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Aqueous solubility of high concentrated caffeine using hydrotrope and the application to the anti-cellulite cosmetics

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ABSTRACT

This study presents measurements of the aqueous solubility of caffeine at a temperature ranging from 5 to 40°C. And the low water solubility of caffeine was increased by using a hydrotropic solubilization system. Solubility was measured with a single hydrotropic system of niacinamide or betaine and a mixed hydrotropic system of niacinamide and betaine. As a result, it was possible to prepare a high-concentration aqueous caffeine solution of about 4% at 5.9°C and about 25% at 39.9°C. The modified Apelblat equation was applied to predict the temperature dependence of caffeine solubility in aqueous solutions containing niacinamide, and our experimental data showed good agreement with the correlated values. We propose the results of this study as basic data for the development of anti-cellulite cosmetics.

1. Introduction

Cellulite is a symptom of female secondary sexual characteristics, and approximately 85 - 98% of post-pubertal women have some degree of cellulite (Avram, 2004). Cellulite is not a pathologic condition but is an aesthetically unacceptable cosmetic problem (Bielfeldt et al., 2008). Caffeine augments cyclic adenosine monophosphate (CAMP) through inhibition of phosphodiesterase, resulting in promoting lipolysis by activating lipase, which converts triglycerides into free fatty acids and glycerol (Hexsel et al., 2005; Monteiro et al., 2019). However, caffeine has a challenge in that it has poor water-solubility of about 2% at 25°C.

The solubilization technique is essential in achieving sufficient concentrations of active ingredients to exert desired effects (Savjani et al., 2012). Hydrotropy is generally defined as a molecular phenomenon whereby adding large amounts of one or more secondary solutes, results in a several-fold enhancement of the aqueous solubility of various poorly water-soluble drugs (Kim et al., 2010; Kunz et al., 2016). The chemical structure of hydrotrope, which mediates this phenomenon, is generally composed of two essential parts, hydrophilic anionic groups and hydrophobic aromatic rings (Nidhi et al., 2011). Hydrotropes allow the dissolution of sparingly water-soluble drugs without forming micelles (Kim et al., 2010).

Niacinamide (nicotinamide) has been widely used as a cosolubilizing agent due to its hydrotropic properties. Betaine (trimethylglycine) is a molecule having both quaternary ammonium hydroxide group and carboxylic acid group in one molecule and exists as a zwitterion in solution or a bound state. Niacinamide and betaine, which are generally used as whitening functional raw materials and moisturizers, respectively, in cosmetics, have low toxicity, high solubility, and are economical (Coffman and Kildsig, 1996; Schott and Han, 1977). In this study, niacinamide and betaine were used as hydrotropes to improve the solubility of caffeine in water, and the evaluation of solubility was conducted through solid-liquid equilibrium data for caffeine.

2. Materials and methods

2.1. Materials

Climbazole was purchased from Tokyo Chemical Industry (Japan). Caffeine (98.5%) and niacinamide (98.0%) were purchased from Daejung Chemicals (Korea). Betaine (99.8%) was purchased from

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Danisco (Finland). Purified water was obtained using a Milli-Q® Synthesis.

2.2. Apparatus and procedures

The solubility of caffeine was measured at various temperatures ranging from 5°C to 40°C at atmospheric pressure using a solid-liquid equilibrium measurement apparatus, and the temperature was controlled by an external thermostat with an accuracy of ±0.05°C. The temperature measurement was conducted using a digital thermometer (model 5618B, Hart Scientific, Inc., USA) with an accuracy of ±0.066°C and an indicator (model 1502A, Hart Scientific, Inc., USA). An excess of caffeine was added to purified water in a 50 ml glass tube. To ensure the solid-liquid equilibrium was reached, the solution was stirred by a magnetic stirrer for at least 48h. After sedimentation of the suspension, the clear supernatant solution was extracted by a pipette and filtered through a disposable hydrophilic syringe filter (2μm). The mass of the filtered solution was recorded, and then the filtered solution was evaporated using a centrifugal vacuum dryer. During the drying process, the samples were weighed repeatedly until constant weight to prove the absence of solvents. All masses were measured using an analytical balance (model EPG 214, Ohaus Corp., USA) with an accuracy of ±0.0001g. All experiments were repeated three or more times to increase the reliability of the results, and data were expressed as mean ± standard deviation (Kim et al., 2014)

3. Results and discussion

3.1. Aqueous solubility of caffeine depending on temperature

Prior to the experiment, the solubility of climbazole in various alcohols was measured at different temperatures to check the reliability of the apparatus and experimental procedure. Our measured values were in good agreement with the published experimental data of Kim et al. (2014), demonstrating that the apparatus and experimental procedure are reliable.

For the manufacture of a high concentration aqueous solution of caffeine and its application to cosmetics, it is required data on the exact solubility within the temperature range in which the cosmetics are distributed. Therefore, the concentration of the saturated solution of caffeine was measured for each temperature in the range of 5-40°C (Table 1). The solubility of caffeine increased as the temperature increased, and the solubility at 25°C was 2.12%, but the solubility at 5°C was 0.93%, indicating that the solubility was significantly reduced at low temperature.

Table 1: Saturation concentration of aqueous caffeine solution as a function of temperature

Temperature (°C)	Saturation concentration (%)
5.9	0.9345 ± 0.0100
11.2	1.1446 ± 0.0354
15.0	1.3611 ± 0.0145
20.2	1.7263 ± 0.0390
25.0	2.1203 ± 0.0204
30.0	2.8129 ± 0.0261
35.0	3.6059 ± 0.0411
40.2	4.4435 ± 0.0413

3.2. Aqueous solubility of niacinamide depending on temperature

In this study, niacinamide was selected as a hydrotropic agent to enhance the solubility of caffeine, and the concentration of the saturated solution of niacinamide was measured for each temperature in the range of 5-40°C as preliminary data (Table 2). The solubility of niacinamide increased with increasing temperature. Even at a low temperature of around 5°C, the solubility is 23% or more, and it can be used even at low temperatures with a concentration of 2-5%, which is the standard for functional cosmetics raw materials.

3.3. Changes in aqueous solubility of caffeine by temperature and niacinamide concentration

The tendency of niacinamide to improve the stability of the caffeine solution at low temperatures by preventing the precipitation of caffeine has been confirmed to some extent (Noh and Chun, 2004), but accurate solubility data required for formulation are scarce. Therefore, solubility was measured at the temperature of 5-40°C and niacinamide concentration of 0-5% by adding excess caffeine to an aqueous solution of niacinamide at the predetermined concentrations. As shown in Fig. 1 and Table 3, the solubility of caffeine increased as the temperature and niacinamide concentration increased. The second hypothesis is that similar to the chaotropic effect of breaking the self-association of water, niacinamide acts as an acceptor for π-electrons and water as a donor for π-electrons, thereby changing the dissolution properties of water. The third hypothesis is that niacinamide forms micellar aggregates in water, and caffeine enters the aggregates (Coffman and Kildsig, 1996; Al-Maaieh and Flanagan, 2002; Kim et al., 2010).

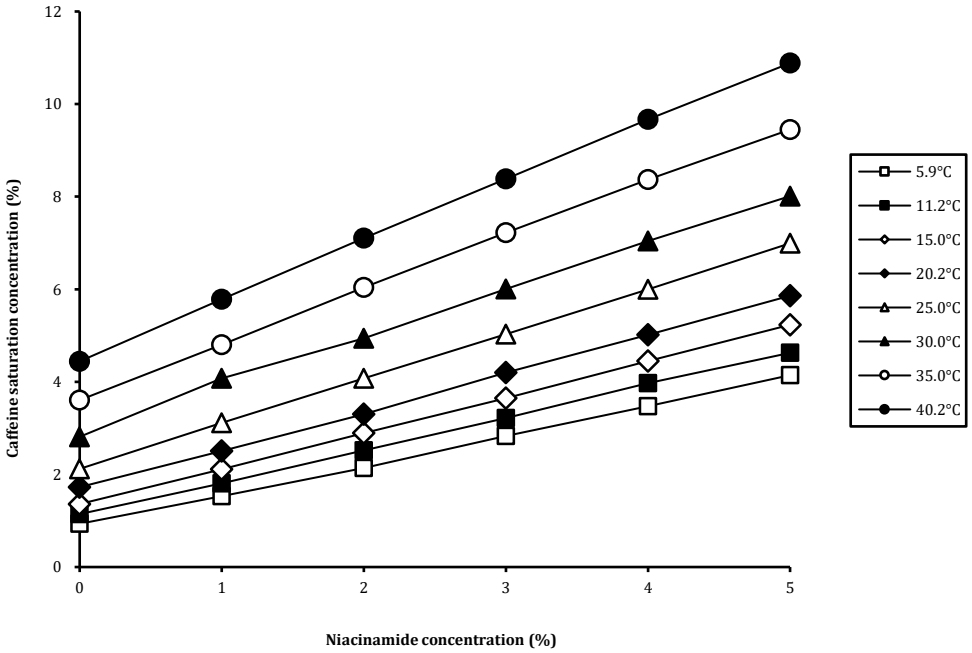

Fig. 1: Correlation between temperature and niacinamide concentration and saturation concentration of aqueous caffeine solution

Table 2: Saturation concentration of aqueous niacinamide solution as a function of temperature

Temperature (℃)	Saturation concentration (%)
5.7	23.6 ± 0.0
10.5	28.7 ± 0.0
15.5	31.9 ± 0.0
21.0	40.0 ± 0.0
24.8	44.6 ± 0.0
30.1	49.0 ± 0.0
35.1	53.4 ± 0.0
40.2	57.5 ± 0.0

Table 3: Saturation concentration of aqueous caffeine solution as a function of temperature and niacinamide concentration

Temperature (°C)	Niacinamide Concentration (%)	Caffeine Saturation concentration (%)	Temperature (°C)	Niacinamide Concentration (%)	Caffeine Saturation concentration (%)
5.9	0.0000 ± 0.0000	0.9345 ± 0.0100	25.0	0.0000 ± 0.0000	2.1203 ± 0.0204
	0.9847 ± 0.0003	1.5291 ± 0.0285		0.9689 ± 0.0006	3.1114 ± 0.0577
	1.9572 ± 0.0003	2.1391 ± 0.0172		1.9185 ± 0.0011	4.0755 ± 0.0545
	2.9150 ± 0.0003	2.8326 ± 0.0095		2.8492 ± 0.0024	5.0275 ± 0.0810
	3.8610 ± 0.0027	3.4740 ± 0.0668		3.7600 ± 0.0014	6.0001 ± 0.0343
	4.7928 ± 0.0009	4.1439 ± 0.0182		4.6504 ± 0.0066	6.9926 ± 0.1327
11.2	0.0000 ± 0.0000	1.1446 ± 0.0354	30.0	0.0000 ± 0.0000	2.8129 ± 0.0261
	0.9819 ± 0.0005	1.8069 ± 0.0491		0.9592 ± 0.0034	4.0782 ± 0.3393
	1.9497 ± 0.0004	2.5173 ± 0.0178		1.9013 ± 0.0003	4.9368 ± 0.0141
	2.9035 ± 0.0007	3.2178 ± 0.0242		2.8199 ± 0.0005	6.0042 ± 0.0154
	3.8412 ± 0.0019	3.9692 ± 0.0467		3.7183 ± 0.0014	7.0433 ± 0.0342
	4.7687 ± 0.0043	4.6262 ± 0.0856		4.5994 ± 0.0014	8.0112 ± 0.0287
15.0	0.0000 ± 0.0000	1.3611 ± 0.0145	35.0	0.0000 ± 0.0000	3.6059 ± 0.0411
	0.9789 ± 0.0003	2.1095 ± 0.0264		0.9520 ± 0.0003	4.8000 ± 0.0263
	1.9421 ± 0.0003	2.8936 ± 0.0137		1.8793 ± 0.0006	6.0371 ± 0.0325
	2.8905 ± 0.0006	3.6485 ± 0.0201		2.7833 ± 0.0004	7.2242 ± 0.0125
	3.8219 ± 0.0007	4.4514 ± 0.0174		3.6651 ± 0.0011	8.3724 ± 0.0265
	4.7384 ± 0.0009	5.2319 ± 0.0183		4.5275 ± 0.0011	9.4498 ± 0.0217
20.2	0.0000 ± 0.0000	1.7263 ± 0.0390	40.2	0.0000 ± 0.0000	4.4435 ± 0.0413
	0.9749 ± 0.0000	2.5085 ± 0.0127		0.9422 ± 0.0003	5.7820 ± 0.0314
	1.9340 ± 0.0000	3.3024 ± 0.0363		1.8579 ± 0.0005	7.1074 ± 0.0258
	2.8741 ± 0.0000	4.1971 ± 0.0394		2.7485 ± 0.0006	8.3840 ± 0.0198
	3.7992 ± 0.0000	5.0189 ± 0.0177		3.6133 ± 0.0011	9.6687 ± 0.0264
	4.7070 ± 0.0000	5.8601 ± 0.0551		4.4558 ± 0.0003	10.8843 ± 0.0062

3.4. Thermodynamic model for prediction of the temperature dependence of caffeine solubility in aqueous solutions with niacinamide

In order to predict the temperature dependence of saturation concentration of caffeine in aqueous solutions with niacinamide, the modified Apelblat model was used. The modified Apelblat model is a semi-empirical model widely used when there is insufficient data on thermodynamic properties. The modified Apelblat equation can be represented as follows:

$$\ln x_1 = A + \frac{B}{T} + C \ln T$$

where x_1 is the mole fraction solubility of caffeine in water; A, B, and C are parameters obtained from the curve fitting of experimental data with a non-linear optimization method; T is the temperature in Kelvin (K).

The experimental data and correlated results are shown in Fig. 2, and the values of three parameters and the average absolute deviation of mole fraction ($AADx$) are displayed in Table 4. The $AADx$ is defined as follows:

$$AAD\chi = \frac{1}{N}\sum_{j=1}^{N}\left|\frac{\chi_{1,j}^{exp} - \chi_{1,j}^{calc}}{\chi_{1,j}^{exp}}\right|$$

The $AADx$ values between experimental data and correlated values were all below 0019, indicating that the experimental data show good agreement with the correlated values obtained by the modified Apelblat model at all temperatures.

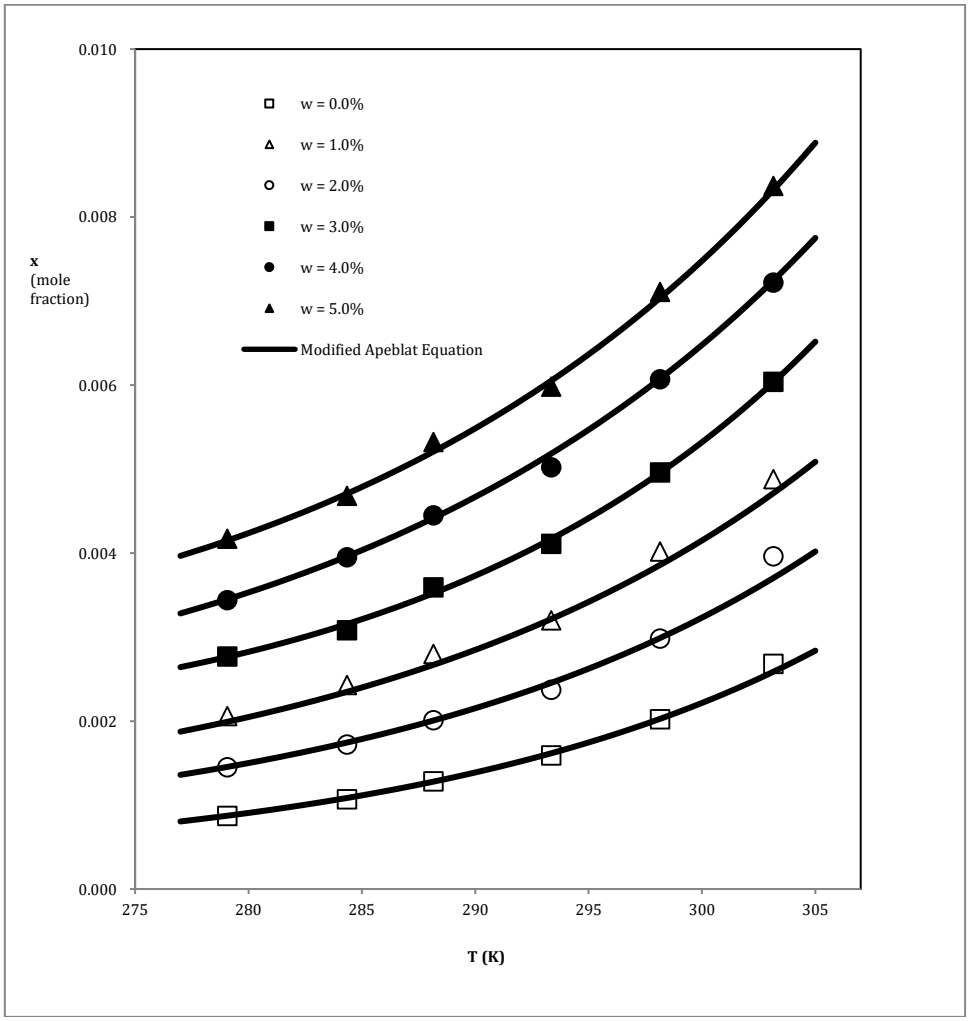

Fig. 2: Experimental data and correlated results about the temperature dependence of caffeine solubility in aqueous solutions with niacinamide

Table 4: Three parameters in the modified Apelblat model for prediction of caffeine solubility in aqueous solutions with niacinamide, and $AADx$ values between experimental data and correlated values

Niacinamide (w/w %)	A	B	C	$AADx$
0.0	-399.91	13897.01	60.92	0.011
1.0	-397.63	14269.90	60.37	0.019
2.0	-395.31	14399.26	59.93	0.010
3.0	-548.42	21367.81	82.92	0.010
4.0	-384.70	14315.25	58.20	0.007
5.0	-399.91	15120.95	60.42	0.008

3.5. Changes in aqueous solubility of caffeine by temperature and betaine concentration

This study also considered betaine as a hydrotropic agent. Since betaine is a zwitterion, it could be hypothesized that as a hydrotropic salt, it would enhance the solubility of caffeine due to the salt-in phenomenon caused by the chaotropic effect. In addition, sucrose is known to induce stacking complexation by promoting the hydrophobic interaction of caffeine-caffeine through the arrangement of water molecules around it (Shumilin et al., 2019), and betaine may also enhance the solubility of caffeine by a similar mechanism. The

effect of betaine on the solubility of caffeine is shown in Fig. 3 and Table 5. The solubility was measured at the temperature of 5-40°C and betaine concentration of 0-5% by adding excess caffeine to an aqueous solution of betaine at the predetermined concentrations. Betaine rapidly increased the solubility of caffeine at high temperatures. That is, betaine did not significantly affect the solubility below 40°C but greatly increased the solubility at 40°C, and the solubility was continuously increased until the betaine concentration was 2%.

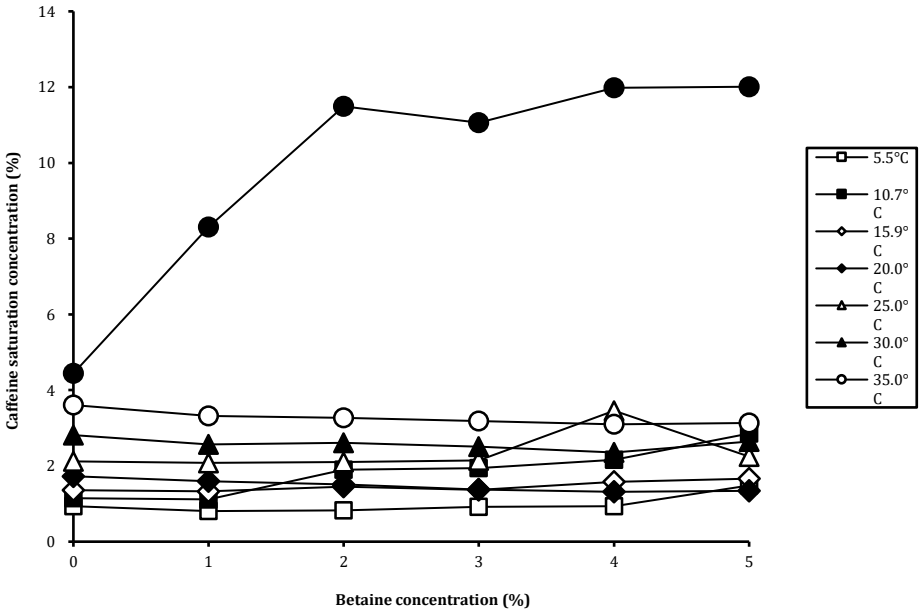

Fig. 3: Correlation between temperature and betaine concentration and saturation concentration of aqueous caffeine solution

Table 5: Saturation concentration of aqueous caffeine solution as a function of temperature and betaine concentration

Temperature (°C)	Betaine Concentration (%)	Caffeine Saturation concentration (%)	Temperature (°C)	Betaine Concentration (%)	Caffeine Saturation concentration (%)
5.5	0.0000 ± 0.0000	0.9345 ± 0.0100	25.0	0.0000 ± 0.0000	2.1203 ± 0.0204
	0.9919 ± 0.0001	0.8071 ± 0.0070		0.9792 ± 0.0004	2.0805 ± 0.0354
	1.9835 ± 0.0004	0.8275 ± 0.0218		1.9579 ± 0.0005	2.1034 ± 0.0235
	2.9724 ± 0.0056	0.9201 ± 0.1860		2.9356 ± 0.0010	2.1479 ± 0.0334
	3.9627 ± 0.0100	0.9323 ± 0.2502		3.8617 ± 0.0082	3.4575 ± 0.2062
	4.9258 ± 0.0295	1.4833 ± 0.5895		4.8879 ± 0.0016	2.2427 ± 0.0314
10.7	0.0000 ± 0.0000	1.1446 ± 0.0354	30.0	0.0000 ± 0.0000	2.8129 ± 0.0261
	0.9888 ± 0.0002	1.1169 ± 0.0158		0.9743 ± 0.0008	2.5699 ± 0.0755
	1.9621 ± 0.0255	1.8962 ± 1.2743		1.9477 ± 0.0010	2.6136 ± 0.0514
	2.9417 ± 0.0178	1.9440 ± 0.5925		2.9248 ± 0.0005	2.5079 ± 0.0182
	3.9136 ± 0.0077	2.1593 ± 0.1937		3.9058 ± 0.0082	2.3544 ± 0.2051
	4.8573 ± 0.0102	2.8549 ± 0.2033		4.8677 ± 0.0017	2.6452 ± 0.0347
15.9	0.0000 ± 0.0000	1.3611 ± 0.0145	35.0	0.0000 ± 0.0000	3.6059 ± 0.0411
	0.9867 ± 0.0005	1.3290 ± 0.0522		0.9668 ± 0.0004	3.3184 ± 0.0365
	1.9710 ± 0.0006	1.4479 ± 0.0300		1.9346 ± 0.0014	3.2698 ± 0.0683
	2.9589 ± 0.0074	1.3696 ± 0.2458		2.9045 ± 0.0018	3.1847 ± 0.0591
	3.9367 ± 0.0008	1.5817 ± 0.0212		3.8761 ± 0.0081	3.0978 ± 0.2030
	4.9169 ± 0.0011	1.6628 ± 0.0221		4.8433 ± 0.0173	3.1349 ± 0.3454
20.0	0.0000 ± 0.0000	1.7263 ± 0.0390	39.8	0.0000 ± 0.0000	4.4435 ± 0.0413
	0.9840 ± 0.0001	1.5961 ± 0.0070		0.9170 ± 0.0246	8.3028 ± 2.4559
	1.9698 ± 0.0003	1.5112 ± 0.0166		1.7702 ± 0.0463	11.4897 ± 2.3157
	2.9586 ± 0.0003	1.3796 ± 0.0089		2.6681 ± 0.0121	11.0637 ± 0.4040
	3.9474 ± 0.0119	1.3158 ± 0.2980		3.5207 ± 0.0503	11.9823 ± 1.2571
	4.9330 ± 0.0047	1.3398 ± 0.0934		4.3995 ± 0.0393	12.0102 ± 0.7870

3.6. Changes in aqueous solubility of caffeine by temperature and betaine concentration in the presence of niacinamide

The mixed hydrotropic solubilization technique has been reported to show a synergistic effect, e.g., increasing the solubility of ketoprofen more than 570-fold by using a mixture of urea, sodium citrate, and sodium acetate (Nair and Rajput, 2010). In this study, the mixed hydrotropic system of niacinamide and betaine was devised. The solubility was measured at the temperature of 5-40°C and betaine concentration of 0-5% under niacinamide concentration of 2% by adding excess caffeine to an aqueous solution of betaine and niacinamide at the predetermined concentrations. The effect of betaine on the solubility of caffeine in the presence of niacinamide is shown in Fig. 4 and Table 6. The addition of betaine did not significantly affect the solubility of caffeine below 35°C but greatly

increased the solubility at high temperatures of 35°C and 40°C.

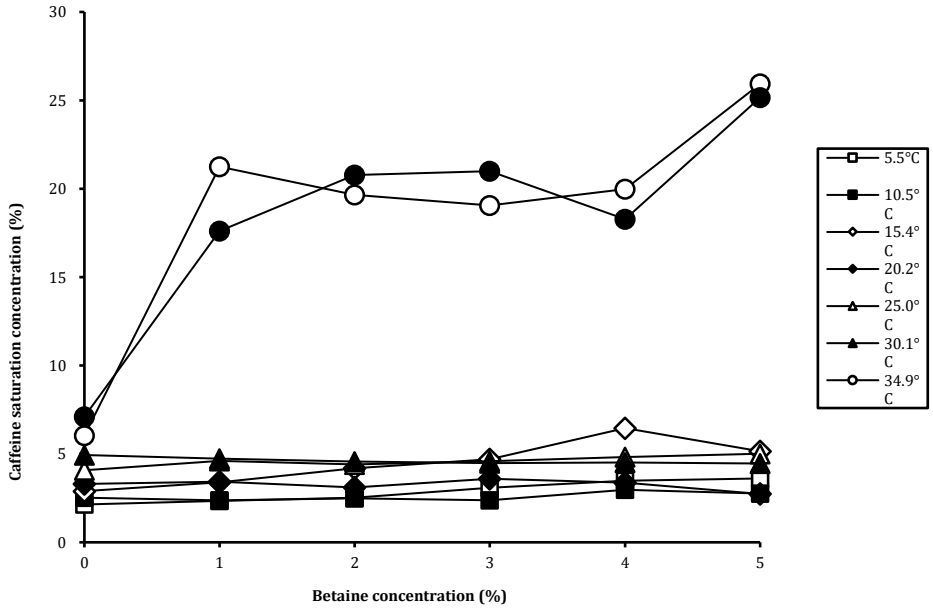

Fig. 4: Correlation between temperature and betaine concentration in the presence of niacinamide and saturation concentration of aqueous caffeine solution

Table 6: Saturation concentration of aqueous caffeine solution as a function of temperature and betaine concentration in the presence of niacinamideTemperature

Temperature (°C)	Niacinamide Concentration (%)	Betaine Concentration (%)	Caffeine Saturation concentration (%)
5.5	1.9572 ± 0.0003	0.0000 ± 0.0000	2.1391 ± 0.0172
	1.9337 ± 0.0061	0.9766 ± 0.0031	2.3375 ± 0.3064
	1.9106 ± 0.0044	1.9496 ± 0.0045	2.5180 ± 0.2253
	1.8803 ± 0.0190	2.9077 ± 0.0293	3.0781 ± 0.9769
	1.8530 ± 0.0145	3.8605 ± 0.0302	3.4884 ± 0.7557
	1.8314 ± 0.0100	4.8194 ± 0.0262	3.6110 ± 0.5244
10.5	1.9497 ± 0.0004	0.0000 ± 0.0000	2.5173 ± 0.0178
	1.9330 ± 0.0011	0.9763 ± 0.0005	2.3739 ± 0.0546
	1.9114 ± 0.0086	1.9504 ± 0.0088	2.4806 ± 0.4407
	1.8937 ± 0.0044	2.9284 ± 0.0068	2.3858 ± 0.2271
	1.8630 ± 0.0178	3.8812 ± 0.0370	2.9694 ± 0.9251
	1.8477 ± 0.0243	4.8623 ± 0.0640	2.7546 ± 1.2805
15.4	1.9421 ± 0.0003	0.0000 ± 0.0000	2.8936 ± 0.0137
	1.9128 ± 0.0019	0.9660 ± 0.0010	3.3955 ± 0.0962
	1.8780 ± 0.0086	1.9163 ± 0.0088	4.1855 ± 0.4380
	1.8488 ± 0.0124	2.8589 ± 0.0192	4.7020 ± 0.6384
	1.7960 ± 0.0151	3.7417 ± 0.0315	6.4572 ± 0.7881
	1.8021 ± 0.0006	4.7425 ± 0.0015	5.1503 ± 0.0299
20.2	1.9340 ± 0.0007	0.0000 ± 0.0000	3.3024 ± 0.0363
	1.9119 ± 0.0036	0.9656 ± 0.0018	3.4372 ± 0.1796
	1.8993 ± 0.0055	1.9380 ± 0.0056	3.0977 ± 0.2797
	1.8703 ± 0.0120	2.8922 ± 0.0185	3.5949 ± 0.6178
	1.8554 ± 0.0086	3.8653 ± 0.0178	3.3670 ± 0.4456
	1.8480 ± 0.0069	4.8632 ± 0.0181	2.7353 ± 0.3614
25.0	1.9185 ± 0.0011	0.0000 ± 0.0000	4.0755 ± 0.0545
	1.8887 ± 0.0033	0.9539 ± 0.0017	4.6092 ± 0.1652
	1.8736 ± 0.0005	1.9118 ± 0.0005	4.4103 ± 0.0266
	1.8509 ± 0.0011	2.8622 ± 0.0017	4.5930 ± 0.0558
	1.8275 ± 0.0011	3.8072 ± 0.0023	4.8191 ± 0.0581
	1.8048 ± 0.0010	4.7495 ± 0.0025	5.0096 ± 0.0505
30.1	1.9013 ± 0.0003	0.0000 ± 0.0000	4.9368 ± 0.0141
	1.8862 ± 0.0001	0.9526 ± 0.0001	4.7357 ± 0.0065
	1.8705 ± 0.0045	1.9087 ± 0.0046	4.5647 ± 0.2315
	1.8530 ± 0.0031	2.8654 ± 0.0048	4.4862 ± 0.1610
	1.8333 ± 0.0048	3.8193 ± 0.0101	4.5181 ± 0.2517
	1.8153 ± 0.0061	4.7772 ± 0.0160	4.4569 ± 0.3196
34.9	1.8793 ± 0.0006	0.0000 ± 0.0000	6.0371 ± 0.0325
	1.5593 ± 0.0307	0.7875 ± 0.0155	21.2466 ± 1.5524
	1.5748 ± 0.0213	1.6070 ± 0.0218	19.6507 ± 1.0889
	1.5703 ± 0.0206	2.4282 ± 0.0318	19.0590 ± 1.0607
	1.5365 ± 0.0321	3.2011 ± 0.0669	19.9720 ± 1.6714
	1.4073 ± 0.0494	3.7035 ± 0.1301	25.9306 ± 2.6025
39.9	1.8579 ± 0.0005	0.0000 ± 0.0000	7.1074 ± 0.0258
	1.6312 ± 0.0739	0.8238 ± 0.0373	17.6153 ± 3.7345
	1.5526 ± 0.0115	1.5843 ± 0.0117	20.7842 ± 0.5864
	1.5327 ± 0.0205	2.3702 ± 0.0317	20.9929 ± 1.0554
	1.5690 ± 0.0267	3.2687 ± 0.0557	18.2835 ± 1.3932
	1.4220 ± 0.0859	3.7420 ± 0.2260	25.1602 ± 4.5204

4. Conclusion

This study aimed to enhance the aqueous solubility of caffeine using the hydrotropic solubilization technique, and the following results were obtained: (1) The solubility of caffeine increased as the temperature and niacinamide concentration increased. (2) Betaine sharply increased the solubility of caffeine at 40°C or more. (3) In the case of the mixed hydrotropic system of niacinamide and betaine, the solubility of caffeine increased dramatically at 35°C or more. Summing up the results, a high-concentration aqueous caffeine solution of about 4% at 5.9°C and about 25% at 39.9°C were prepared, and these results are proposed as basic data for the development of cosmetics for cellulite treatment.

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Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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