative preservatives should be added to the water phase.

- Slightly water soluble alternative preservatives should be dissolved in a water miscible solvent for addition to the water phase.
Order of Addition in Emulsions

- Add to the cool-down phase (e.g. <50°C) after emulsion has formed.
- For emulsions that are stabilized by liquid crystals, add ethylhexylglycerin to the hot water phase prior to emulsification.
- Certain alternative preservatives may cause the destabilization of the emulsion (e.g. Caprylyl Glycol).
- To prevent destabilization of the emulsion, may need to increase the concentration of the emulsifier in the formulation (e.g. Glyceryl stearate, PEG-7 Glyceryl cocoate, Laureth-3, Lecithin, etc.).
pH Affects

- **Physical Stability**
  - A low or higher pH of the formulation may cause degradation of an alternative preservative.

- **Antimicrobial Activity**
  - The optimum level of antimicrobial activity for an alternative preservative may be effected if the formulation is at the incorrect pH.
Temperature Affects

- If a formulation is held at a high temperature for a long period of time, the alcohol component of certain non-traditional or alternative preservatives could evaporate from the formulation leading to preservation issues during consumer use.
- Phenethyl Alcohol and Caprylyl Glycol
- Phenoxyethanol and Caprylyl Glycol.
- Phenoxyethanol, Caprylyl Glycol, and Hexylene Glycol
Preservative Adequacy of a Product Formulation

- Need to determine the stability of the antimicrobial activity of the preservative system in a product formulation over time.

- Preservative Challenge Testing
  - Initial Sample (Reference).
  - Artificially Aged Accelerated Sample.
  - Artificial aging conditions must follow the Arrhenius Reaction Rate Theory

  \[
  \text{Accelerated Aging Rate (AAR)} = Q_{10}^{\left[(\text{Te}-\text{Ta})/10\right]}
  \]

  where: \( Q_{10} \) = Thermodynamic Temperature Coefficient
  \( \text{Ta} \) = Ambient temperature
  \( \text{Te} \) = Elevated Temperature
  \( Q_{10} \) = Reaction Rate = 2

  \[
  \text{Accelerated Aging Time Direction (AATD)} = \frac{\text{Desired Real Time}}{\text{AAR}}
  \]
Preservative Challenge Test

Definition: A microbial challenge test that determines the antimicrobial effectiveness of a preservative in a product formulation or an unpreserved product formulation against selected test microorganisms.
Preservative Challenge Test Method

GENERAL ASPECTS

- Standardized Microbial Suspension
- Inoculated Product
- Removal of 1.0 gram Aliquots at Specified Intervals
- Neutralization of Preservative Antimicrobial Activity
- Recovery of Surviving Microorganisms
- Calculation of Percent or Log₁₀ Reduction
Different Types of Preservative Challenge Test Methods

- Pharmacopoeia Challenge Test Methods
  - USP Antimicrobial Effectiveness Test
  - BP/EP Test for Efficacy of Antimicrobial Protection
  - JP Preservatives - Effectiveness Test

- Consensus Challenge Test Methods
  - CTFA (PCPC) – 5 types of challenge test methods
  - ASTM E640-78 – Standard Test Method for Preservatives in Water Containing Cosmetics

- Standard Challenge Test Methods
  - AOAC 998.10 – Preservative Challenge Efficacy Test of Non-Eye Area Water Miscible Products
  - ISO 11930 – Cosmetics - Microbiology - Efficacy Test and Evaluation of Preservation of a Cosmetic Product

- In-House Challenge Test Methods

- Other Challenge Methods - D-Value (Linear Regression), Direct Contact Membrane Filtration, PET Method for Powdered Eye Shadows
Irritation/Sensitization Factors

- Need to evaluate the presence of an alternative preservative in a product formulation for the possibility of causing one or both of the following responses during consumer use:

  - **Irritation**
    - Acute (Single Application)
    - Cumulative (Repeated Exposure)
    - Photoirritation

  - **Sensitization**
Cost Implications

- Use may add cost to the formulation because:
  - An alternative preservatives generally cost more than traditional preservatives.
    - Phenoxyethanol, Caprylyl Glycol, Hexylene Glycol:
      - In comparison to the cost of Methylparaben, there is a (+) 1200% cost difference per pound.
      - In comparison to the cost of Phenoxyethanol, there is a (+) 1800% cost difference per pound.
    - Glyceryl Caprate:
      - In comparison to the cost of Methylparaben, there is a (+) 88% cost difference per pound.
  - A higher concentration of an alternative preservative maybe needed.
    - A use concentration of 1-5% vs. 0.5 to 1.0% in comparison to traditional preservative use levels.
Conclusions

➢ The usage of alternative preservatives are new options for preserving product formulations.

➢ Need to consider many factors before using an alternative preservative in a product formulation.
Questions
Thank You