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Delivery of Smart, Functional Innovative Materials: A Supramolecular Chemistry Approach to Anti-Aging & Acne Products

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Recently, the importance of introducing supramolecular chemistry to cosmetics and personal care has become evident. Rather than synthesize a new molecule by linking the covalent chemical bonds in the desired arrangement of different atoms or groups via a series of chemical reactions, the two or more molecules chosen are designed in such a way that they self-assemble into organized entities. These generate new or enhanced functionality useful for cosmetic and personal care applications. Based on this concept, a smart hydrogel delivery system has been created which undergoes transformation from a liquid at room temperature to a shear sensitive hydrogel upon contact with skin.

Further, supramolecular salicylic acid has also been developed which is soluble in water without the need of any other solvents at low pH. This material can be readily incorporated into either unbuffered or buffered formulations.

Introduction

Supramolecular chemistry has expanded the scope of synthetic chemistry and grown rapidly in the last few decades [1,2,3,4,5]. The technology provides an approach to formation of Nano scale systems and allows design and development of smart, functional materials with applications ranging from biology to materials science. While traditional synthetic chemistry deals with covalently bonded molecules, supramolecular chemistry deals with organized entities of intermolecular complexes. Such complexes consist of the association of two or more molecules held together by non-covalent intermolecular bonds. Examples of these include: hydrogen bonds, dipole-dipole interactions, van der Waals forces, cation-pi interactions, pi-pi bonds, CH/pi interactions, or hydrophobic effects, and etc.

Supramolecular chemistry may be defined as "chemistry beyond the molecule". Its development requires the use of multidisciplinary science- combined with the specific manipulation of selective non-covalent intermolecular interactions.

The most important benefits of such complexes, especially in the field of cosmetics and personal care, are their reversibility and the fact that one or more properties that can be changed in a controlled manner by external stimuli, such as temperature, pH, moisture, stress and etc.

A Smart Hydrogel Delivery System

Hydrogels are ideal vehicles for the delivery of cosmetic and personal care ingredients. Typical thermo-reversible hydrogels previously known are those that remain in a viscous gel form below the gel melting temperature and are capable of transforming into a fluid liquid above the gel melting temperature. By contrast, reverse thermo-reversible hydrogel systems are known in which the system viscosity increases with an increase in temperature and decreases with a decrease in temperature. Such a system exhibits a solution to gel (sol-gel) transition which transforms a low viscosity solution to a higher viscosity gel form as the temperature increases. The sol-gel transition temperature of such a reverse thermo-reversible hydrogel system can be controlled by adjusting the solution concentration to produce compositions that exhibits a sol-gel transition at physiologically useful temperatures. **Such smart hydrogel systems constitute one of the most promising avenues for the development of novel cosmetic and personal care products.** In these cases, the product has a low viscosity at room temperature, and then exhibits a sharp viscosity increase resulting in transformation to a shear-sensitive gel form following a temperature increase from room temperature to the temperature of human skin which is about 32-33 °C or 90-91 °F.

Such smart hydrogel delivery systems are useful wherever it is desirable to handle a composition in a liquid state, or the performance of the composition in a gel form, such as solubilizing active ingredients in a liquid state and producing sustained or controlled release of active ingredients in the (delivery) gel state.

There are several known polymeric materials that exhibit reverse thermo-reversible behavior in water. These include: poly(N-isopropylacrylamide), poly(ethylene glycol)-b-poly(lactic acid)-b-poly (ethylene glycol) and poly(ethylene oxide)-b-poly(propylene oxide)-b-poly (ethylene oxide) copolymers. Aqueous solutions of these polymeric materials display sol-gel transition temperatures. They demonstrate sharp viscosity increases and transform from a low viscosity solution to a hydrogel when the temperature increases across the sol-gel transition temperature of the system.

To achieve the desired sol-gel transition temperature at physiologically useful temperatures, a higher concentration of the above-mentioned polymeric materials has to be used. This in turn increases the solution viscosity and can result in unfavorable physiological interaction and toxicity concerns during use. For example, about 18-20 wt. % aqueous solution of Poloxamer 407, a poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) block polymer available commercially from BASF, are needed to produce a sol-gel transition temperature at about 25 °C. The freedom to use these polymeric materials in water with adjustable sol-gel transition temperatures at physiologically useful temperatures without employing higher concentrations of these polymeric materials is limited.

As described above, recent advances in supramolecular chemistry have made it possible to develop smart hydrogel systems that transform from a liquid to a shear- sensitive hydrogel upon contact with skin without above mentioned disadvantages [6]. One such system consists of water- soluble supramolecular complexes specially designed for formulating smart thermo-responsive hydrogel products for cosmetic and personal care applications [7]. An example of such a material is IntelliGel® BS, manufactured by Broda Tech, LLC. The complexes are readily soluble in water and form a clear, transparent hydrogel with a desirable sol-gel transition temperature at physiologically useful temperatures.

This useful system is comprised of a water-soluble block copolymer and at least one of a class of water insoluble, associative gelling adjuvants. The associative gelling adjuvants are water- insoluble and are not capable of viscosifying or gelling water when they are present in water by themselves! **Due to their unique complex structure comprised of both hydrophilic and hydrophobic chain segments, such materials can also help dissolve water- insoluble, or sparely soluble active ingredients without need of any other solvents.** *Such materials have an excellent safety profile for applications such as anti-aging skin care products.* Products formulated with such a delivery system will exhibit a transition from liquid to gel upon contact with skin at room temperature. They also have other sensory benefits such as improving skin texture; smooth fine lines and leaving a long lasting, virtually non-detectable film on skin. **As such, materials like these offer a new approach to anti-aging products.**

A smart hydrogel delivery system can be prepared by dissolving such complexes in water, either at room temperature or heated at about 60 °C. The sol-gel transition temperature of the delivery system can be controlled by solution concentration. Figure 1 show before and after liquid- to- gel transition pictures of an experimental smart hydrogel system from room temperature in a fluid liquid form at 22 °C (a) to a higher temperature in a solid gel form at 26 °C (b). The experimental solution prepared has an inherent sol-gel transition temperature at 24 °C.

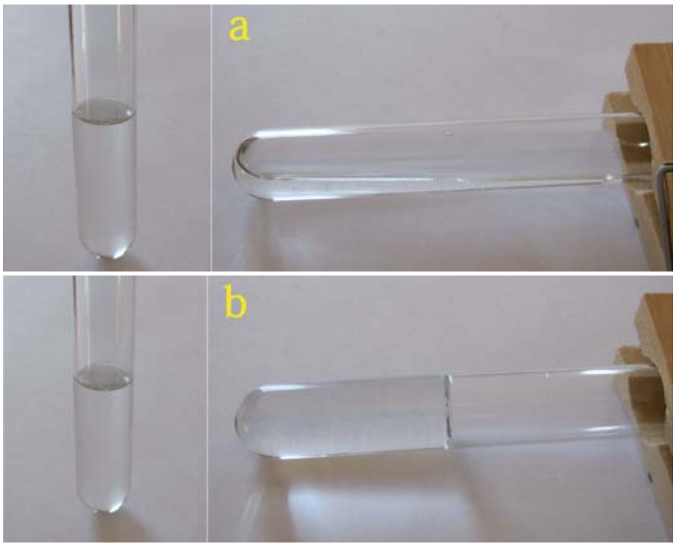

Figure 1: (a) is in a fluid liquid state at 22 °C, and (b) is in a solid gel state at 26 °C. The experimental solution has an inherent sol-gel transition temperature at 24 °C.

The reverse thermo-reversible property of such gels can be utilized as a smart thermo-responsive delivery system for the formulation of smart cosmetic and personal products. **Such products will stay in a liquid form at room temperature and subsequently transform to a shear sensitive hydrogel upon contact with skin after application.** This “magic” transition in product form upon application on skin is a very attractive feature which offers the opportunity of novel claims and consumer appeal for cosmetic and personal care products.

For example, an anti-aging serum composition was developed with IntelliGel® BS having a sol-gel transition temperature at about 29 °C as shown in Table 1. The formula is a clear and transparent liquid at room temperature and can transform into a shear sensitive gel upon contact with skin after application.

No	Ingredients	Wt.%
1	IntelliGel® BS [a]	16.0
2	De-ionized water	73.4
3	Humectants	7.0
4	Anti-aging actives	2.5
5	Other actives	0.5
6	Other ingredients	0.2
7	Preservatives	0.2
8	Fragrances	0.1

Table 1: Anti-aging Serum

Such gels can also be formulated into a sprayable product. The following alcohol-free insect repellant spray composition is prepared as show in Table 2. The formula is a clear and transparent composition which forms an invisible, long lasting and virtually non-detectable film on skin after application.

No	Ingredients	Wt.%
1	IntelliGel® BS	14.0
2	De-ionized water	69.7
3	IR 3535	10.0
4	Propylene glycol	3.0
5	PEG-400	3.0
6	Preservatives	0.2
7	Fragrances	0.1

Table 2: Alcohol-free insect repellant spray composition

Water-Soluble Supramolecular Salicylic Acid

Salicylic Acid is a naturally occurring active ingredient and can be found in many plants, such as willow bark. It is also known as beta hydroxy acid or BHA and has both cosmetic and medicinal benefits. Salicylic acid has been introduced as a key ingredient in many cosmetic products and also OTC (over-the-counter) drug products over the last several decades. The use of salicylic acid for the treatment of acne, skin wrinkling, skin pigmentation, warts, freckles, dandruff or other skin-related problems is well known in the preparation of cosmetic, personal care and dermatological formulations. Salicylic acid is lipophilic and works as an exfoliating agent to penetrate into the pores, dissolve dead skin cells and enhance skin cell turnover. This cell renewal is accompanied by an overall improvement in the appearance of the skin texture with smoothing effect in a reduction of fine lines and wrinkles.

Studies have shown that salicylic acid is less irritating than skin care products containing alpha-hydroxy acids but has similar or better results in improving skin conditions [8,9,10]. A recent clinical study also demonstrates that salicylic acid is as effective as benzoyl peroxide in acne treatment while provides additional skin care benefits not achievable with acne treatment products containing benzoyl peroxide [11].

Salicylic acid is a weak acid in a colorless crystalline form and is poorly soluble in water (2 g/L at 20 °C). It is soluble in ethanol, propanol, acetone, ethers and other organic solvents that are usually unsafe for use on human skin.

Typical problems that occur when using salicylic acid in preparing cosmetic and personal care products are that the salicylic acid tends to form crystals on standing and precipitate out within various un-buffered formulations. The recrystallization of salicylic acid in the formulation not only significantly reduces the bioavailability of the active ingredient but also cause skin irritation. It is a common practice in the industry to increase the pH with sodium hydroxide. This technique neutralizes part of the free salicylic acid to form water soluble salicylates which increases solubility and therefore reduces recrystallization of salicylic acid in the formula. This approach avoids possible skin irritation caused by low pH systems. Although this common practice helps formulation chemists achieve stable products containing salicylic acid and avoids possible skin irritation; it reduces the efficacy of the salicylic acid and results in a product that is therapeutically less effective.

It is well known that changes in pH have a profound influence on many aspects of the action of therapeutically active ingredients. Salicylic acid is a weak acid in which the proportion of the unionized and ionized components is dependent on the pH of the medium according to the well-known Henderson-Hasselbalch equation (1):

$$pH = pK_a + \log_{10}\left(\frac{[A^-]}{[HA]}\right) \qquad (1)$$

Here, [HA] is the molar concentration of the unionized weak acid, $[A^-]$ is the molar concentration of ionized base and K_a is the acid dissociation constant.

Salicylic acid has a pKa of 3 with a pH value well below 3. Table 3 lists calculated molar percentage of unionized salicylic acid form as a function of pH value based on Henderson-Hasselbalch equation (1). The calculation indicates that it will have only 50% un-ionized salicylic acid at pH 3.0, 23.8% unionized salicylic acid at pH 3.5 and 9.1% unionized salicylic acid at pH 4.0.

pH	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Unionized salicylic acid (mole %)	96.9%	90.9%	75.8%	50.0%	23.8%	9.1%	3.1%	1.0%

Table 3: Unionized salicylic acid (mole %) as a function of pH

The therapeutic action of salicylic acid may be attributed to that of either the ionized or the un-ionized acid fractions alone, or to a combination of both types of fractions and depends on the routes of administration. The efficacy of the skin care product containing salicylic acid depends mainly on the availability of free salicylic acid [12], which is limited with buffers and high pHs. The un-ionized salicylic acid is lipid-soluble and thus diffuses more effectively across the hydrophobic skin epidermal barrier. This allows it to penetrate the pores. By contrast, the ionized fraction is water-soluble, and therefore transfer across the skin's epidermal layer is either zero or negligible. This affects the distribution of the salicylic acid or alters the rate of transfer and attainment of equilibrium concentration at the site of action on the skin.

A number of strategies have been developed for the delivery of salicylic acid in the past. These include encapsulation of salicylic acid particles [13] and the esterification of salicylic acid with polymeric polyols for controlled release [14]. However, these approaches provide only partial solutions for the delivery of salicylic acid with limitations in formulation freedom and reduced therapeutically efficacy. To overcome technical challenges, a recent advancement in supramolecular chemistry has been developed to selectively self-assemble poorly water- soluble salicylic acid into water- soluble organized entities in the form of intermolecular complexes [6]. This novel technological approach utilizes non-covalent, reversible, intermolecular bonding to form water- soluble supramolecular salicylic acid complexes. These properties are quite useful for the delivery of salicylic acid to achieve maximum efficacy and reduced skin irritation at low pHs.

One such complex is a water- soluble supramolecular salicylic acid [15], such as SupraSalix™-16* Supramolecular salicylic acid is readily soluble in water to form a clear and transparent solution with a pH below 3. The release of salicylic acid can be achieved through the dissociation of hydrogen bonded water soluble complexes in water. **Aqueous solutions or hydrogels containing salicylic acid intermolecular complexes are stable over a wide temperature range without recrystallization or discoloration.**

Such complexes provide water- soluble salicylic acid at low or controlled pHs to help achieve maximum efficacy with virtually no skin irritation. By contrast, Salicylic acid can cause irritation even at low use level in the formulation at low pHs [16]. Clinical evaluations of Human Repeat Insult Patch Test (RIPT) for skin irritation and skin

Figure 2: Pictures of before and after acne treatment with formula containing 2% effective salicylic acid at a pH below 3.

sensitization on 50 subjects indicates that there are no identifiable signs or symptoms of primary irritation or sensitization noted for the formulation containing 2% effective salicylic acid at pH 2.5-2.8. This makes it an effective raw material to delivery water soluble salicylic acid at low pHs for people with sensitive skin. The supramolucular salicylic acid provides benefits of salicylic acid with high efficacy at low pHwithout typically associated skin irritation.

The water-soluble supramolecular salicylic acid can meet one of the most demanding formulation challenges typically associated with the use of salicylic acid at low pHs. It can be formulated into various existing products, or newly developed formulations, by simply dissolving SupraSalix* in water without the need for any additional solvents, such as ethyl alcohol, followed by incorporating into various systems either in unbuffered or buffered formulations. However, caution must be exercised when formulating at low pH to avoid ingredients that are susceptible to hydrolytic degradation in acidic conditions.

Supramolecular salicylic acid shows high efficacy in reducing blemishes, soothing inflammation, improving skin appearance and accelerating skin's clarifying process without skin irritation comparing with other OTC acne products on the market. Studies on an OTC acne treatment product, containing 2% effective salicylic acid, demonstrate superior overall performance than existing products. Figure 2 shows pictures of before and after acne treatment with formula containing 2% effective salicylic acid at a pH below 3.

Salicylic acid is a multifunctional active ingredient and can be used in a variety of cosmetic and personal care products. **The potential applications of supramolecular salicylic acid include, but not limited to skin care, anti-acne, anti-dandruff shampoo, hands and foot care, anti-bacteria hand soap bars and cleansers [17], and etc.**

For example, salicylic acid can relieve inflammation and redness. Supramolecular salicylic acid can be easily incorporated into shaving products that contain salicylic acid to help get a closer shave and prevent breakouts. Shaving products containing salicylic acid will help prevent pores from clogging and avoid razor burn while shaving. Aftershave products containing salicylic acid will help to reduce oil secretion, control the enlarged pores and tighten the skin, prevent inflammation and redness caused by close shaving, and kill bacteria. In addition, alcohol-free shave and aftershave products formulated with supramolecular salicylic acid will help keep skin better hydrated.

Conclusions

Smart, functional supramolecular complexes* have been developed by selective intermolecular self-assembly of reversible, non-covalent intermolecular bonds based on the association of two or more molecules. This unique technical approach creates smart and functional innovative materials useful for the development of innovative cosmetic and personal care products.

** manufactured by Broda Tech, LLC.*

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