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Article

How to Predict Efficient Active Delivery in Cosmetics Using HSP

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TAGS: Skin Care   Cosmetic Formulations   Cosmetic Active Ingredients

Active ingredients are vital to many cosmetic formulations and yet they can be difficult to work with. They can destabilize formulations and loose efficacy during storage. By using a joint approach of practical Hansen Solubility Parameter (HSP) determination (using HSPiP), theoretical HSP predictions and then implementation using Formulating for efficacy (FFE™), this article will show an intelligent way to formulate for optimized active ingredient delivery.

In this article, the HSP of an oil-based active ingredient and a water-based active ingredient will be determined and then implemented in the formulation of an emulsion system.

Lyco-Sol™ by Gattefossé

It is an oil-soluble **antioxidant**, with the cosmetic active ingredient of Tomato lycopens. **Lycopene** has been of great interest to the cosmetic industry due to its strong in vitro antioxidant activity[1]. Lycopene can replenish cutaneous antioxidant supply and reduce/prevent UV-induced skin damage[1,2]. Lycopene may also be able to **reduce skin aging**, and formation of furrows and wrinkles[3].

Developing topical formulations for lycopene is challenging due to its strong lipophilicity, which makes it insoluble in several commonly used cosmetic oils. Additionally, its strong lipophilicity also limits its penetration across the stratum corneum (SC) (i.e., epidermis’ outermost layer) and into viable skin layers due to its affinity with SC components and tendency to be retained in this layer[4].

Matrixyl® 3000 from Sederma (Croda)

It is a hydrophilic peptide blend; it contains the cosmetic active ingredients **Palmitoyl Tripeptide-1** & **Palmitoyl Tetrapeptide-7**. Palmitoyl tripeptide-1 is a messenger peptide for collagen renewal. It is comparable to retinoic acid with regards to its activity; however, it does not trigger irritation.

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It stimulates collagen and glycosaminoglycan synthesis, reinforces the epidermis, and helps diminish wrinkles[5]. Palmitoyl tetrapeptide-7 is a fragment of immunoglobulin G. Palmitoyl tetrapeptide-7 decreases IL-6 secretion by keratinocytes in a basal setting and serves as an **anti-inflammatory ingredient** after UVB exposure[6].

Practically Determining the HSP of Commercial Active Ingredients

VLCI practically determined the HSP of Lyco-Sol™ and Matrixyl® 3000. This was achieved by adding 0.25 g of the active ingredients (in their recommended use level of 3% and 5%, respectively) to 5 mL of various solvents and solvent blends with a known HSP. The samples were shaken and left to dissolve. The samples were then visually assessed with a qualitative rank from 1 to 6 (see Figures below)), where '1' meant the product was completely dissolved, and '6' meant there was no interaction between the solvent and the product. Scores from 2-5 indicated various stages of dissolution.

The Visual Differences seen in the Lyco-Sol™ Samples

The Visual Differences seen in the Matrixyl® 3000 Samples

When solvents are combined, the HSP of the resulting blend changes to one that lies between the original solvents, in proportion to the amount of each solvent used. By using sets of solvent blends that cross the boundary of the polymers' solubility sphere, it was possible to accurately define the outer limit of the sphere.

For more information on the HSPs, see the articles:

Develop Better Cosmetics Via Science-based Formulation using HSP
Predicting Ingredient Compatibility Using HSP in Cosmetic Formulations

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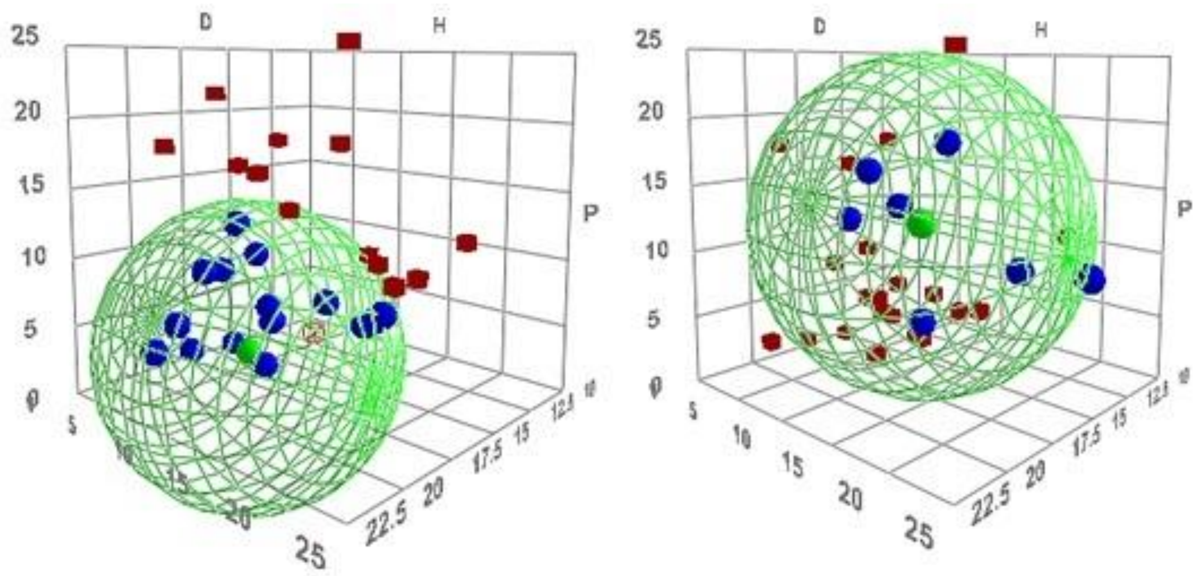
This ranking data was then entered into the HSPiP software, which defined a 3D spheroidal cluster of the solvents that dissolved the test material. This cluster is called the **Hansen Solubility Sphere** and its central coordinates (**δD**, **δP** and **δH**) define the core solubility parameters of the test material as shown in the figure below:



The HSP Sphere of Lyco-Sol™ (left) and Matrixyl® 3000 (right)

The software also performed an analysis of the "fit" of the data to the parameters it had determined, highlighting the validity of the result, which could indicate if more experimental data was needed.

Product Name	D	P	H	R
Lyco-Sol™	17.57	2.48	7.50	11.4
Matrixyl® 3000	19.66	13.95	17.55	11.0

As expected, the water-soluble Matrixyl® 3000 had larger Polar and Hydrogen bonding values than the oil-soluble Lyco-Sol™.

Selecting Compatible Solvents for Dissolving Actives

For ingredient suppliers, HSP can help determine which solvent(s) the active ingredient should be pre-dissolved in. The FFE software predicts the Ingredient Active Gap (IAG), i.e., the similarity of the cosmetic active ingredient and cosmetic ingredient.

Using Lyco-Sol™ as an example, there was an IAG of 6.33 between apricot oil and lycopene. In

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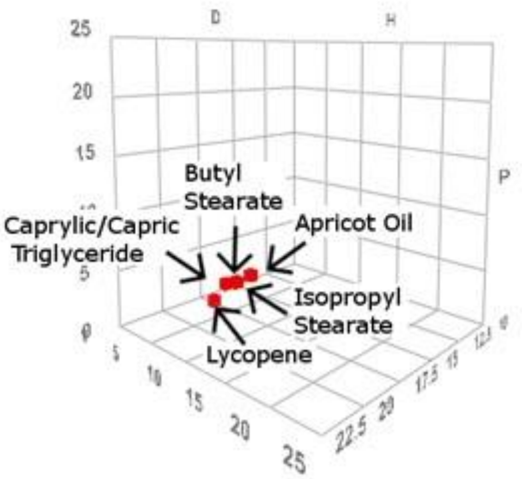
general, the smaller the IAG, the more alike the active ingredient and cosmetic ingredient, and as "like dissolves like" the solubility will be higher, this is akin to the HSP distance on HSPiP.

The table and figure below show that apricot oil is relatively close to lycopene; however, there are some other cosmetic ingredients, which are more compatible with lycopene.

Ingredient	IAG to Lycopene
Caprylic/capric triglyceride	1.7
Butyl stearate	2.8
Isopropyl stearate	3.01
Apricot oil	6.33



Lycopene and Oils in HSP Space

Practical HSP vs Predicted HSP?

However, these two cosmetic active ingredients are not supplied as pure ingredients, they are available as blends. The INCI names below define the component of each blend.

Matrixyl® 3000 INCI: Glycerin, Aqua (Water), Butylene Glycol, Carbomer, Polysorbate 20, Palmitoyl Tripeptide-1, Palmitoyl Tetrapeptide-7

Lyco-Sol™ INCI: Prunus Armeniaca (Apricot) Kernel Oil, Solanum Lycopersicum (Tomato) Fruit/Leaf/Stem Extract

From this, it is clear that the HSP, as practically determined, will be characterizing the blend of ingredients, of which, those in a higher concentration (e.g. glycerin and apricot oil) will have the largest effect. This information is valuable for formulating with the active ingredients into a stable system but the HSP of the pure actives is needed to predict the delivery of the active ingredients. HSP of the pure actives can be predicted by either HSPiP or FFE™.

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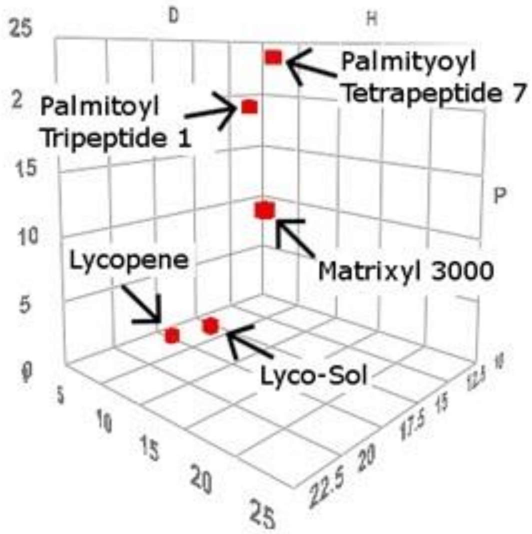
The table below lists the predicted vs determined HSP for the active ingredients:

Ingredient	HSP Method	D	P	H	MVol	ASG	Melting Point (°C)
Lyco-sol™	Determined	17.57	2.48	7.5	-	-	-
Lycopene	Predicted	17.3	0	1.7	598.8	10.2	158.7
Matrixyl 3000	Determined	19.66	13.95	17.55	-	-	-
Palmitoyl Tripeptide-1	Predicted	16.5	20	10.2	519.7	16.4	178.9
Palmitoyl Tetrapeptide 7	Predicted	15.9	23.8	11.8	588.7	16.4	178.9

In each case, the HSP of the overall blend was different from the HSP of the pure active ingredient as shown in the figure below:



HSP of the Active Ingredients

The FFE software determined the active skin gap (ASG), which refers to the compatibility of the ingredient and the outer layer of the skin (i.e., stratum corneum, SC). In general, the smaller the gap, the more compatible the ingredient is with the SC. This means that it will also 'mix' better with the skin. Skin penetration can be considered as a way of 'mixing' the ingredient and the skin; therefore, formulators generally like smaller ASG numbers.

All 3 active ingredients in this study had a relatively large ASG, indicating that skin penetration of these ingredients can be challenging. There are cosmetic active ingredients whose ASG is smaller. An example is octadecenedioic acid, a well-known **skin whitening agent**; its ASG is 3.07.

Active Ingredient Delivery; Oil Phase Formulation

The ability of HSP to improve delivery of an active ingredient was tested, by designing the oil phase. A typical face cream usually contains about 20% oil phase. In this example, the recommended concentration of 5% Lyco-Sol™ was used along with two emollients that provide a good skin feel and may even be able to help the delivery of Lyco-Sol™ into the skin.

1. First, two randomly selected emollients were tested; heptyl undecylenate (10%), a light emollient, and isopropyl myristate (5%), which is known for its ability to enhance the penetration of certain active ingredients into the skin[7].
2. Then, two emollients recommended by FFE were tested, including glyceryl myristate (9.9%) and C12-15 alkyl benzoate (5.1%).

Table below shows a randomly selected emollient combination, and an optimized **emollient** combination recommended by FFE for Lyco-Sol, and the results of the skin penetration simulation.

		Concentration (%)	MVol	IAG	SFG	On at 24h (%)	In at 24h (%)	Out at 24h (%)
Randomly selected emollients	Heptyl undecylenate	10	324.4	5.38	27.5	90	9	1
	Isopropyl myristate	5	315	5.75				
Emollients selected by FFE	Glyceryl myristate	9.9	310.1	8.14	7.7	69	27	5
	C12-15 alkyl benzoate	5.1	334.6	5.02				

In the table, "On" means percentage left on the surface of the skin, "In" means percentage in the epidermis and "Out" means percentage in the dermis (and beyond).

The molar volumes (MVol) of all emollients were fairly similar to each other and also to that of Lyco-Sol™. The IAG values were comparable as well. The biggest difference was seen in the skin formulation gap (SFG), which refers to the closeness of the skin and the formulation. The smaller the gap, the closer the skin and formulation and higher the chances that the cosmetic active ingredient would penetrate into the skin, instead of staying on the surface of the skin and being washed away at the end of the day.

As UV-induced skin damage occurs in the epidermis and dermis, it is important for lycopene to be available in these layers. As we can see from the simulation data, the emollients selected based on their HSP were much more efficient at delivering the active ingredient into these layers, so the customer would get the most benefit from their product.

Active Ingredient Delivery; Water Phase Formulation

Matrixyl® 3000 is a water-soluble active. In this example, the water phase of an emulsion was designed.

- First, propanediol (5% concentration) was selected as a **humectant**, Matrixyl® 3000 was used in its recommended concentration of 3% and water made up the remaining 62%. Propanediol has a low molar volume (72.5), but it has a good ISG and IAG.
- Then, FFE suggested pentylene glycol to improve this blend. Pentylene glycol is a moisturizer, it has a higher molar volume (105.7), and its IAG and ISG are similar to that of propanediol.
- Finally, FFE suggested ethoxydiglycol as a **potential good solvent**. It has an even higher molar volume (135.2), its IAG is slightly higher than that of propanediol and pentylene glycol, while its ISG is lower than that of the other two ingredients (*see the table below*).

Table below shows a randomly designed water-phase, and a water-phase optimized by FFE for Matrixyl 3000, and the results of the skin penetration simulation.

	INCI Name	Concentration (%)	MVol	IAG	ISG	On at 24 h (%)	In at 24h (%)	Out at 24h (%)
Sample 1	Water	62	18	26.19	7.1	83.5	16.1	0.4
	Propanediol	5	72.5	8.05	11.72			
Sample 2	Water	57	18	26.19	7.1	65.8	33.9	0.3
	Propanediol	5	72.5	8.05	11.72			
	Pentylene glycol	5	105.7	7.61	12.52			
Sample 3	Water	52	18	26.19	7.1	54.5	45.4	0.1
	Propanediol	5	72.5	8.05	11.72			
	Pentylene glycol	5	105.7	7.61	12.52			
	Ethoxydiglycol	5	135.2	10.58	6.81			

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In the table, “On” means percentage left on the surface of the skin, “In” means percentage in the epidermis and “Out” means percentage in the dermis (and beyond).

Matrixyl® 3000 supports the activation of the cutaneous repair process, in particular at the papillary dermis (i.e., the uppermost layer of dermis)[8]. Since the main target area is the dermis, an increase in “In” would be desired from the formulation. When looking at the penetration data in the table above, one can tell that the optimized formulation enhanced the delivery of Matrixyl® 3000 into the skin significantly.

Conclusion

By using practical and theoretical HSP determinations, the formulation process was performed efficiently and used intelligent predictions at multiple stages. This study demonstrated how raw material suppliers can utilize these techniques for the selection of solvents for their active ingredients while formulating the final products in order to:

- Dissolve their ingredients
- Ensure compatibility and stability

Moreover, it was also demonstrated how different layers of the skin can be effectively targeted for active delivery by implementing HSP, which ultimately improves efficacy.

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