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THE STUDY ON STABLE EMULSION SYSTEM AND SELECTIVE ADDITION OF ACTIVE INGREDIENT IN W/O/W ONE STEP MULTIPLE EMULSION

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Synopsis

It was possible to produce W/O/W one step multiple emulsion on the system which satisfied following conditions.

1. 1~5% of hydrophilic liquid surfactant over HLB20 and lipophilic liquid surfactant which has HLB 3~5
2. Non wax copolymers as oil thickener
3. More than 0.5% of carbomer as aqueous thickener
4. The manufacturing process which neutralize the dispersed carbomer (2.0% in water), after emulsifying.

For the selective addition into inner and outer aqueous phase, we melted the glucose in water before emulsifying . Using an Anthrone analysis method, we analyzed the encapsulation yield of glucose in inner water phase. It was possible to raise the water encapsulation yield of the multiple emulsion through the following conditions.

1. Using of anionic hydrophilic surfactant(HLB≧40) and lipophilic surfactant (HLB 3~5)
2. Controlling the ratio of hydrophilic surfactant and lipophilic surfactant
3. Strengthening interface with increase of non wax oil thickener.

When the separated adding process of glucose was adopted, approximately 85% of glucose was added selectively within inner aqueous phase.

Introduction

Because the multiple emulsion have the merits such as controlled release and encapsulation of active ingredients, skin compatibility and performance, excellent feeling. It is studied extensively in the field of pharmaceutical , cosmetics and food. However the multiple emulsion, which goes on W/O emulsion firstly and then stabilization and re-emulsification process should be proceeded, requires a lot of manpower and time as well as large amount of surfactant and raw-material when compared with O/W emulsion. In this article, we studied a new method that firstly it goes on emulsion system which

produces W/O/W emulsions via ordinary O/W emulsion manufacturing process at room temperature, and stabilization of that system. Also we studied the way to add active ingredients within inner water phase selectively, with monitoring the encapsulation yields of glucose in inner water phase by using Anthrone analysis method.

Materials

Surfactant

One step multiple emulsion needed two type of surfactants. One is liquid hydrophilic (HLB>20) and the other is liquid lipophilic (HLB 3~5)

Hydrophilic type

Potassium cocoyl hydrolyzed collagen (Lamepon S, Henkel)
Sodium lauryl ether sulfate (Sunfom SPES, Sunjin)
T.E.A lauryl sulfate (Sunfom TP, Sunjin)
Sodium lauryl sulfate (Sunfom SP, Sunjin)
Ammonium lauryl sulfate (Hicolin APS, Taedong)
Sucrose laurate (DK Ester SL-18A, DKS International)
Polyoxyethylene (20) sorbate monooleate (Tween 80, I.C.I)
PEG-60 hydrogenated castor oil (Cremopher RH-60, BASF)
PEG-12 Nonylphenyl ether (Emalex NP-12, Nihon Emulsion)

Lipophilic type

Cetyl dimethicone copolyol (Abil WE-09, TH Goldschmidt AG)
Polyglyceryl-2-dipolyhydroxy stearate (Dehymuls PGPH, Henkel)
Polyglyceryl-6 ricinoleate (Hexaglyn PR-15, Nikkol)

Oil: Octyl palmitate, Almond oil, Cyclomethicone, Squalane, Methylpolysiloxane
Oil thickener: Cetyl alcohol, Beeswax, Geahlene 1600 (Mineral oil and hydrogenated butylene / ethylene/stylene copolymer (and) hydrogenated ethylene / propylene / stylene copolymer, Penreco)
Thickener: Cabomer(Carbopol 940, BF Goodrich), Xanthan Gum, Magnesium aluminum silicate. Polyvinylalcohol.
Neutralizer: T.E.A
Preservative: Methyldibromo Glutanitrile and phenoxyethanol
Water: Deionized and distilled water
Reagent: Glucose

Methods

Preparation of multiple emulsion

For the convenience of experiments, most of emulsification process have been carried out at room temperature. Firstly , weighing and agitating of the water phase contains glucose and T.E.A were carried out. After weighing oils, lipophilic surfactant and hydrophilic surfactant were added into oil phase separately and agitated for 2 min. Then oil phase was poured into water phase and the first

emulsification process was carried out for 3 min. at Homo mixer 2000RPM. After it entered into the dispersed carbomer(2% in water) second emulsification process was carried for 3 min. at a increased agitation speed of 4000RPM, then finally enter into preservative with a well agitation.

Measurements

Microscopic observation

The droplets of W/O/W emulsions were observed by using microscope (Light microscope, OLYMPUS Chemical Co.) and Image analyzer (Nexus Inc.)

Dialysis of W/O/W emulsion

10 grams of the prepared W/O/W emulsion were placed in a cellulose tube (Dialysis tubing, SIGMA Chemical Co.) and were dialyzed against 390 ml of deionized water for 24 hours at room temperature . 1.0ml of dialyzed water were sampled to microanalyze the quantity of glucose contained in outer water phase of W/O/W emulsion.

Microanalysis of glucose

Anthrone method was applied to estimate the quantity of glucose (ref. Kor. J. Mycol vo1 16, No. 3, 162-174,1988)

1. After standard solution (glucose : 100 μg/ml solution) was charged into test tubes with different amounts of 0.0, 0.2, 0.4, 0.6, 0.8, and 1.0ml, each additional filling up with distilled water to make a constant volume of 1.0ml.
2. 5.0ml of cold Anthrone reagent (200mg of Anthrone was solubilized in 5ml of absolute EtOH, then 75% of H_2SO_4 was added to be 100ml) was added into each test-tubes and quickly started the agitation with vortex mixer, then heated in a boiling water bath for 10 min.
3. Simultaneously, 1.0ml of dialyzed samples were also heated in a boiling water bath for 10 min., after mixed with 5.0ml of cold Anthrone reagent
4. The test tubes and samples were moved into an ice bath.
5. Absorbance was measured at 625nm (Quantitative analysis with calibration Curve)

$$\text{Yield} = \frac{1 - \text{estimated concentration of glucose}}{1} \quad 100\ (\%)$$

Results and Discussion

The emulsifier combination for stable multiple emulsion

Through various combination of hydrophilic surfactants (HS) and lipophilic surfactants (LS) (Table 1) (Table 2), we found that the combination of HLB≅40 and HLB<5 surfactants produce one step multiple emulsions. As shown in Table 3, the combination of sodium lauryl ether sulfate and polyglyceryl-6 ricinoleate produced most stable and highest yield multiple emulsion. (Figure 1) However low HLB surfactants such as PEG-12 nonyl phenyl ether, PEG-60 Hydrogenated castor oil and sucrose laurate produced low yield and non multiple emulsion.

Table 1. The test formula for W/O/W emulsion

Component	Content (%)
Hydrophilic surfactant	4.2
Lipophilic surfactant	0.3
Octyl palmtate	10.0
Amond oil	2.0
Squalane	2.0
Cyclomethicone	3.0
Methylpolysioxane	0.5
Carbomer (2%)	25.0
Glucose	0.4
T.E.A	0.5
Preservative	0.1
D.I-Water	To be 100

Table 2. The used surfactants for test

Hydrophilic Sufactant	HLB	Lipophlic Surfactant	HLB
Sodium lauryl ether sulfate	≅ 40	Polyglyceryl-6 ricinoleate	3.2
T.E.A lauryl sulfate	≅ 40	Polyglyceryl-2-dipolyhydroxy stearate	5.0
Sodium lauryl sulfate	≅ 40	Cetyl dimethicone copolyol	≅ 5.0
Ammonium lauryl sufate	≅40		
Potassium cocoyl hydrolyzed collagen	40		
Sucrose laurate	17		
Polyoxyethylene(20) Sorbate monooleate	15		
PEG-60 hydrogenated Castor oil	14		
PEG-12 Nonylphenyl ether	13		

Table 3. Multiplicity and stability of multiple emulsion depending on the combinations of hydrophilic surfactants and lipophilic surfactants

Lipophilic surfactant Hydrophilic surfactant	Cetyl dimethicone copolyol	Polyglyceryl-2-dipolyhydroxy stearate	Polyglyceryl-6 ricinoleate
Sodium lauryl ether sulfate	A	A	A
T.E.A lauryl sulfate	C	A	A
Sodium lauryl sulfate	D	A	A
Ammonium lauryl sufate	D	A	A
potassium coocyl hydrolyzed collagen	B	A	A
Sucrose laurate	D	D	C
Polyoxyethylene(20) Sorbate monooleate	C	D	D
PEG-60 hydrogenated Castor oil	D	D	C
PEG-12 Nonylphenyl ether	D	D	D

Multiplicity and stability of multiple emulsion is
A : very good B : good C : Bad D : Very bad

Yields depending upon the change in composition of SLES and PGR

Base on experimental results that combination of SLES (Sodium lauryl ether sulfate) and PGR (Polyglyceryl-6 ricinoleate) was good emulsifier system for multiple emulsion. The changes of yield depending upon the changes in their composition were measured (Table 3). As a result of measurement, the yield of multiple emulsion were related to concentration of PGR. But, as the concentration of PGR were exceeded (PGR/SLES>1), the yield decreased. (Table 4) (Table 5) The results of microscopic observation were also in accordance with the yield. As the concentration of PGR increased, the size of inner water phase increased. When the concentration of PGR was exceeded (PGR/SLES>1), the particles of inner water phase was broken. (Figure 2) (Figure 3)

Table 4 .The yield of multiple emulsions according to PGR changes at constant SLES (4.2%)

The content of PGR (%)	Yield (%)	Ratio (PGR/SLES)
0.0	16	0.000
0.1	32	0.0244
0.2	35	0.048
0.4	39	0.095
0.8	51	0.190
1.5	64	0.357
3.0	73	0.714
6.0	59	1.429

Table 5. The yield of multiple emulsions according to SLES changes at constant PGR (4.2%)

The content of SLES (%)	Yield (%)	Ratio (PGR/SLES)
0.1	10	42
0.2	15	21
0.4	19	10.5
0.8	20	5.25
1.5	22	2.8
3.0	50	1.4
6.0	68	0.7

Thickener effect

In order to examine the effects on the stability and yield depending upon the thickeners, Carbomer , xanthan gum, magnesium aluminum silicate and polyvinylalcohol were tested. The role of thickener was very important due to its unstability for the firstly emulsified emulsion which prepared by the combination of two kinds of surfactants with extreme difference in HLB. Without thickener, those emulsion were quickly separated just after emulsification process. Only Carbomer produced stable emulsion.

The content of carbomer

The stability and yield of multiple emulsions were increased rapidly by just 0.1% of carbomer. And related to concentration of carbomer slowly. When 0.5% of carbomer was added, the stability and yield were satisfactory

Wax effect

The solid waxes such as cetanol and beeswax broke multiplicity when 2% of them were formulated. Non wax oil thickener gave positive effects to multiple emulsions.

Manufacturing by cold process

For the convenience of experiments and prevention of denaturation of raw materials, most of experiments were carried out at room temperature. Also the experiments were able to be carried out at high temperature

Separated adding process of glucose

It is theoretically impossible to achieve 100% selectivity by simply adding glucose into water. Therefore we introduced separated adding process of glucose

Firstly glucose was solubilized into a small quantity of water, then it was added oil phase with lipophilic surfactant. After agitated well, it goes on emulsifying process with hydrophilic surfactant. As a result of that process, approximately 85% of glucose encapsulation yield was gained. (Figure 4)

Conclusion

From this experiments we were able to produce relatively stable multiple emulsion in one step process by following conditions.

1. Using of anionic liquid hydrophilic surfactant (HLB≅40) and liquid lipophilic surfactant (HLB 3~5)
2. Controlling the ratio of hydrophilic surfactant and lipophilic surfactant
3. 0.5% of carboxy vinyl polymer as aqueous thickener
4. Using of non wax oil thickener

However, since the multiple emulsion by one step process which was stabilized by using a strong thickener without considering the principle of HLB, It needs further research and development for the progress of stabilization in future. In these experiments, glycerine was not used because it interferes the analysis of glucose. When 10% of glycerine was used, the stability of formula was improved considerably. Another difficult point is that the selective addition of ingredient. The selective addition could be achieved significantly by considering the changes in the ratio of surfactants(LS/HS), by the increase of inner water phase quantity and by strengthening interface of emulsions.

However, it is theoretically impossible to achieve 100% selectivity. Consequently for the complete selectivity, we had to adopt two step process partially. In spite of those difficulties, one step multiple emulsion by low temperature emulsification is expected to draw a strong attention from large areas of industry such as cosmetics, food processing, and pharmaceutical applications due to its strong points of lower cost and benefits of multiple emulsion rather than conventional O/W emulsion

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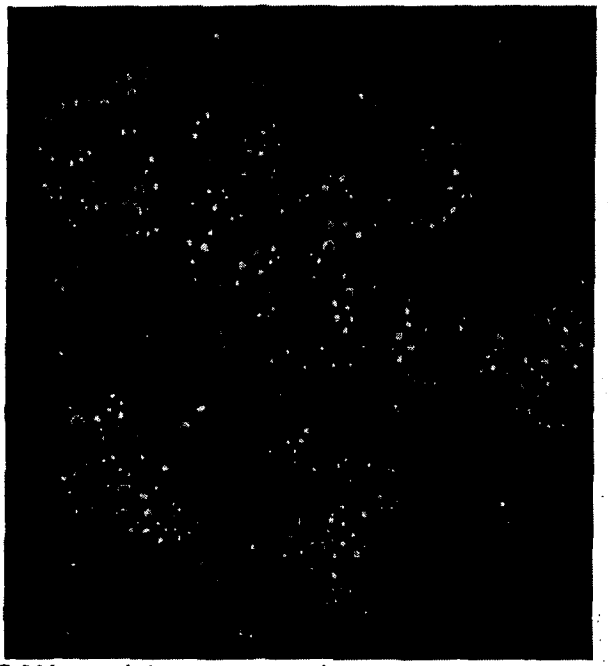

Figure 1. The W/O/W emulsion observed by microscopy and image analyzer. (4.2% of SLES and 0.3% of PGR were formulated) 400

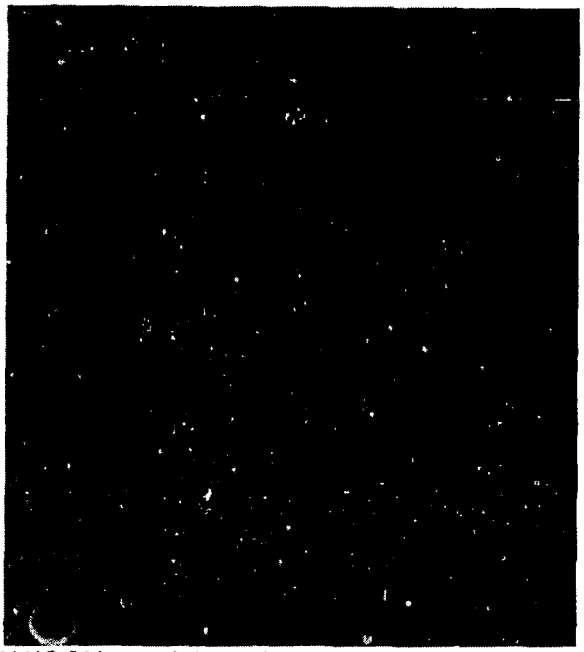

Figure 2. The diluted W/O/W emulsion observed by microscopy and image analyzer. (4.2% of SLES and 3.0% of PGR were formulated) 400

Figure 3. The diluted W/O/W emulsion observed by microscopy and image analyzer. (4.2% of SLES and 3.0% of PGR were formulated) 1000

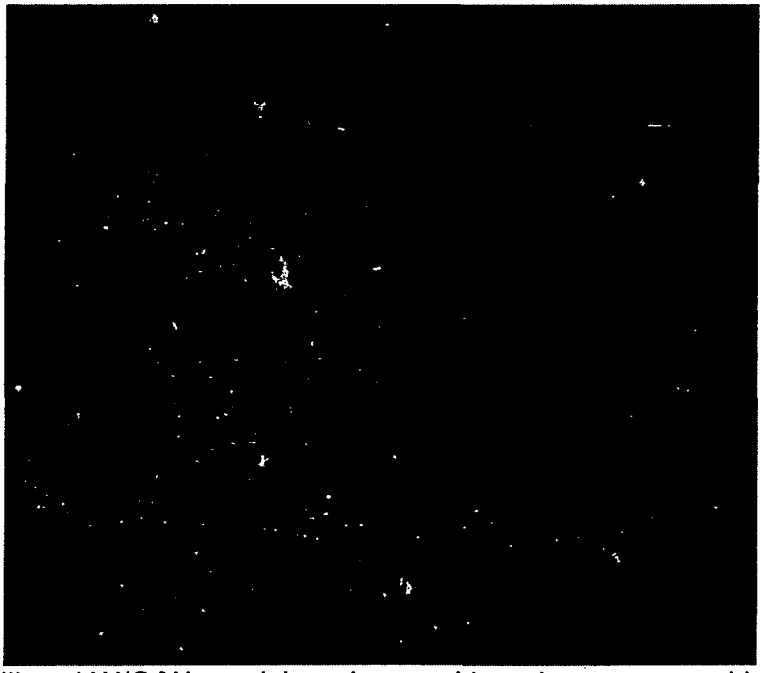

Figure 4. The diluted W/O/W emulsion observed by microscopy and image analyzer. (separated adding process of glucose was introduced to raise the yield) 400