Esters with Improved Hydroalcoholic Solubility

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Background

Hydroalcoholic solutions are mixtures of water (hydro) and ethanol (alcohol). The use of this type of solution occurs commonly in pharmaceutical applications where increased solubility of actives in increased by moving from an aqueous solution to hydroalcoholic based formulations. As personal care products.

In the preparation of products with materials that contain actives, water can commonly be ineffective in providing the desired solubility. Organic solvents, while of interest, often are of limited use due to concerns over toxicity and irritation.[1] Aromatic compounds can cause paralysis of the central nervous system and are irritating to the skin. Methanol is toxic; butyl and amyl alcohol are irritating. This leaves only a handful of compounds useful to the formulator. These include glycerin, ethanol, isopropyl alcohol, propylene glycol, and hydroalcoholic soluble esters. Simple fatty esters like stearyl stearate are insoluble in water and hydroalcoholic solutions, limiting their usefulness to oil based products and emulsions.

Solutions are being used with increased frequencies that have water and alcohol, most commonly ethanol. These hydroalcoholic solutions are of growing importance to the cosmetic chemist. The ability to add other materials like esters to improve the cosmetic aesthetics is of great importance, since hydroalcoholic solutions lacking soluble emollients and feel modifiers are not well accepted by consumers.

Definitions

In the pharmacy field, several different terms are used to describe specific types of alcoholic, or hydroalcoholic solutions.

*Spirit*s- alcoholic or hydroalcoholic solutions of volatile substances, commonly volatile oils in alcohol. The alcohol concentration ranges from 62-85%. This type of product often is used as a flavors. Addition of water to spirits often results in a turbid suspension or phase separation,

Tinctures **–** alcoholic or hydroalcoholic solutions of non-volatile compounds. An example is Tincture of Iodine. This tincture is prepared dissolving iodine in alcohol. This product was commonly used as an antiseptic. The concentration of the active generally is no higher than 20g of active in 100 ml of solvent. Tinctures are commonly used to improve the efficiency of extraction of water based systems for actives extracted from cellular sources and from plant exudates.

Cosmetic Usage of Hydroalcoholic Products

Hydroalcoholic cosmetic compositions are often topically applied to skin, to treat the face. Fine lines, wrinkles, hyper-pigmentation, and pore problems are of great concern to consumers.[2] Hydroalcoholic solutions have been disclosed to treat pimples, and red spots.[3] The formulation includes alpha hydroxy acid, bisabolol and glycyrrhizinate salts.

It has also been found that ethanol denatured with menthol promotes shrinkage of the skin pores when applied topically[4]. The preferred concentration of menthol is 1.3 to 2% by weight, while the preferred concentration of ethanol ranges from 12% to 20% by weight. The preferred water concentration ranges from 40% to 70 % by weight. The cosmetic products that can be made using this technology include cleansers, toners, creams, gels, serums, masks and lotions. Humectants are additives used in the formulation, The humectants are polar materials and include glycerin, propylene glycol, sorbitol, ethoxylated glycerin and related materials. Emollients are also added. They are silicones, hydrocarbons and esters. Because of their limited solubility in these systems emollient materials are used at either low concentrations, or in emulsions.

A study was undertaken to determine if esters could be made that have improved hydroalcoholic solubility,

Esters

The presence of one or more hydroxyl groups in the ester increases polarity and consequently two hydroxy acids were chosen for evaluation. The acid shown below (Table 1 and 2) was reacted with the specified alcohol (Table 3) to make the desired ester (Table 4 and 5) and water.

Table 1 **Hydroxy Di-acid** **(1) Malic Acid**
HOC(O)-CH$_2$-CH-C(O)OOH **|** **OH**

Table 2 **Di-hydroxy Di-acid** **(2) Tartaric Acid**
HOC(O)-CH-CH-C(O)OH **| |** **HO OH**

Table 3 Alcohol Reactants	
No.	**Alcohol**
1.	Butanol
2.	Amyl alcohol
3.	Hexanol
4.	Methylamyl alcohol
5.	Octanol

Table 4
Hydroxy Di-esters
(1) Malic Acid Based

|

ROC(O)-CH_2-CH-C(O)OR
|
OH

Table 5
Di-hydroxy Di-esters
(2) Tartaric Acid Based

ROC(O)-CH-CH-C(O)OR
| |
HO OH

Hydroalcoholic Solubility

The procedure shown in Table 6 is used to determine if the ester is soluble at 5% in a hydroalcoholic solution made up of half water, half ethanol. In subsequent studies, the concentration is increased by 1% until a haze is noted. The last sample that remained clear is reported as the end point.

Table 6 **Hydroalcoholic** **Test Method** **1:1 Water to EtOH** **5% Ester**
1. Add 47.5 grams of ethanol. 2. Add 5 grams of ester. 3. Mix well 4. Record clarity. 5. Add 47.5 grams of DI water. If a solution was attained at this 5 % concentration, the above was repeated increasing the concentration of ester one percent at a time, until a haze is noted.

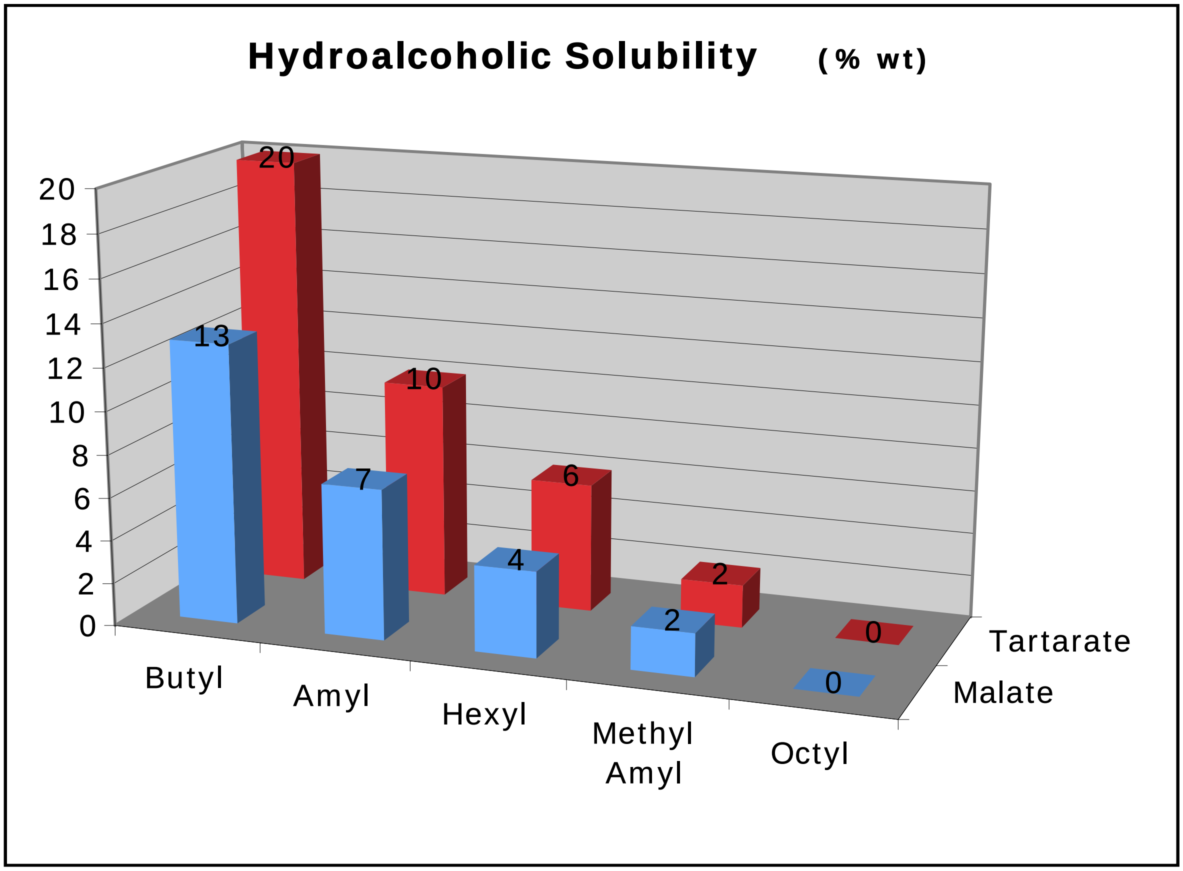
Results

The results of the study are shown in Tables 7 and 8, and graphically in Graph 1.

Table 7 Hydroalcoholic Solubility Malate Esters		
1:1 EtOH / H_2O % Weight		
Alkyl Group	M.W.	H.A. Solubility
Butyl	246	13
Amyl	274	7
Hexyl	303	4
MethylAmyl	303	2
Octyl	331	0

Table 8 Hydroalcoholic Solubility Tartaric Esters		
1:1 EtOH / H_2O % Weight		
Alkyl Group	M.W.	H.A. Solubility
Butyl	262	20
Amyl	290	10
Hexyl	319	6
MethylAmyl	319	2
Octyl	346	1

Graph 1



Conclusions

1. As the molecular weight of the alcohol increases, the hydroalcoholic solubility decreases. That is the resulting ester becomes more hydrophobic.

2. Branching in the ester also decreases hydroalcoholic stability. That is the resulting ester becomes more hydrophobic.

3. The tartarate esters, because of their additional hydroxyl groups exhibit improved hydroalcoholic solubility in linear systems having 6 or less carbon atoms.

4. Introducing branching into the C6 hydrophobe results in two esters that have the same hydroalcoholic solubility.

References

1. Pharmaceutical Solutions II: Nonaqueous, Inter-net article

2. US Patent Application 2006/0110416, Ryles at al, May 25, 2006

3. U.S. Patent 5,428,710 to Slavtcheff at al

4. US Patent Application 2006/0110416, Ryles at al, May 25, 2006