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Increasing Solubility Of Active Pharmaceutical Ingredients In Topical Creams Using Soluplus®

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INCREASING SOLUBILITY OF ACTIVE PHARMACEUTICAL INGREDIENTS IN TOPICAL CREAMS USING SOLUPLUS®

A Masters Thesis

Presented to

The Graduate College of

Missouri State University

In Partial Fulfillment

Of the Requirements for the Degree

Master of Science, Chemistry

By

Roni Balzam

May 2016

INCREASING SOLUBILITY OF ACTIVE PHARMACEUTICAL INGREDIENTS

IN TOPICAL CREAMS USING SOLUPLUS®

Chemistry

Missouri State University, May 2016

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ABSTRACT

More than 40% of new chemicals developed in the pharmaceutical industry have poor solubility in aqueous solutions. Active Pharmaceutical ingredients (API) cannot reach their molecular targets in the body if the drug remains undissolved in the gastrointestinal system. One way to approach this problem is by using solubilizing agents. One such agent is a thermo-responsive, tri-block co-polymer which is marketed as "Soluplus®" (SP) by BASF Corporation. A part of this project is to thoroughly characterize various phase properties of SP such as cloud points and gel points temperatures. In current application, SP was incorporated into the creams formulations as an emulsifier to determine the effects on API solubility. The analysis included centrifugations and UV-Vis studies to determine the concentrations of the API in the cream's phases. The results of the cloud and the gel points of SP curves matched the curves from polymers containing the individual building blocks of SP. The results of the current application showed that the presence of SP in acid and salt Ibuprofen increased the partitioning of API into the water phase.

KEYWORDS: Soluplus® (SP), Ibuprofen (Ibp), creams, water phase, oil phase, cloud points temperatures, gel points temperatures, solubility, polymeric micelles.

This abstract is approved as to form and content

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Dr. G. Alan Schick
Chairperson, Advisory Committee
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

1.1 The Solubility Issues of Active Pharmaceutical Ingredients (API's)

More than 40% of new chemicals developed in the pharmaceutical industry have poor solubility in aqueous solutions.[1,2] Solubility is the tendency of any chemical in any physical form to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution, which can be dependent on the nature of the solvent, temperature, and pressure. The International Union of Pure and Applied Chemistry (IUPAC) defines solubility as a proportion of specific solute in a specific solvent for saturated solution.[3] Equilibrium occurs when dissolution and phase joining have the same rate.[1] Dynamic equilibrium is the cause of solubility resulting from simultaneous and opposite processes of dissolution and phase joining.

Solubility plays a major role in the pharmaceutical industry. The Biopharmaceutic Classification System (BCS) is a scheme developed to classify each drug based on drug solubility and gastrointestinal permeability. Solubility and permeability were chosen because they control the rate and extent of drug absorption. The solubility of the drug determines the highest-dose strength of an immediate release product.[1,4] For a drug to be considered to have a very high dose strength, it should be soluble in 250 ml or less in aqueous solution within the range of 1-7.5 pH scale.[5] Each drug is classified into four fundamental classes based on their solubility and cell permeability (Table 1, Figure 1).

Table 1. The Biopharmaceutic Classification System†

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

†See Ref. 4.

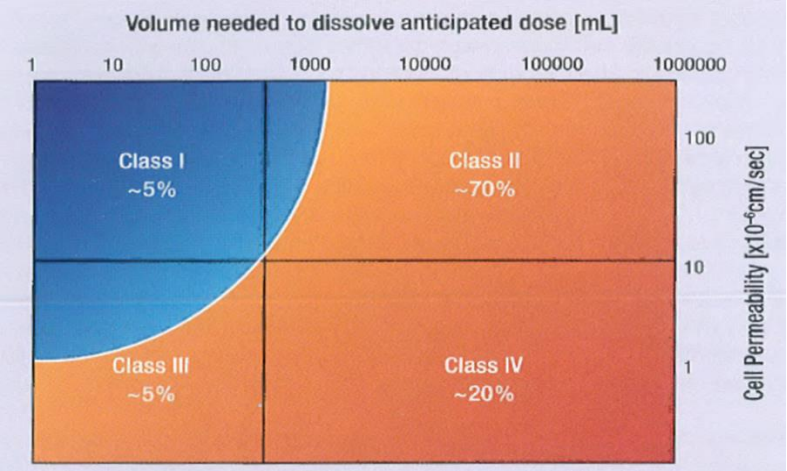


Figure 1. The BCS is illustrated in terms of volume of aqueous that needed to dissolve anticipated dose for solubility, and cell permeability.[17]

Low solubility will require a dose escalation until the drug concentration in the blood is within the therapeutic drug concentration range. In oral applications, high doses can cause toxicity in the gastrointestinal system, and eventually lead to reduction in patient compliance. In addition, developing a high dose drug is challenging due to difficulty of formulating powders and tablets.[2] Around 50-60% of the drugs are classified as Class II drugs – low solubility and high permeability.[6] In some cases, even small increases in the solubility can improve the bioavailability of the drug.

Researchers in the pharmaceutical industry are focusing on ways to overcome the solubility issues. Methods to improve solubility include:

- Addition of polar functional groups: placing a polar functional group in the structure of a molecule that is not soluble in aqueous solution in order to improve the solubility of the drug. Example: sulindac is an inactive drug, but after reduction it becomes active as sulindac sulfide.[7]

- Polymeric micelles: cores/shells structures formed by amphiphilic block copolymers. These polymeric micelles can entrap hydrophobic drugs and be used for intravenous delivery.[8] Example: diblock polymer polylactic acid – polyethylene glycol (PLA-PEG) and triblock polymer PLA-PEG-PLA are been used to help increase drug delivery.[9]

- pH modification and salt forms: in this approch, the drug undergoes pH modification in order to be more soluble, or it generates a salt. Currently this is the most common approach because 70% of drugs are ionizable and slightly basic.[9] Examples: Telmisartan is an insoluble drug at pH of 3-9. However, the current formulation includes sodium hydroxide, which increase the pH.[10] Atazenavir is insoluble in water as a free base. The salt form improves significantly the bioavailability of the drug.[9,11]

- Solid state modification: amorphous forms: this approach includes a change of the solid state to make the drug more soluble. Drugs with a stable crystal form have higher lattice energy and are much less soluble than disordered amorphous forms. [9]

- Co-solvency and surfactant solubilization: conjugation of a solvent with a surfactant, and in some cases with pH modification, to increases solubility in water.[9] Examples: ethanol is 80% of Tacrolimus formulation; glycerin is 32.5% of Epinephirine formulation etc.

1.2 Usage of Polymeric Micelles to Increase Drug Solubility

A solubilizing agent that was studied in my project is Soluplus®, which forms polymeric micelles to help solubilize drugs. Polymeric micelles are formed from the self-assembly of amphiphilic block copolymers, which contain a combination of hydrophilic and hydrophobic segments in an aqueous environment.[12] The self-assembly of amphiphilic block copolymers in water is based on non-polar and hydrophobic interactions between the lipophilic core-forming polymer chains, leading to better

aqueous solubility.[13] The ability to form a core-shell structure is entropically favored, and occurs above their critical micelle concentration (CMC).[12] The hydrophobic moieties are separated from the outside aqueous surrounding, and thus form an inner core where the hydrophilic moieties form a shell or corona (Figure 2).[12,14]

This unique behavior attracted the interests of pharmaceutical's development researchers for solubilization of poorly soluble drugs.[14] Polymeric micelles have high drug-loading capacities in their hydrophobic inner core,[14] and they can solubilize poorly water-soluble drugs by incorporating them in this core. The micelles can deliver the drug to target sites when the concentration exceeds the intrinsic solubility of the drug – which makes them more available in the body.[15] Moreover, they have a slow rate of dissociation that enabling retention of loaded drugs for longer periods of time, increasing the accumulation of a drug at the target site.[14] In addition, a drug inside the core is protected from any contact with the gastrointestinal tract, which can lead to degradation and metabolism.

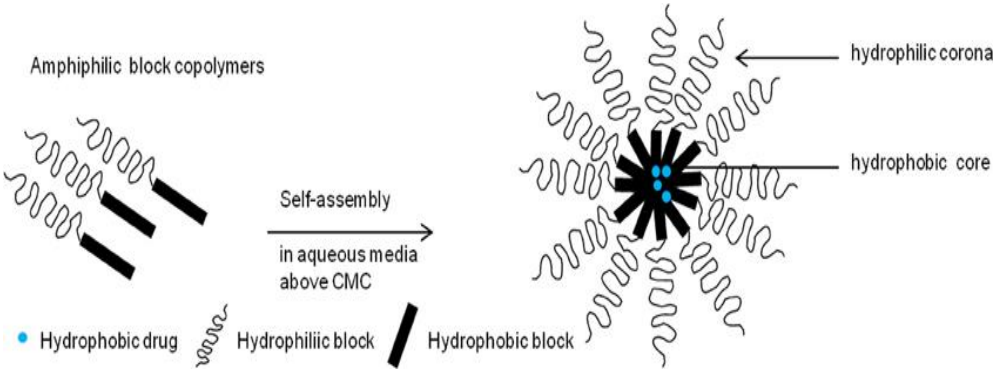


Figure 2. The formation of a drug-loaded polymeric micelle in aqueous media occurs through self-assembly of amphiphilic copolymers, resulting in a hydrophobic core and hydrophilic corona.[12]

Two types or more of monomeric units, in our case three, which differ in their solubility, are the building blocks of copolymers. They are organized into a polymeric chain as random, block, and graft (the focus of my project) copolymers (Figure 3). My project focuses on graft copolymer Di-block (A-B) and tri-block (A-B-A)-copolymers which can be prepared from the same hydrophilic and hydrophobic monomeric units.[16] The most abundant and efficient hydrophilic block for both di- and tri-block copolymers is poly (ethylene oxide), which is more commonly referred to as - poly(ethylene glycol) (PEG).[12]

PEG's high solubility in water and hydration makes it the most popular hydrophilic block polymer. Tri block copolymers that contain PEG and hydrophobic propylene oxide units are used the most as tri-block pharmaceutical polymers.[16]

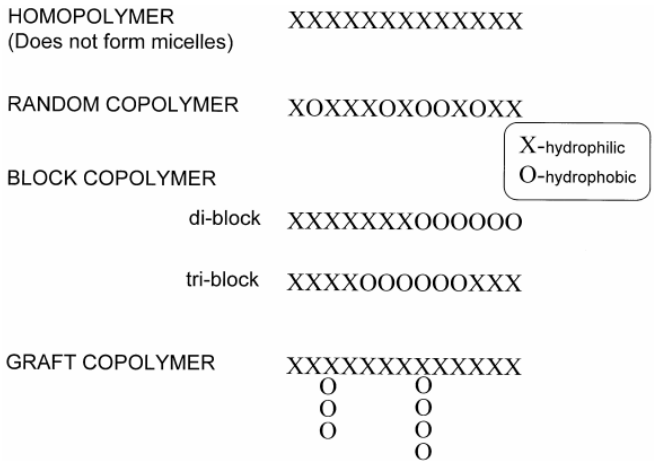


Figure 3. Copolymer structures**.** The structural type of copolymers: random, block, and graft.[16]

1.3 Soluplus®

Soluplus® (SP) is a novel amphiphilic polyvinyl caprolactam (PVLC)-polyvinyl acetate (PVAc)-polyethylene glycol (PEG 6000) tri-block graft copolymer made by the BASF cooperation. The hydrophilic PEG block segments are the backbone while the lipophilic monomers PVLC and PVAc are the side chains. The structure is shown in Figure 4. The molecular weight of SP is 118,000g/mol with a PVCL-PVAc-PEG mass ratio of 57:30:13, respectively. It is a free flowing white to slightly yellowish granule.[17]

SP was mainly design for the preparation of solid solutions. Studies showed that it is soluble in organic solvents such as acetone, ethanol, DMF, and methanol. Moreover, SP is ideal for hot melt extrusion with excellent extrudability and easy processing because its glass transition temperature is fairly low. This low temperature helps APIs with high or low melting points to be extruded easily without degradation.[17] Also, SP is thermally stable and can withstand the temperatures as high as 220°C without degradation.[18]

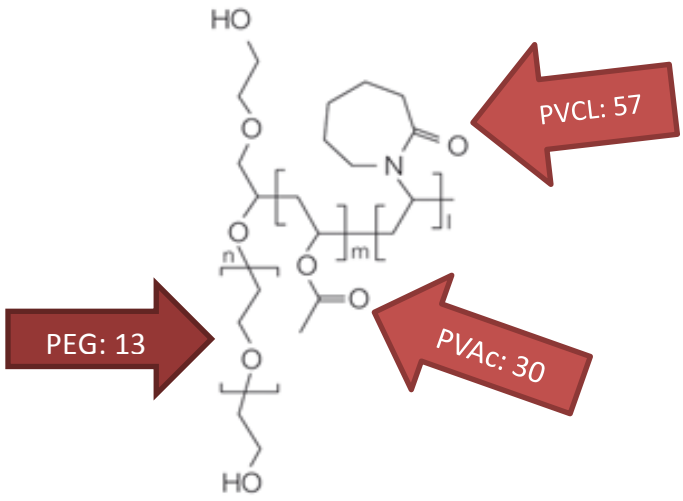


Figure 4. SP structure. The three different block polymers shown are PVCL, PVAc, and PEG with ratio of 57:30:13.[17]

Due to its amphiphilic structure, SP forms polymeric micelles along with the APIs, and can increase the solubility of insoluble drugs in aqueous solution.[18,19] Figure 5 shows an illustration of the mechanism of the interaction between SP and an API.

The stability of polymers with API's is dependent on their length and their molecular weight. Polymers with higher molecular weight, such as SP can have greater entanglement with drug molecules. Moreover, since it has multiple binding sites in the lipophilic residues, it has even better entanglement compared to polymers that lack those sites. Thus, SP is allowing the drug to maintain in the solution for longer time. SP also showed stronger intermolecular interactions with the API, creating better stabilization and prevention of crystallization, and hence, the drug release is slower.

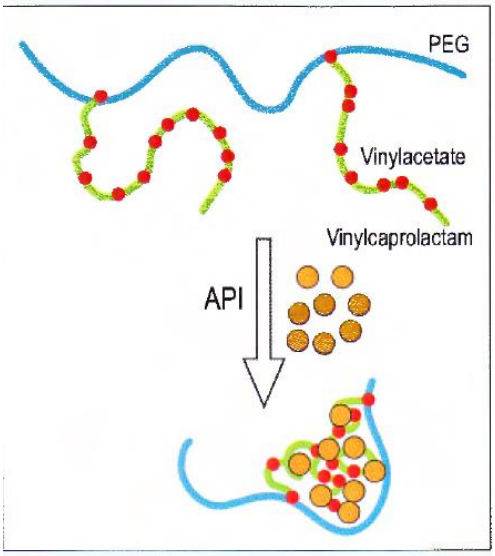


Figure 5. Interaction between SP and an API.[19]

Solubility of various oral drugs in water was shown to increase after the addition of SP.[17] Because of this, SP also is believed to have potential to increase solubility of

drugs in topical creams. Thus, my thesis aims to determine the magnitude of solubility change after the addition of SP to ibuprofen in topical creams.

1.4 Physical Properties

Physical properties such as molecular weight, boiling point, melting point, color and density are basic properties that important to know especially for a new chemical developed in the market. Other properties such as cloud point and gel point, are important physical characterizations of polymers that should be known.

In general, cloud point is the initial temperature where the solution gets cloudy.[20] By definition it is the temperature where phase separation starts. The appearance of cloudiness is due to the formation of polymer-rich emulsion droplets, and the concentration of the polymer affects the cloud points. The lower critical solution temperature (LCST) is the lowest temperature where the solution gets cloudy.[21]

Gel points is the temperature where the gel appears for the first time.[22] IUPAC defines gel point as the "point of incipient network formation in a process forming a chemical or physical polymer network, where the gel point is expressed as an extent of chemical reaction."[23]

Beside the importance of knowing the physical properties for safety reasons, cloud points and gel points are valuable properties in terms of solubility and sensory evaluations. The solubility of API with SP is based of formation of the self-assembly and creation of micelles, while the cloudiness is inversely since it is a phase separation. Moreover, clear gel that gets cloudy after rubbing it on the skin, could lead to bad sensory evaluation and penitent compliance.

1.5 Transdermal Drug Delivery System

Transdermal drug delivery systems deliver therapeutically appropriate amounts of a drug to the body across the skin.[24] and are designed to reach systemic blood levels.[25] They provide alternatives to oral, intravascular, subcutaneous, and transmucosal routes.[26] The human skin contains two distinct layers: the stratified avascular cellular epidermis, and an underlying dermis of connective tissue (Figure 6).[25] With regards to drug penetration, the outer layer, stratum corneum (SC), is the barrier that provides the rate limiting step.[24,25] The stratum corneum is an approximately 30-microons thick structure and renews itself at the same time it acts as a barrier and protects against environmental toxins.

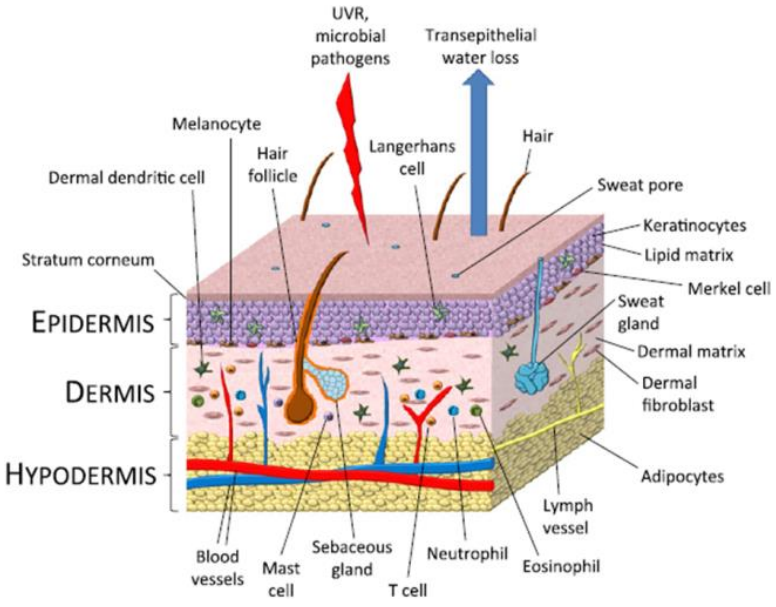


Figure 6. Schematic representation of skin structure.[27]

The major penetration route of drugs across the SC is through the intercellular region, which is a space that contains lipids and glycoproteins.[24] The permeation of a

drug through the skin depends on the drug's physiochemical properties, such as: molecular weight (less than 500Da), pKa of the drug, stability of the formulation, binding affinity, its lipid solubility and high lipophilicity. Also, the permeation depends on low therapeutic dose, integrity and thickness of the SC, and skin hydration.[25,26]

Transdermal systems have been an important drug delivery technology for the past 30 years.[24,25,26] This technology, in which the drug penetrates the skin and gets into the systemic circulation, has several advantages over oral delivery applications:[24,25]

- Avoids chemically hostile gastrointestinal (GI) environment and doesn't have GI physiologic contraindications of oral route.
- Avoids the first-pass inactivation by the liver when the drug is absorbed and irritate the GI mucosa.
- Increases patient compliance.
- Offers an alternative to patients who are having trouble swallowing tablets/capsules and overcoming it by crushing the tablets. This can destroy any controlled release characteristics of the tablets.
- Allows administration of drugs with narrow therapeutic window and effective use of drugs with short biological half-lives.
- Offers better flexibility of dosage since it can be easily terminated by removal of the transdermal drug.

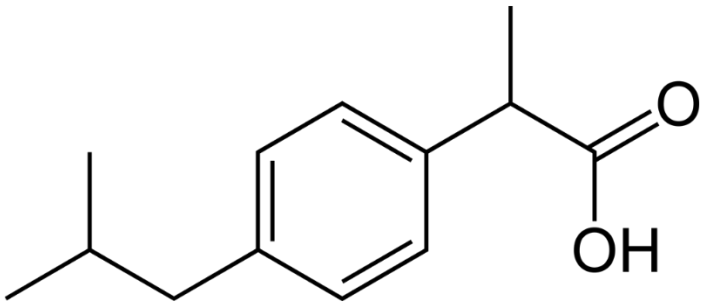
1.6 Ibuprofen (Ibp) for Use in Topical Formulations

An inflammatory response is activated by the human body when there is tissue damage. Increasing vascular permeability, local damaged tissues and dilation of local blood vessels are parts of the inflammatory reaction that occurs. The inflammatory cells release arachidonic acid metabolites, such as cyclooxygenase (COX) enzyme, in order to heal the damaged tissues.[28] Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce prostaglandin synthesis by COX inhibition at the site of pain and inflammation.[29] The

first type of NSAIDs were oral salicylate compounds that were extracted from willow bark.[28,29] Today, NSAID drugs, which are the number one prescribed drug in the world, have more than 25 different oral applications, but only a few topical formulations that are commercially available.[28,29]

However, oral NSAIDs have some critical adverse effects such as increased risk of bleeding, kidney dysfunction, and GI irritation and ulceration.[28] Topical formulations are a way to overcome the adverse effects of oral NSAID. They are applied locally, around the affected area, and can provide effective concentration at the target tissues without producing the systemic levels.[29]

Ibuprofen (Ibp, named from (RS)-2[4- **i**so**bu**tyl**phen**yl] **pro**panoic acid), an NSAID drug that BASF Corp. is marketing, is designed to help with reducing pain, fever, and inflammation. The free acid structure is not soluble in water but is soluble in organic solvents. Ibp has a phenyl moiety (Figure 7) that absorbs light at 272nm, by measuring in a UV range, allowing research data on the drug to be easily investigated.



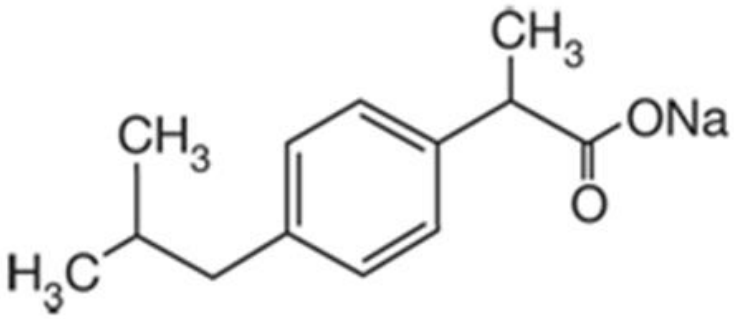


Figure 7. The structure of free-acid Ibp (top) and dodium salt Ibp (bottom).[30]

Advil Gel, Nurofen Gel, and Ibuactive are examples of different types of topical pain relievers that include Ibp. Currently, Ibp is present in many places in the world as a topical cream, however are not available in the United States, and they are in the process of being filed for approach. Thus, Ibp would make a good candidate for my study.

2 MATERIAL AND METHODS

2.1 Source of All Chemicals

A cream is classified as an emulsion, which is by definition a colloidal dispersion comprising two immiscible liquids, usually water and oil. The oil phase is dispersed as droplets in the aqueous phase. Cream requires an oil and water phase, as well as an emulsifier to stabilize the dispersion.[31] An emulsifier is an amphiphilic molecule that has a hydrophilic part and lipophilic part, and when added to an oil in water mixture, situates at the interface. This arrangement anchors the hydrophilic part in water and the lipophilic part into oil.[32] SP is an amphiphilic polymer and therefore could act as an emulsifier. Thus, SP was incorporated into the cream formulations as a co-emulsifier.

In these cream recipes, water and glycerol, the humectant which keeps the solution moist, are the primary components of the water phase. The cetyl alcohol and cocoyl caprylocaprate are the oil phase. Cetyl alcohol imparts the desired consistency and helps to enhance the stability and viscosity of the cream. SP, CS20, and PS60 serve as the emulsifiers. All chemicals were provided by BASF Corporation and are listed in Table 2 as the components of the cream formulations, along with the percentage of each. For the Ibp solubility studies the 95% ethanol was used its name was UltraPure 190 Proof Ethyl Alcohol (1/4 micron filtration), and it came from Fisher Scientific.

2.2 Instrument Descriptions

UV/Vis Absorption: Perkin-Elmer Lambda 650 UV-Vis Spectrometer and Agilent Technologies Cary 60 UV-Vis Spectrometer were used in lower critical solution temperature, and in determining concentrations of Ibp.

Table 2. Cream recipes for Base Cream #1 and Base Cream #2

Name of Compound	Compendial Name	Broad Classification	%
	Base Cream #1		
DI water	water	Solvent	71
Kollisolv G99	glycerol	humectant	5
Kolliwax CA	cetyl alcohol	consistency factor	10
Kollicream 3C	cocoyl caprylocaprate	emollient	10
Kollihor CS 20	macrogol cetostearyl ether 20	emulsifier	1/4†
Soluplus®	PVCL-PVAc-PEG	emulsifier	3/0†
	Base Cream #2		
DI water	water	Solvent	71
Kollisolv G99	glycerol	humectant	5
Kolliwax CA	cetyl alcohol	consistency factor	10
Kollicream 3C	cocoyl caprylocaprate	emollient	10
Kolliphor PS60	polysorbate 60	emulsifier	1/4†
Soluplus®	PVCL-PVAc-PEG	emulsifier	3/0†

†Total percentage of emulsifier is 4%, rather it is just of one emulsifier or 1% with 3% SP.

Lambda 650 has a temperature control application that can heat or cool the sample. However, it doesn't measure the actual temperature in the sample itself. This application was used in the cloud points study. In addition, a small stir bar was placed inside the sample cuvette while the absorbance was collected during the cloud points study. Experimental parameters: the wavelength for the cloud points study was 500nm which is a wavelength at which nothing in the solution absorbs. The path length was 1 cm, the data interval was 1nm, and the scan speed was 266.75nm/min. each measurement took

between 15-20 minutes. For Ibp studies the path length was 1 mm and the range of wavelength was between 310-250nm. Most of the measurements in the Ibp studies were measured using Cary 60 UV-Visible spectrometer. The scan parameters in this instruments were wavelength range between 310-250nm, path length of 1mm, and 0.5nm for data interval and scan rate of 300nm/min. The method remained the same throughout all the experiments. The Lambda 650 UV-Vis did not have baseline correction setup, hence, it was done manually. The Cary 60 has a base line correction, and it was used with majority of the samples analysis.

Formulation station: this included a programed hot plate, IKA® Eurostar power control visc 4 blade mixer, and all the ingredients from Table 2.

Centrifuge: Sorvall RC-5B Refrigerated Superspeed Centrifuged by Du-Pont Instrument, was the centrifuge that was used in determination of Ibp study. The speed was 18,000 rpm and the temperature could not drop below 25°C and could not be higher than 35°C.

2.3 Procedure

Determination of Cloud Points. Cloud points were measured by using optical transmission of UV-Vis as a function of temperature in different concentrations of SP in aqueous solution. Different sample compositions, ranging from 0.5-40% SP in aqueous solution, were made and stored in the cooling room. The measurements of the absorbance readings included setting up the instrument as illustrated in Figure 8. A temperature probe was placed inside the solution using a ring stand with a three finger clamp in a way that it did not interfere the beam of the instrument. The probe was connected to a Vernier Labquest controller that measured the temperature every 30

seconds. The temperature probe was used to ensure the temperature reading corresponded to sample itself, since the temperature controller was capable of monitoring only the temperature of the sample block as a whole. In order to prevent interference from room light, the instrument's sample chamber was covered with black cloth.

Figure 8. UV-Vis setup for cloud points

In the next step, the solution temperature was set higher than the cloud point (around 45°C), and once it reached the temperature, the cooling/heating turned off. After turning off the heat, the absorbance readings were measured every 3-5 seconds. At high temperatures the sample was very opaque, resulting a high absorbance reading that corresponding to the scattering of the light that doesn't go through the sample. As the temperature decreased the solution became less opaque, thus decreasing the apparent absorbance readings.

The absorbance readings and temperature data were collected until the solution was cooled to a temperature below the cloud point – around 20°C. Each concentration was analyzed at least 3 times and then a plot of absorbance readings versus temperature

for each composition was plotted. At high temperature, the absorbance reading is high, but when the sample is cooled down, the absorbance reading decreased. Once the solution becomes "clear" (SP is not typically clear even at low temperatures) the curve levels off. The cloud point was defined as the point on the absorbance reading vs. temperature plot where the absorbance began to rise abruptly – i.e., the inflection point. This point was determined by taking the best fit line for the most linear regions before and after the absorbance greatly increased (see Figure 9).

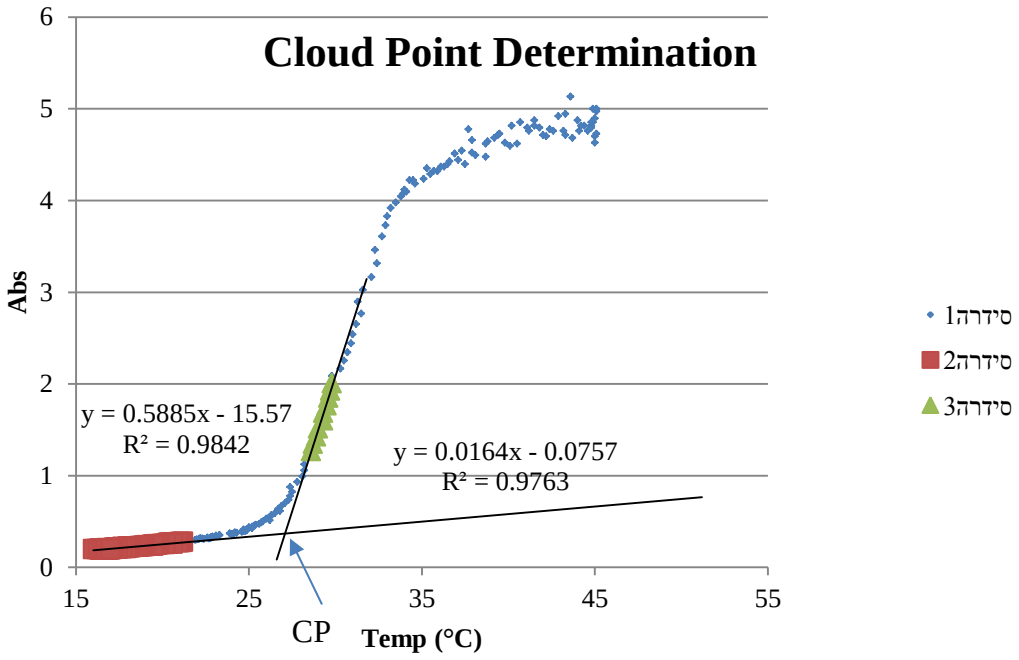


Figure 9. Absorbance vs temperature for determination of cloud point. The red and green points were used to determine the best fit lines for defining the inflection point (CP).

Determination of Gel Points. Aqueous solvent samples were prepared with SP concentrations from 5% to 30% at 2.5% increments. To measure the gel point for a given concentration, a 400mL beaker filled with water was placed on a hot plate with a ring

holder. A lab stand was set up with two clamps, where the lower clamp was used to hold the test tube of SP solution being tested and the higher clamp was used to hold a temperature probe. The test tube was submerged in the water bath so that the entirety of SP solution was under water, but so that the opening at the top was above the water level (Figure 10). The temperature probe was connected to a digital thermometer used for reading the temperature of the SP solution. Reading the temperature from the actual SP solution, and not from the water bath, is vital to ensure accurate readings. Also, the temperature probe was held so that its tip was in the middle of the SP solution, and not touching the glass of the test tube. This allowed the reported temperature to correspond to the actual sample solution. This also allowed for stirring the bath to provide a uniform temperature throughout.

Figure 10. Gel point set up

Each solution was heated and checked multiple times before the gel point was recorded. To determine a gel point the test tube was turned by 90° at a given temperature

for 5 seconds. If the solution did not exhibit any motion once it turned, the gel point was recorded. If the solution moved, then it was returned to the water bath. (Fig.11). Each sample was checked 3 times, and the average temperature was calculated and reported.

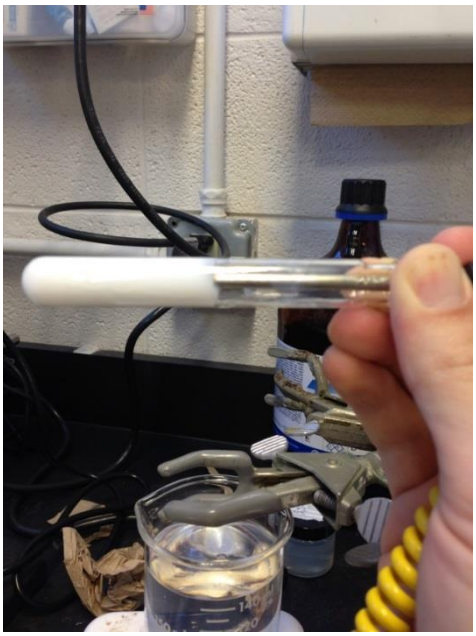


Figure 11. Determination of a gel point. The solution was turned 90 degrees, and once it did not exhibit any movement the gel points was called.

Sample Formulation/Preparation. The cream formulations followed the recipes in Table 2.The formulation procedures followed approximately those given in the original recipes where SP was added as an emulsifier and substituted part of the original emulsifier. All ingredients (Table 2) were added to a large beaker typically 4500 mL (Figure 12A). The mixture was heated to approximately 60°C on a programmable hot plate (Figure 12B). Once the target temperature was reached, the solution was mixed for 2 minutes using a mixer equipped with a flat 4-blade impellor at a high mixing rate

(approx. 400 rpm; Figure 12C). The hot plate was then replaced with a non-heated plate and the solution was mixed for an additional 15-20 minutes at a low mixing rate (approx. 200rpm). Once the cream formed, it was transferred to a storage jar (Figure 12D). The stored creams were allowed to sit undisturbed at room temperature (~22°C) and under ambient lighting for at least 24 hours before analysis.

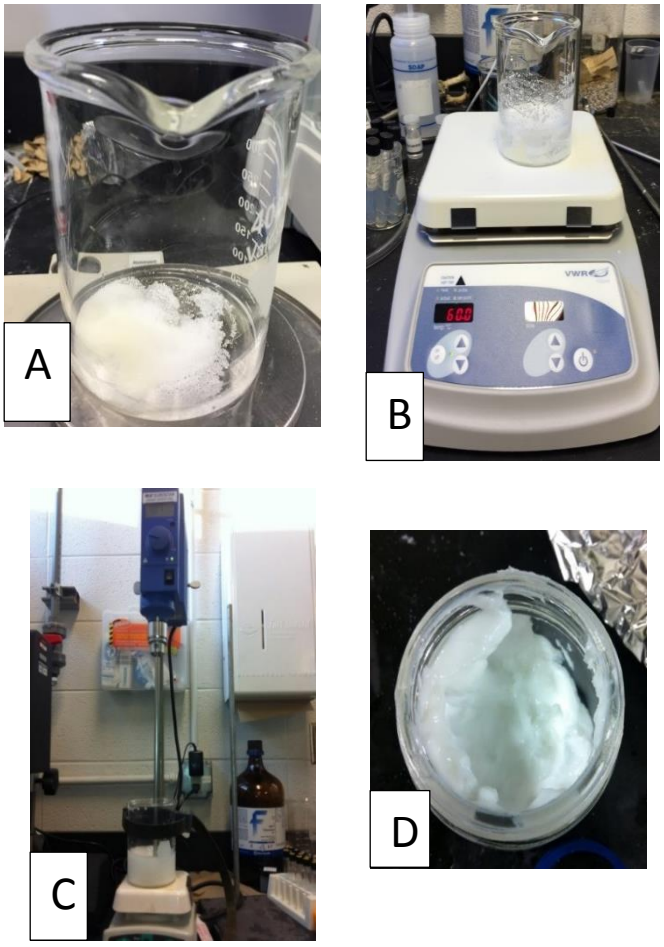


Figure 12. Images of the cream formulation process: (A) all the ingredients are added together to a 400ml beaker. (B) the ingredients are heated up to 60°C (C) once temp was reached, the ingredients are mixed at high speed for two minutes, then at lower rate for another 15-20 minutes, resulting (D) the cream was transferred to a storage jar.

Determining concentrations of Ibp. For the solubility studies, different creams were formulated in order to determine how the presence of SP affects the distribution of Ibp (or its sodium salt form) between the phases of typical creams (water, oil, and solid). Descriptions of the sample variations are given in Table 3.

Table 3. Experimental formulations based on BASF Base Creams 1 and 2*

	Base Cream 2					**Base Cream 1**			
Sample #	g H-Ibp	g Na-Ibp	g SP	g PS60	**Sample #**	g H-Ibp	g Na-Ibp	g SP	g CS20
203	1			4	**103**	1			4
204	1		3	1	**104**	1		3	1
205		1		4	**105**		1		4
206		1	3	1	**106**		1	3	1
207	5			4	**107**	5			4
208	5		3	1	**108**	5		3	1
209		5		4	**-**				
210		5	3	1			**-**		

* Only modifications to the standard formulations are given. All other ingredients are incorporated as described in the original formulations (Table 2).

After the creams were left undisturbed at room temperature (~22°C) and under ambient lighting for at least 24 hours, each cream was divided into four (4) centrifuge tubes with approximately 15g of sample placed in each tube (Figure 13).

The tubes were centrifuged for 90 minutes at 18,000 rpm. After centrifuging the tubes, 3 phases were observed: oil which was on top, solid (cream) in the middle and water was observed in the bottom (Figure 14). Each of the liquid phases were extracted at this point using digital pipettes. The oil phase was easy to the collect because it was on top. However, the water phase was a bit more challenging because the solid phase "blocked" it. To collect the phase, part of the solid phase was moved aside using a spatula. The mass of each sample extraction was measures, and by density and final

mass the volume was calculated. The mass was measured, and using the density the volume was found (Figure 15).

Then two samples in a range of 0.2-1ml from each liquid phase were diluted with 95% ethanol and were analyzed by UV-Vis spectroscopy. In the end 16 samples (8 each from the oil and water phases) of each jar of cream were analyzed (Figure 16). Table 4 gives the sample numbers, as well as the calculations to find the concentrations of the Ibp.

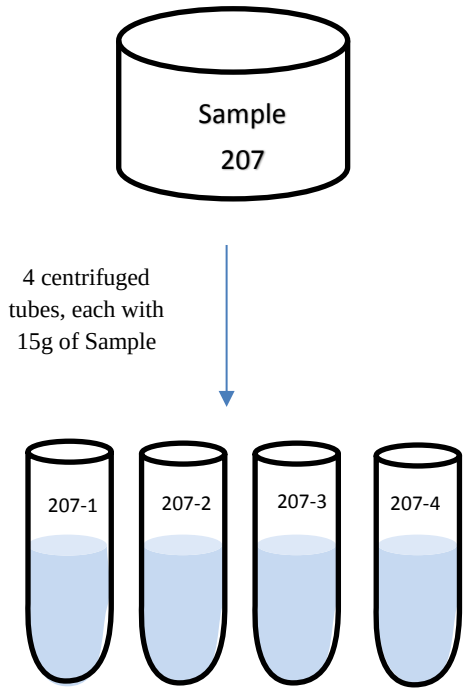


Figure 13. Dividing the cream into four centrifuged tubes

.

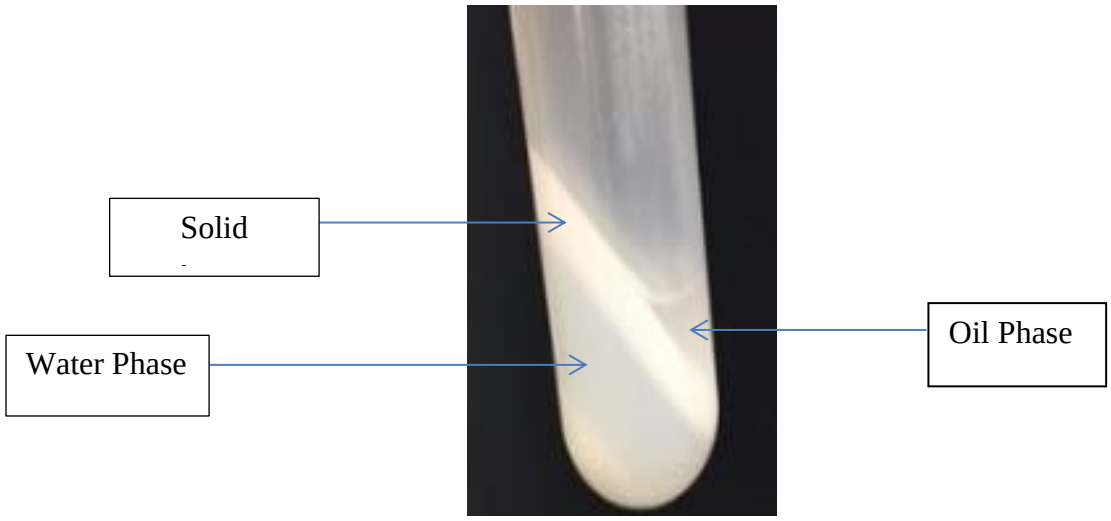


Figure 14. Three phases for a cream: oil on top, solid in the middle and water on the bottom.

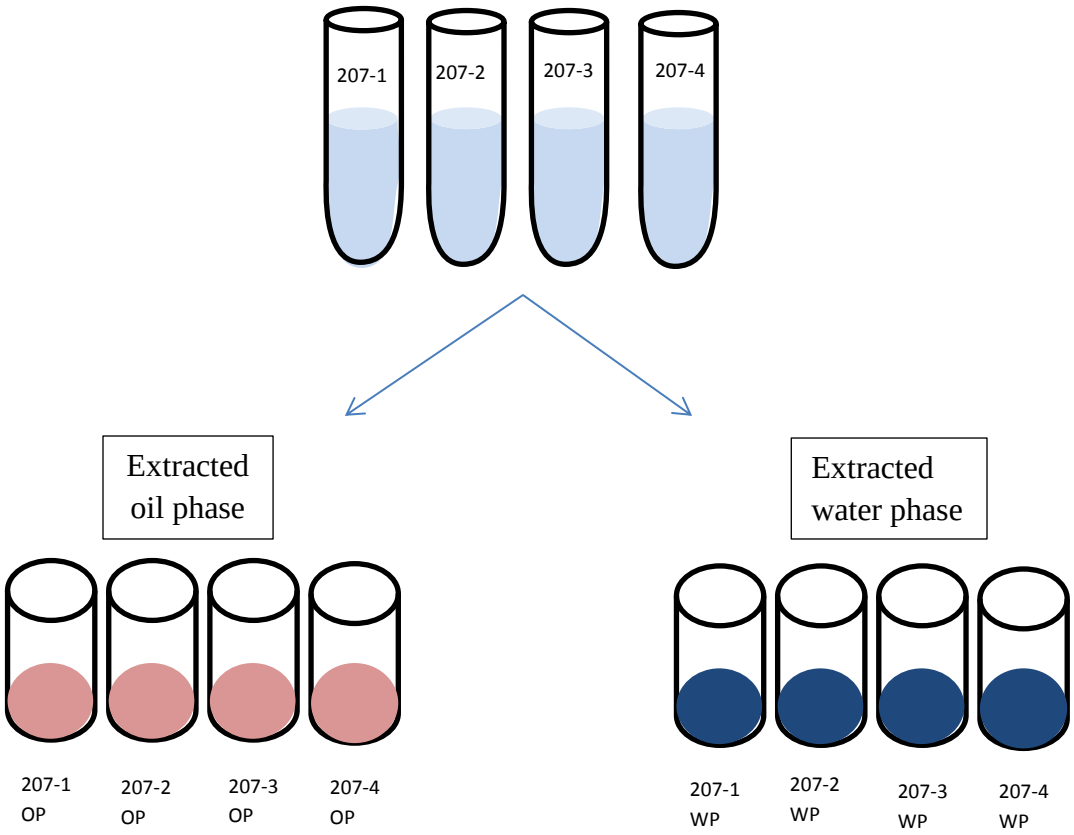


Figure 15. Each liquid phase was extracted into small beakers

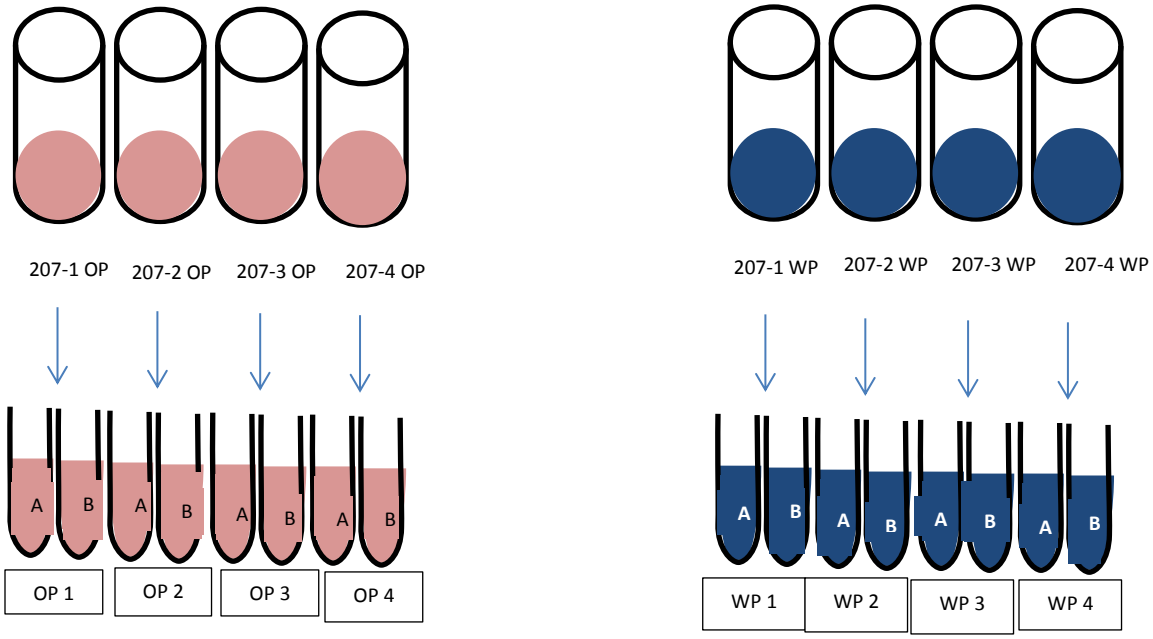
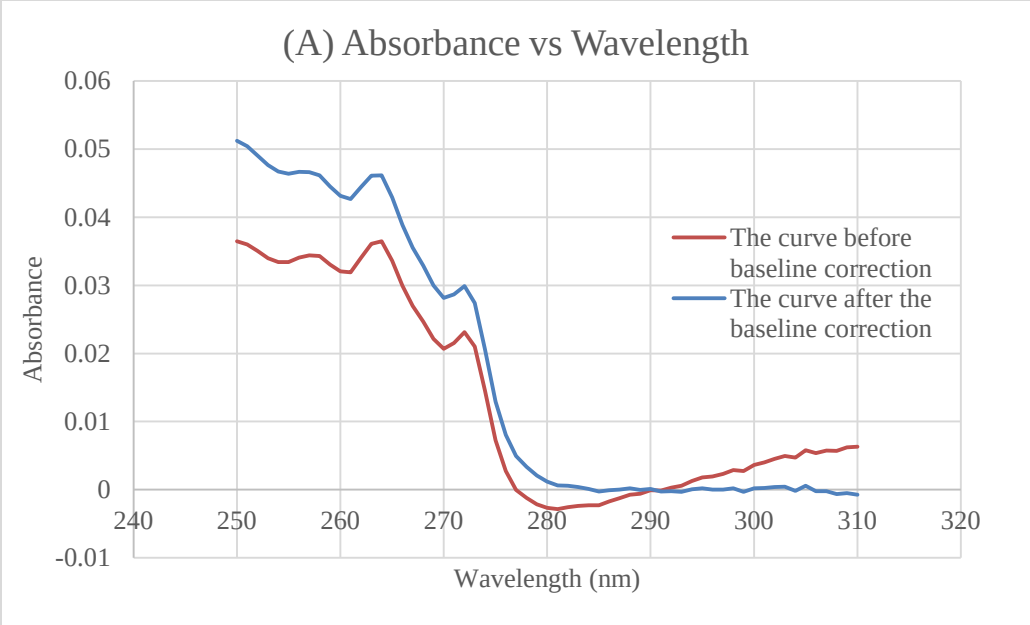


Figure 16. Two samples from each liquid phase were diluted with 95% ethanol for evaluation by UV-Vis spectroscopy. OP is the oil phase and the WP is the water phase. Cuvette 1 OP A is one of the two samples that contains oil phase from centrifuge 1.

Some spectra were collected without automatic baseline correction. For these samples the baseline correction was done manually as illustrated in Figure 17A. A linear baseline was determined from the recorded spectrum in the 285-305-nm range and was subsequently subtracted from the original spectrum. Some spectra were collected with the automatic baseline turned on, so no manual process was needed (see Fig. 17B for a representative spectrum).



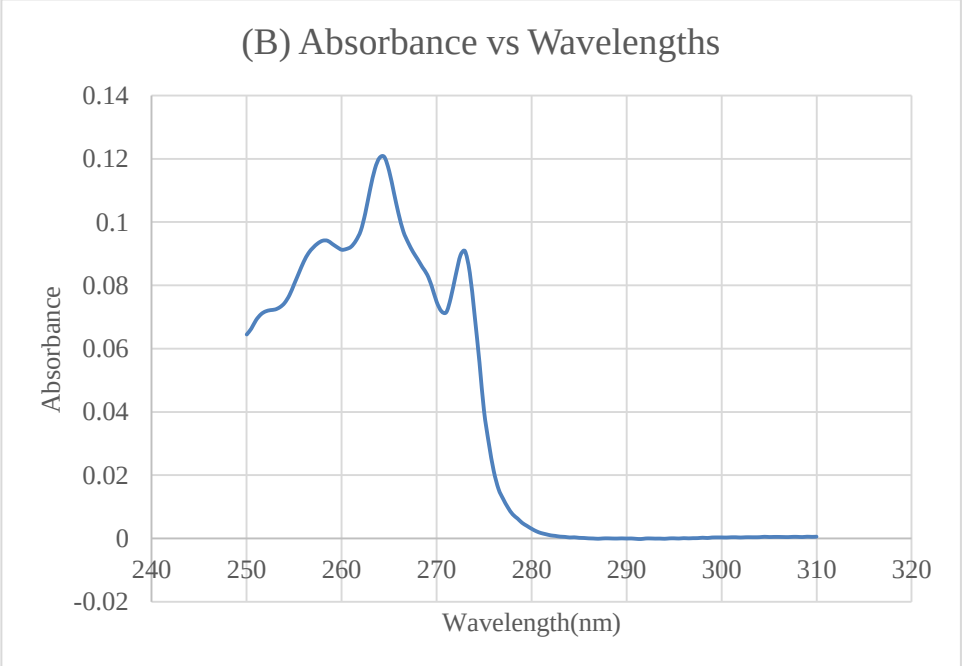


Figure 17.UV-Vis spectra of Ibp solutions (A) is a spectrum from Lambda 650 UV-Vis, which doesn't have a base line correction, and the correction was made manually. (B) is a spectrum from the Cary 60 which has baseline correction.

The absorbance of each sample was determined at the peak maximum that was found around 272nm for H-Ibp and at 273nm for Na-Ibp, and used to determine a concentration from the calibration curves shown in Fig. 18.

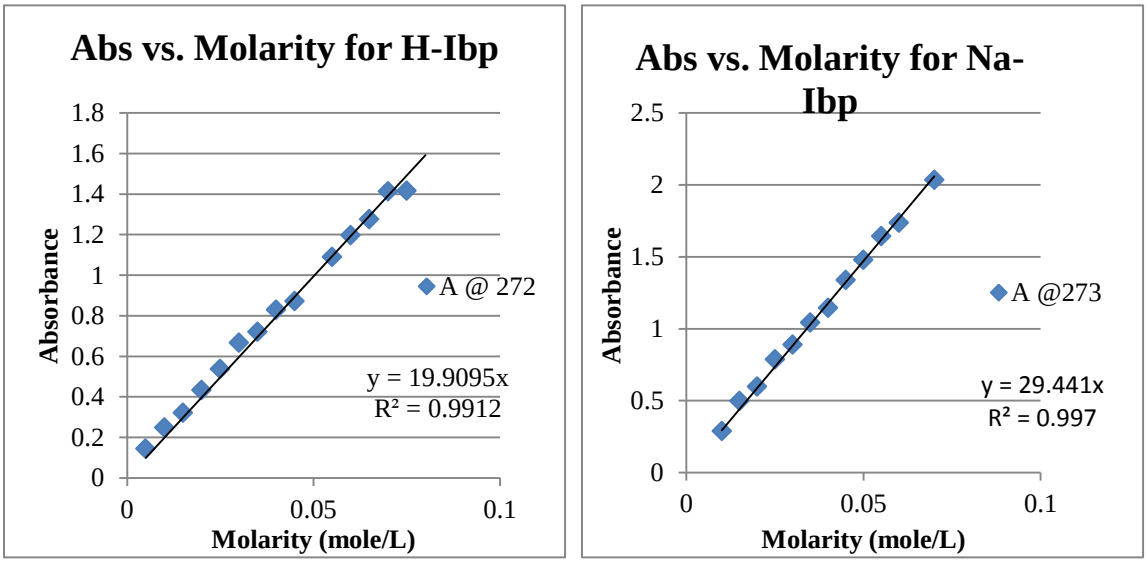


Figure 18. Calibration curves for determination of molarity of Ibp in the phases. The absorbance for H-Ibp was collected at 272nm, and the absorbance for Na-Ibp was collected at 273nm. The solvent that was used is 95% ethanol.

From these equations [H-Ibp] = A/19.9095 and [Na-Ibp] = A/29.441 the concentrations of diluted samples were calculated.

The following calculations proceed in order to find the average concentration (g/ml) in each centrifuged tube: first the calculated molarity of original sample was found by:

$$concentration\ of\ diluted\ sample * dilution\ factor$$

$$= calculated\ molarity\ of\ original\ sample$$

Then to find the number of moles:

$$\frac{Calculated\ Molarity\ of\ original\ sample * volume\ of\ total\ sample\ (ml)}{1000} = \#moles$$

To find the concentration in g/ml in each phase, the numbers of moles were converted to grams (MW=206.29g/mol for H-Ibp and 228.29 for NaIbp), and the result was divided by the volume of total sample. Figure 19 shows a representative example of the calculations that were done for Cream 207 in order to find the average concentration of Ibp in each phase of the cream.

Sample	Calculations									Averages (g/mL)		
207	volume of total sample (ml)	volume of sample exracted (ml)	Dilution factor in alcohol	Abs at peak	Concentration of diluted sample (M)	Calculated Molarity of original sample(M)	moles of Ibp	grams of Ibp	g/ml	Indiv Samples	overall	Std Dev.
1 OP A	0.949	0.200	10.0	1.23	0.0619	0.619	0.000587	0.121	0.128	0.128	0.126	0.00635
1 OP B				1.24	0.0621	0.621	0.000589	0.122	0.128			
2 OP A	1.005			1.28	0.0643	0.643	0.000646	0.133	0.133	0.134		
2 OP B				1.31	0.0656	0.656	0.000659	0.136	0.135			
3 OP A	0.9610			1.14	0.0575	0.575	0.000552	0.114	0.119	0.122		
3 OP B				1.21	0.0609	0.609	0.000585	0.121	0.126			
4 OP A	0.9584			1.13	0.0565	0.565	0.000542	0.112	0.117	0.120		
4 OP B				1.20	0.0602	0.602	0.000577	0.119	0.124			
1 WP A	7.153	1.00	10.0	0.127	0.00638	0.0638	0.000457	0.0942	0.0132	0.0144	0.0130	0.00125
1 WP B				0.150	0.00753	0.0753	0.000539	0.111	0.0155			
2 WP A	7.359			0.126	0.00632	0.0632	0.000465	0.0959	0.0130	0.0132		
2 WP B				0.129	0.00648	0.0648	0.000477	0.0984	0.0134			
3 WP A	7.094			0.119	0.00599	0.0599	0.000425	0.0876	0.0124	0.0127		
3 WP B				0.126	0.00634	0.0634	0.000450	0.0928	0.0131			
4 WP A	7.276			0.108	0.00543	0.0543	0.000395	0.0815	0.0112	0.0117		
4 WP B				0.118	0.00591	0.0591	0.000430	0.0887	0.0122			

Figure 19. A screen shot of a representative spreadsheet for determining [H-Ibp] in creams (Cream 207 shown).

Statistical Analysis for the Results. The first statistical test that was performed on the data was the Q-test in order to disregard values that were statistically out of range. The results of the comparisons – SP present or absent, the type of the emulsifier, and the type of the Ibp should be checked for statistical differences. To determine the statistical

differences the one-way analysis of variance (ANOVA) was used. ANOVA tests between the means of three or more checks to see if there are any significant differences between the means of three or more independent or unrelated groups.[33] The Levene's test was used to check if the samples have variances that are equal across groups or samples. The data failed the test since we have different variances.[34] Welch and Brown-Forsythe tests were used to confirm significance due to unequal variance as determined by a Levene's test. Pairwise comparisons were determined by the Games-Howell post-hoc test that checks if the groups are significantly different when the group has unequal size and or unequal variances. Changes were considered to achieve significance when $p < 0.05$, which corresponds to a confidence interval of 95% or better. All statistical analyses were conducted using SPSS statistical software (IBM, Armonk, NY, USA, release 21).

3 RESULTS

3.1 Phase behavior of SP

Determination of Cloud Points. Each sample of SP with various concentrations, in a range between 0.5-40%, were analyzed three times as describe in Section 2.3. The average temperature and the standard deviation are presented in Table 4 and plotted in Figure 20.

Table 4. Cloud points results: the average temperature and standard deviation for each SP concentration

Cloud Points for SP					
% Wt	T (°C)	SD (°C)	% Wt	T (°C)	SD (°C)
0.5	29.9	0.519	16	28.2	0.0586
1	30.9	0.315	17	27.7	0.268
2	30.4	0.21	18	28.4	0.397
2.5	30.8	0.485	19	28.6	0.264
3	30.6	0.794	20	28	0.183
4	29.5	0.159	21	28.6	0.158
5	29.4	0.027	22	28.4	0.732
6	28.7	0.137	23	29.3	0.351
7	28.4	0.0586	24	28.8	0.329
8	27.6	0.371	25	28.6	0.267
9	27	0.275	26	29	0.0417
10	26.7	0.361	27	29.2	0.0347
11	27	0.148	28	30.2	0.114
12	27.2	0.227	29	30.7	0.241
13	28.2	0.306	30	28.8	0.0289
14	28.3	0.469	35	29.4	0.433
15	27.6	0.155	40	30.9	0.24

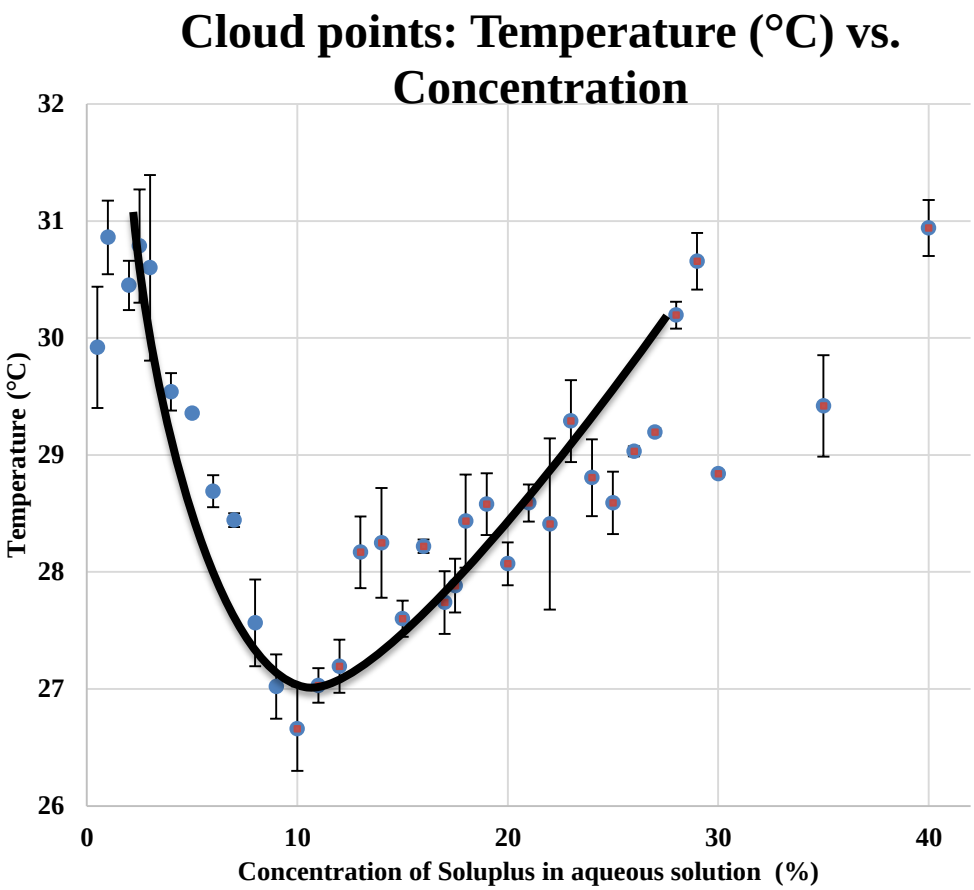


Figure 20. The average cloud point temperatures for each SP concentration presented in Temp vs. SP Concentration graph. The error bars corresponds to the +/- standard deviation.

The results show that overall, the cloud points decreases between 1-10% SP concentration range and then increases with increasing SP concentration. This behavior of SP resembles the behavior of PVCL, one of SP's polymer blocks (Figure 20).[35]

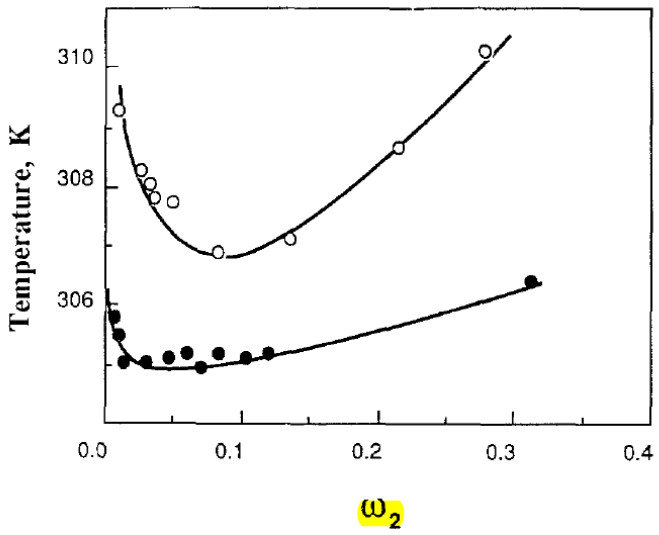


Figure 21. Cloud Points of PVCL in aqueous solution. The shape of the SP curve is similar to the to the PVCL one. The ω_2 represents the partial weight fractions of water and PVCL.[36]

Determination of Gel Points. Each SP concentration was analyzed three times as described in Section 2.3.2. The range of the concentrations was between 5-30%. The upper sol-gel transition temperature, USGT (the temperature at which the gel becomes liquid again) was analyzed between concentrations of 12.5-17%, and the results of the study are presented in Table 5.

Table 5. Gel points results: the Avg temperature and Standard deviation for each SP concentration. Concentration below 10% never gelled.

Gel Points for SP											
Concentration %wt	5.0	7.5	10.0	12.5	15.0	17.5	20.0	22.5	25.0	27.5	30.0
Avg Temp °C	N/A	N/A	53.7	45.7	42.9	40.1	39.6	38.3	33.5	32.9	30.5
StDev	N/A	N/A	1.15	2.29	1.44	1.22	1.15	0.38	0.12	0.06	1.4
Avg USGT °C				60.3	63.8	68.5					
StDev				1.5	1.0	0.5					

The plot of sol-gel transition temperature versus the composition of SP is shown in Figure 22. The gel points for a different tri-block polymer contains two PEG blocks – PEG-PLGA-PEG – were studied and the results showed similar behavior as it was observed with SP (see Figure 23).[36]

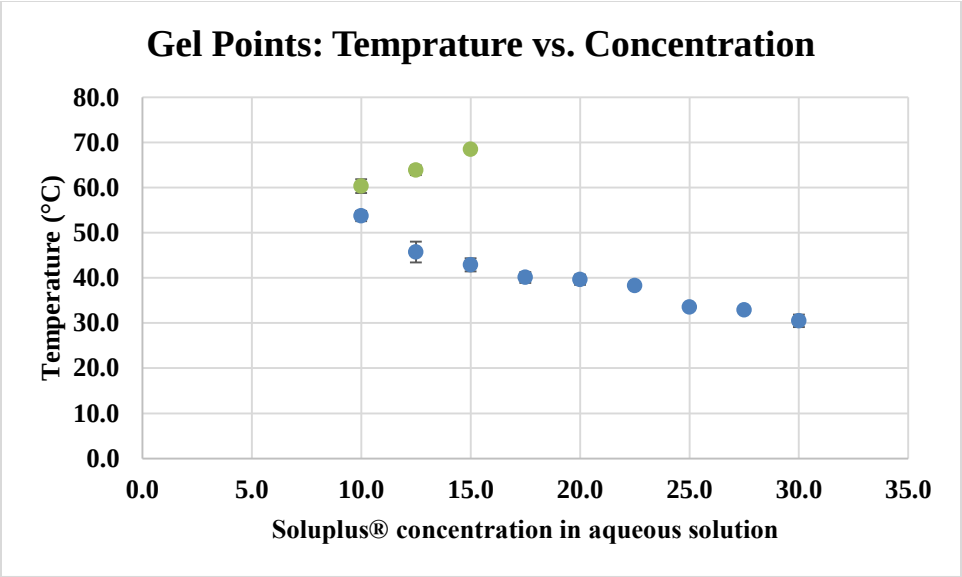


Figure 22. The Average gel point for each SP concentration presented in Temp vs. SP Concentration graph. The concentrations below 10% never gelled.

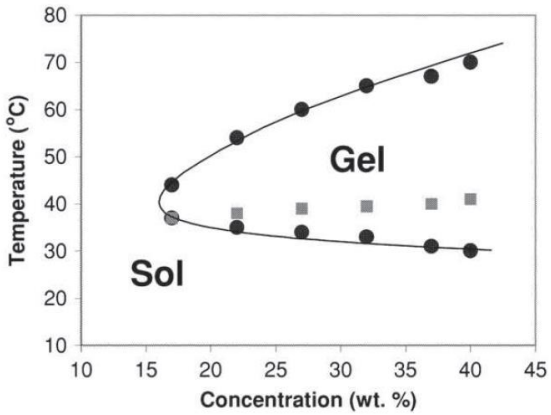


Figure 23. Gel Points of tri block copolymer that contains two PEG units in aqueous solution. The shape of the SP curve is similar to the PEG copolymer.[37]

3.2 Ibp Solubility Studies

Each Base Cream #2 (BC2) was analyzed 3 times as describe in section 2.3. Each Base Cream #1 (BC1) was analyzed twice. All the average concentrations of Ibp from centrifuge tubes were calculated and tabulated. Overall, there were approximately 12 repetitive measurements of Ibp concentrations in BC2 and 8 for BC1 creams. Table 4 shows a representative set of calculations that were performed to determine the concentration of Ibp in each centrifuge tube, and then for each cream. Then the average concentrations of all the three runs were calculated along with the corresponding standard deviations (see Table 6 and 7 for BC #1, and Table 8 and 9 for BC #2). The concentration of Ibp was calculated in g/mL, however the final average concentrations are given in mg/mL. The total average of Ibp concentrations in the creams were plotted as graphs.

Table 6 Individual and Averaged Concentrations of Ibp in the oil phase for BC1 Batches

Cream Code	Batch #1	Batch #2	Average	StDev
	mg/ml	mg/ml	mg/ml	mg/ml
103	59.3	56.0	56.6	2.3
	59.4	55.5		
	58.5	54.4		
	56.7	53.0		
104	52.4	46.4	49.5	5.1
	59.0	44.9		
	49.6	45.6		
	53.3	44.4		
105	3.08	4.71	3.4	0.84
	2.27	4.17		
	2.35	3.43		
	3.33	3.70		
106	n/a	6.35	7.3	1.0
	n/a	8.63		
	n/a	7.58		
	n/a	6.63		
107	173	182	179	6.3
	175	180		
	169	184		
		187		
108	153	173	160	6.2
	155	160		
	159	160		
	156	164		

Table 7. Individual and Averaged Concentrations of Ibp in the water phase for BC1 Batches

Cream Code	Batch #1	Batch #2	Average	StDev
	mg/ml	mg/ml	mg/ml	mg/ml
103	1.98	1.47	1.77	0.29
	2.14	1.64		
	2.09	1.50		
	1.93	1.44		
104	3.06	1.28	2.3	1.1
	3.89	1.00		
	3.21	1.07		
	3.06	1.66		
105	12.7	12.4	12.6	0.24
	12.9	12.4		
	12.5	12.4		
	13.0	12.6		
106	13.6	13.4	13.5	0.21
	13.6	13.3		
	13.8	13.2		
	13.5	13.2		
107	10.3	10.3	12.4	2.1
	12.1	11.6		
	15.5	12.1		
		14.9		
108	17.0	14.5	15.4	1.5
	17.8	13.3		
	14.8	13.9		
	16.0	15.4		

Table 8.Individual and Averaged Concentrations of Ibp in the oil phase for BC2 Batches

Cream Code	Batch #1 mg/ml	Batch #2 mg/ml	Batch #3 mg/ml	Average mg/ml	StDev mg/ml
203	57.4	59.0	63.2	59.9	3.9
	56.2	60.1	62.5		
	56.2	56.4	66.0		
	57.7	56.7	67.5		
204	32.4	44.0	44.2	41.6	2.4
	30.9	47.6	48.8		
	31.0	46.5	49.4		
	31.4	46.7	46.8		
205	4.45	2.66	5.21	4.01	0.74
	3.92	3.08	4.41		
	4.11	3.86	4.89		
	3.73	3.76	3.81		
206	n/a	n/a	n/a	n/a	n/a
	n/a	n/a	n/a		
	n/a	n/a	n/a		
	n/a	n/a	n/a		
207	128	171	184	166	33.3
	134	178	191		
	122	181	197		
	120	n/a	214		
208	139	150	158	152	11.2
	140	158	160		
	145	153	159		
	135	166	171		
209	1.69	6.03	3.89	4.4	2.1
	1.66	5.98	4.38		
	1.78	5.22	4.38		
	n/a	8.62	4.34		
210	n/a	4.20	6.12	5.7	1.4
		3.93	5.62		
		4.24	7.86		
		5.74	7.95		

Table 9. Individual and Averaged Concentrations of Ibp in the water phase for BC2 Batches

Cream Code	Batch #1 mg/ml	Batch #2 mg/ml	Batch #3 mg/ml	Average mg/ml	StDev mg/ml
203	0.294	4.38	0.138	0.62	0.44
	0.540	3.61	0.172		
	0.600	8.23	1.29		
	0.729	3.83	1.21		
204	1.55	2.466	2.43	2.13	0.44
	1.52	2.37	2.59		
	1.57	2.646	2.43		
	1.62	2.186	2.14		
205	12.13	11.27	12.6	12.1	0.69
	12.77	11.32	11.8		
	12.67	11.27	13.1		
	12.56	11.15	12.5		
206	12.14	13.3	14.05	13.4	0.70
	12.76	13.5	14.1		
	12.67	13.7	14.37		
	12.57	13.5	13.89		
207	14.4	9.54	8.84	10.8	1.9
	13.2	9.50	9.44		
	12.7	9.68	10.23		
	11.7	n/a	9.61		
208	5.78	7.85	6.21	6.4	1.1
	5.65	7.54	5.67		
	5.23	7.58	5.64		
	5.28	8.16	5.78		
209	51.4	60.3	57.1	57.1	4.8
	51.3	61.7	58.6		
	51.2	62.6	58.5		
	50.5	63.3	59.0		
210	58.6	59.8	60.4	59.6	0.57
	58.8	59.8	59.5		
	59.1	59.9	60.5		
	59.8	60.0	59.4		

Effect of SP on Ibp Solubilities in BC2 formulations. In Table 2 in Section 2.3 there is a full description of the sampling codes. In Figure 24 the average concentrations are presented as columns and the standard deviation represented by the error bars.

Figure 24A and 24B show that free acid Ibp (H-Ibp) is partitioning significantly more into the oil phase compared to salt Ibp (Na-Ibp), seen in both 1% Ibp creams (Creams 203, 204) and 5% Ibp creams (Cream 207, 208). The concentrations of H-Ibp was higher in 5% creams, however, it did not increase by 5-fold as it was expected – ~60mg/ml in Cream 203 and ~165mg/ml in Cream 207. As shown in Figure 24A, Cream 006 exhibit no oil phase. Another observation from the Figure 24A and 24B, is that 1% H-Ibp cream without SP (203) had higher concentration of H-Ibp in the oil phase compare to the creams with SP (204). For the 5% Cream type, the results were not significantly different to 95% level of confidence and suggest that SP does not have a large effect on the solubility of H-Ibp in the oil phase.

As expected, since Na-Ibp is soluble in water, the results in Figures 25A and 25B show that Na-Ibp is partitioning significantly more in the water phase compared to H-Ibp. These observations are true for both 1% Ibp and 5% Ibp creams. Creams with 5% Na-Ibp (Creams 209&210) had around 5-fold increasing from 1% Na-Ibp (Creams 205&206). For H-Ibp, Cream 207 had more than 5-fold increasing with regards to Cream 203. Cream 208 had around 3-fold increasing with regards to Cream 204. Creams that contain SP tend to have higher concentrations of H-Ibp in the water phase compare to creams without SP. These results are true for all creams except Cream 208 (5% H-Ibp, 3g SP), which had less Ibp concentration in the water phase compared to cream 207 (H-Ibp, no SP). This result is unexpected, as SP as an emulsifier and as a solubilizing agent should

helped H- and Na-Ibp become more soluble in the water phase, compared to the PS60 emulsifier alone. Creams with Na-Ibp had around the same concentrations in the water phase in creams with SP and without. All the results are statistically different to 95% confidence.

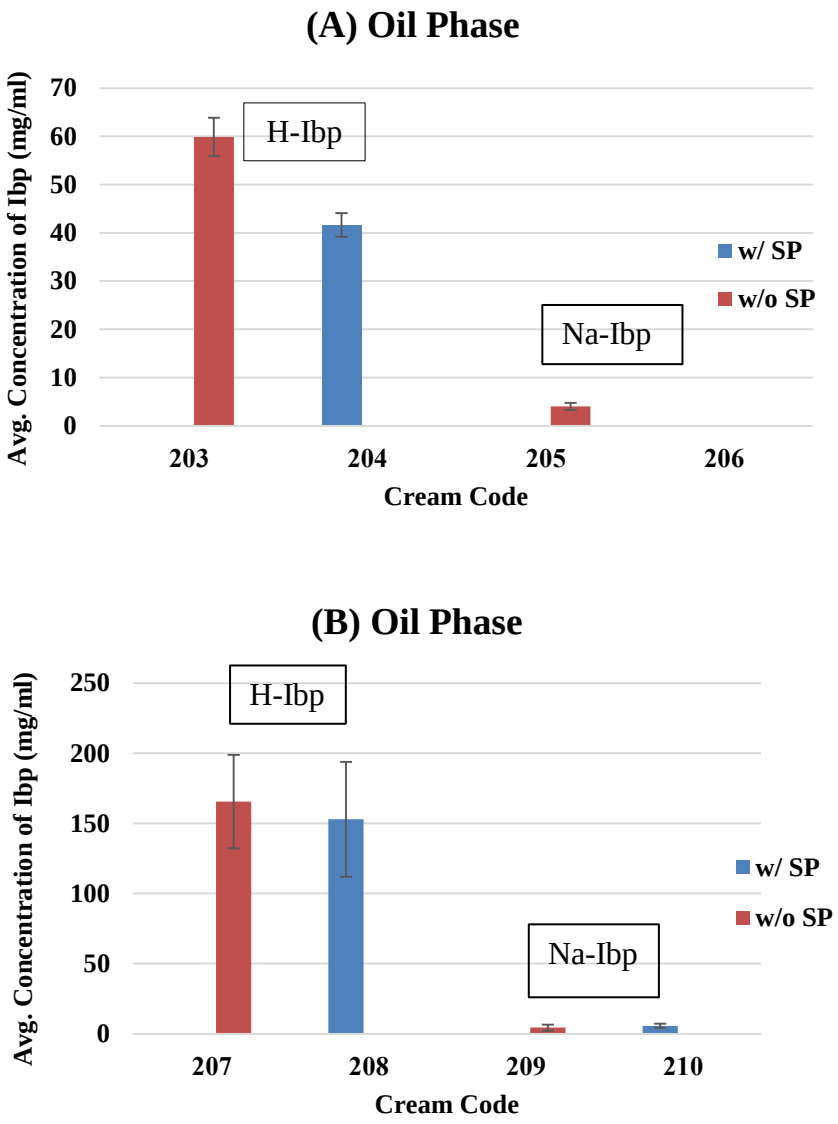


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Figure 24. Average concentrations of ibuprofen in the oil phases in BC2 formulations containing (A) 1% H-Ibp in 203&204, 1% Na-Ibp in 205&206 (B) 5% H-Ibp in 207&208, 5% Na-Ibp in 209&210. Error bars represented the standard deviation.

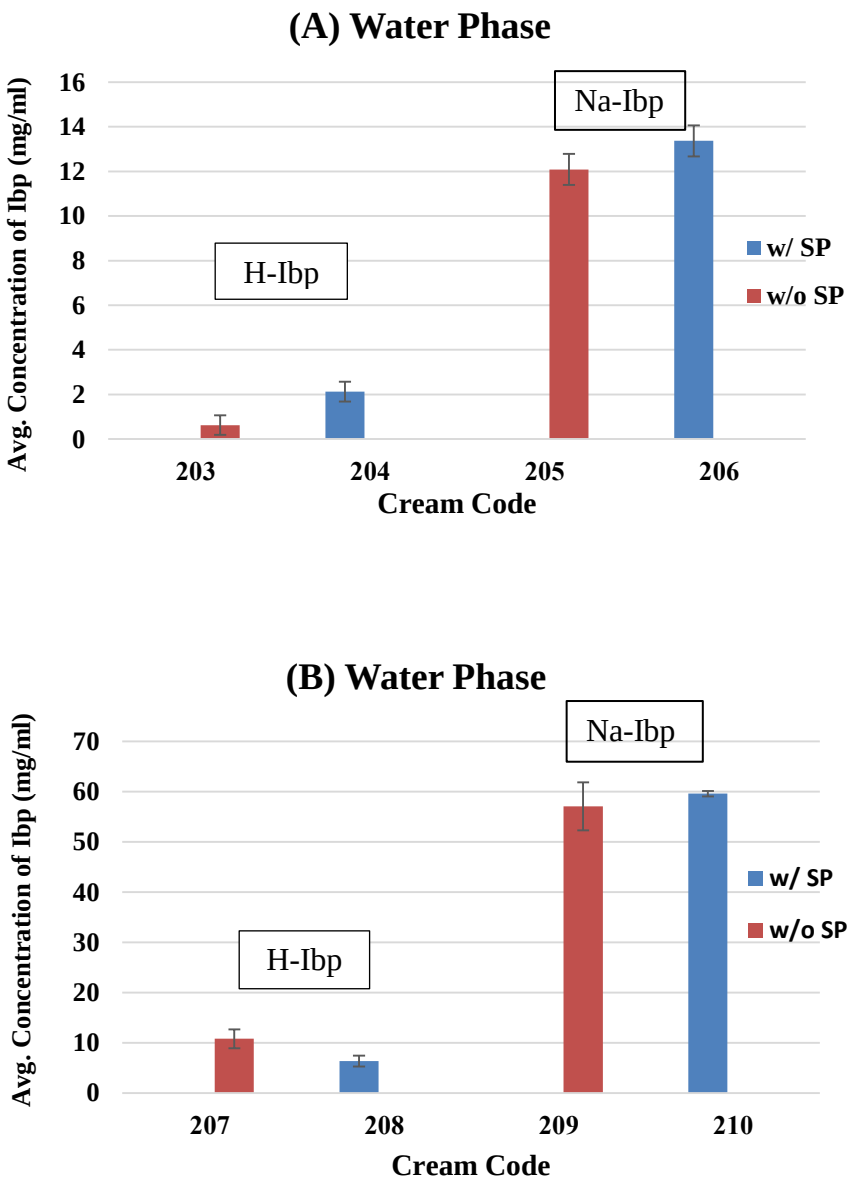

Figure 25. Average concentrations of ibuprofen in the water phases in BC2 formulations containing (A) 1% H-Ibp in 203&204, 1% Na-Ibp in 205&206 (B) 5% H-Ibp in 207&208, 5% Na-Ibp in 209&210. Error bars represented the standard

Effect of SP on Ibp Solubilities in BC1 formulations. Similar to what happened in BC2, H-Ibp in BC1 partitioned mostly into the oil phase, while Na-Ibp partitioned mostly into the water phase. Unlike Cream 206, which did not produce an oil phase, Cream 106

produced a significant amount of oil phase. Moreover, as it seen in Figure 26A, the concentration of Na-Ibp was higher compared to 105 (the same formulation but without SP; see Table 3). This implies that SP helped to partition more Na-Ibp into the oil phase of this cream formulation. Creams that contained SP and 1% Na-Ibp had higher concentrations in the oil phase compared to creams that did not contain SP. The 5% H-Ibp formulations showed more partitioning into the oil phase of Cream 107 (no SP) compared to Cream 108 (SP). These results were different to 95% confidence interval.

Figure 26B shows that creams with SP had higher concentrations of both types of Ibp in the water phase. However, only in creams with Na-Ibp and SP the results were different to 95% confidence interval. There were no significant differences to within a 95% confidence interval between creams that had SP and cream that did not for both 1% and 5% H-Ibp cream types in the water phase.

Comparison Between the Emulsifiers PS60 and CS20. When comparing the oil phase of BC1 and BC2, H-Ibp partitioned slightly more into the oil phase of Cream 203, compared to 103. Cream 104 had higher concentration of H-Ibp in the oil phase compared to Cream 204 (Figure 27A). Both Cream 107 and Cream 108 had slightly higher concentrations of H-Ibp in the oil phase compared to Cream 207 and Cream 208 respectively (Figure 27B).

Cream 205 had slightly higher concentration of Na-Ibp compared to Cream 105. Cream 206 did not exhibit any oil phase, whereas Cream 106 did (Figure 27C).

The comparison between 103 and 203 and 106 and 206 are significant different to 95% confidence interval, however the rest of the results are not. Overall, it seems that

CS20 together with SP as emulsifiers effect the solubility of that H- and Na-Ibp in the oil phase. PS60 tends to have better solubility of H- and Na-Ibp in the oil phase without SP.

For the water phase, all BC1 creams had higher concentrations of H- and Na-Ibp compared to the BC2 creams (see Figures 27A-C). Though, only the significant difference to within a 95% confidence interval was between the emulsifier in Cream 108 and 208.

The results in Figures 28 show that creams with SP and CS20 as emulsifiers had higher concentrations of H- and Na-Ibp in final forms. This suggests that the combination of both emulsifiers helps to partition the H- and Na-Ibp into the water phase much more compared to one emulsifier or PS60 with SP.

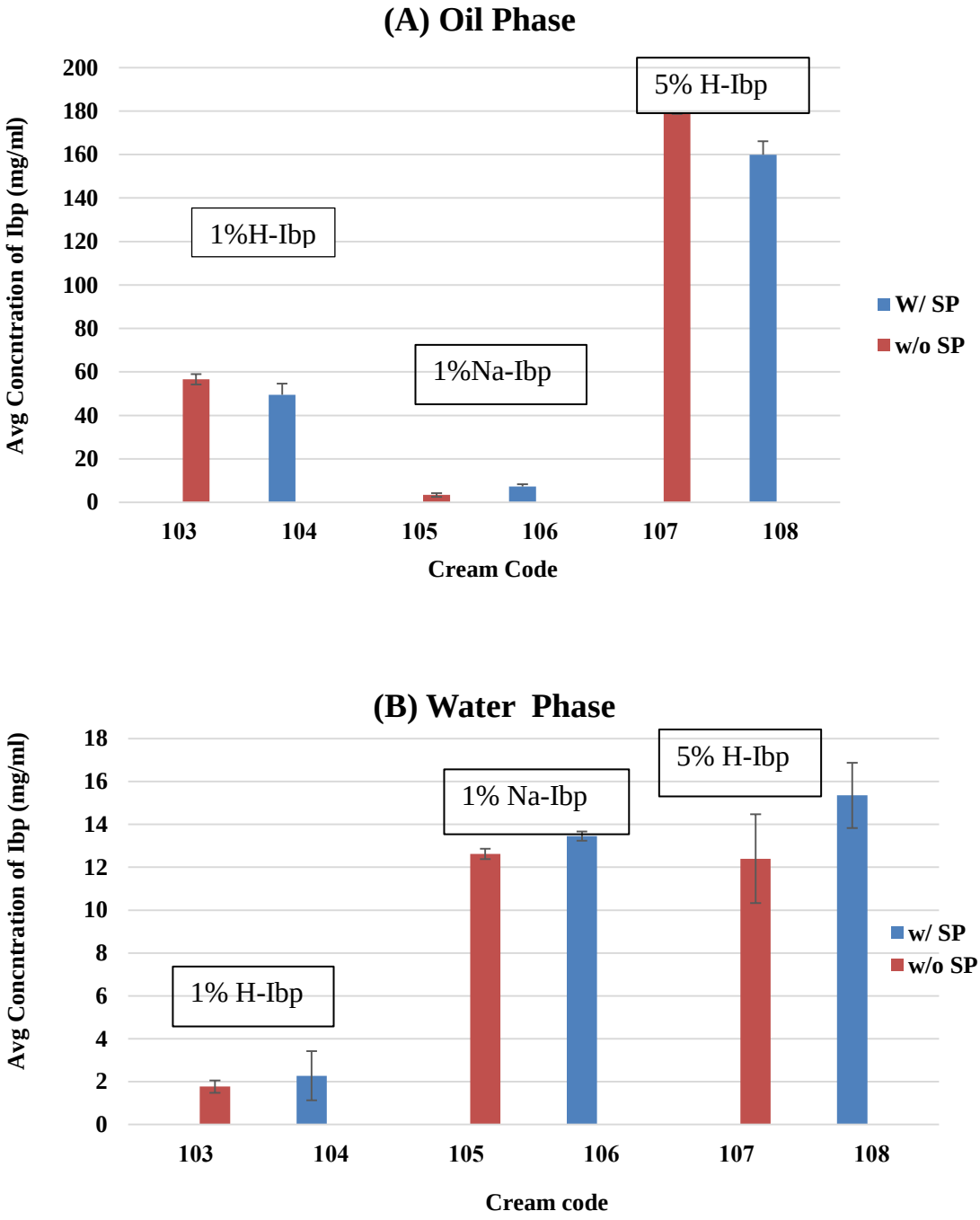

Figure 26. Average concentrations of ibuprofen in BC1 formulations: (A) oil phase and (B) water phase. The Error bars are the StDev.

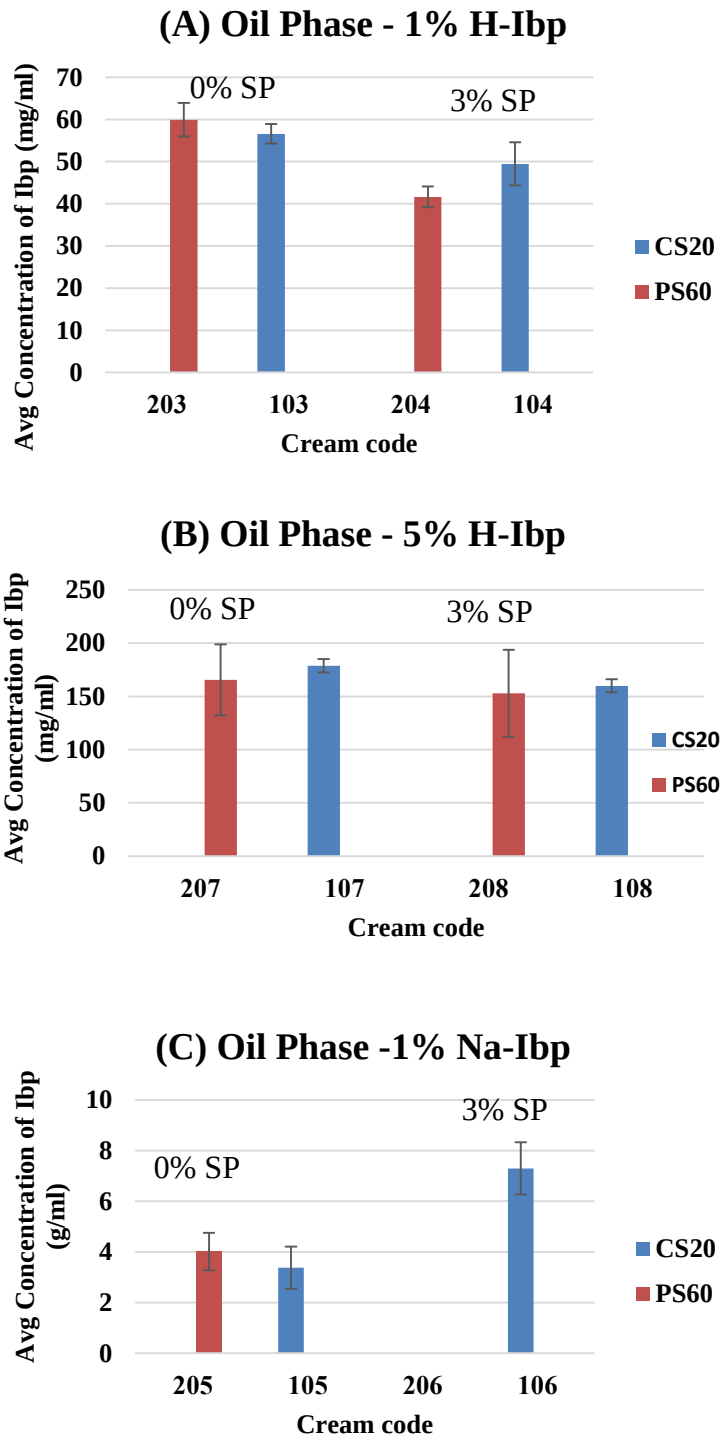

Figure 27. Comparison between two emulsifiers - PS60 and CS20 in the oil phase. (A) 1% H-Ibp; (B) 5% H-Ibp; (C) 1% Na-Ibp. The Error bars are the StDev.

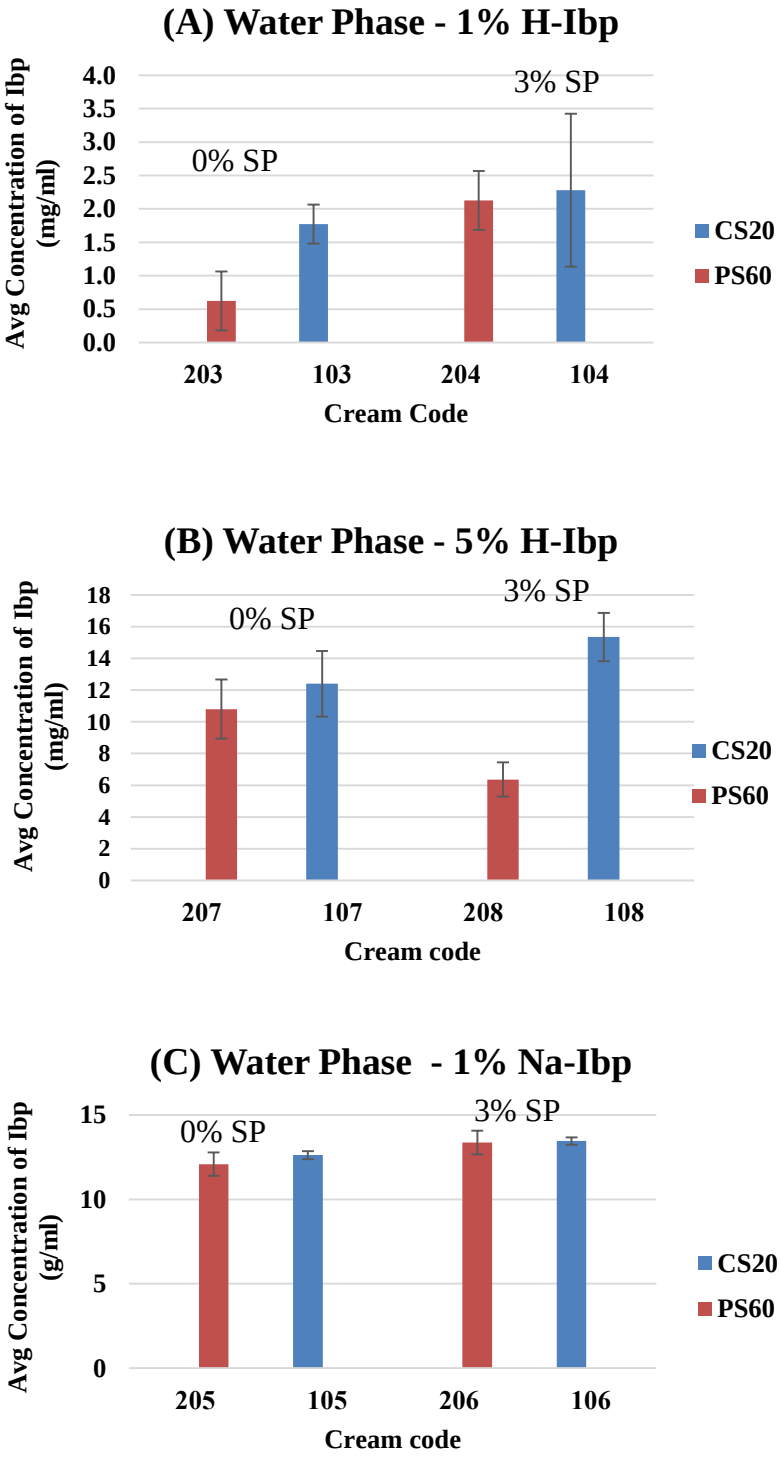

Figure 28. Comparison between two emulsifiers - PS60 and CS20 in the water phase. (A) 1% H-Ibp; (B) 5% H-Ibp; (C) 1% Na-Ibp.

4 DISCUSSION

The physical properties of each new product on the market should be studied and evaluated for future use. Hence, the physical properties of SP, a new potential product, were studied in my research. The cloud point curve of SP shown in Figure 20 is similar to that of PVCL in Figure 21. The gel point curve of SP (Figure 22) also is similar to the curve of a different triblock copolymer that contains PEG (Figure 23). From these results, it likely that PVCL may be responsible for the cloud point behavior of SP. PEG is probably not the part responsible for the sol-gel behavior of SP, but these speculations will require future investigations. This topic will be discussed further in the Future Work section.

SP was designed to be used as a solubilizing agent in oral drugs and specifically for hot melt extrusion processing. Another potential application is the use of SP as a solubilizing agent in topical creams and gels. My research evaluated the partitioning of the APIs (H- and Na-Ibp) in skin cream formulations, where SP was incorporated into the cream formulations as a co-emulsifier. H-Ibp is insoluble in aqueous solution and soluble in organic solvents, while Na-Ibp is soluble in aqueous phases and rather insoluble in oil phases. Thus, the unaided partitioning of H-Ibp primarily into the oil phase and Na-Ibp primarily into the water phase was expected and observed. Another observation from this study was the higher concentrations of H- and Na-Ibp in the water phase in creams that contained SP compared to creams without it. However, the higher concentration of H-Ibp in the water phase in Cream 207 (no SP) compared to Cream 208 (w/ SP) was unexpected.

SP, PS60 and CS20 are the emulsifiers that were used in the creams formulations (see Section 2.3). By definition, they are amphiphilic polymers (PS60 and CS20 are fairly small compared to SP) that can potentially form polymeric micelles and entrap the drug in their core. The formation of the polymeric micelle occurs only when the concentration of the emulsifier exceeds the critical micelle concentrations (CMC),[37] The concentration above which micelles form. The CMC values are influenced by the molecular weight of the polymer and the hydrophobicity of the core forming block copolumers.[38] Hence, it was expected that SP's CMC was smaller compared to PS60 (7.6 mg/L,[17] and 18.9 mg/L,[39] respectively). These values are suggesting that SP formed more polymeric micelles with the H- and Na-Ibp entrapped inside the core and eventually causing it to dissolve better in the aqueous environment. Since SP is soluble in water, the drug should exhibit a higher concentration in the water phase compared to the drug without SP. In addition, the volume of the water phase was larger and some of the oil phase was slightly smaller in creams that contained SP compared to creams that did not. A possible explanation could be the formation of SP micelles around oil droplets in addition to the SP micelles around H- and Na-Ibp through a similar mechanism.

Drug loading capacity, the maximum amount of drug contained within the polymer, could be another aspect that suggests the differences in the water phase between creams that contained SP and creams without it. The compatibility of the drug and a polymer used for encapsulation, as well as the chemistry of the hydrophilic core of the polymer, can suggest how efficient the drug loading capacity is. Similar structure and polarity between the drug and polymer can lead to a better compatibility. Also, good compatibility between the drug and polymer core can help with drug entrapment and

micelle stability. Modification and derivatization, such as adding a longer hydrophobic block, were shown to help the drug loading and the micelle stability.[38,40] The drug loading capacity also increases with increasing concentration of the drug – the higher the concentration, the bigger the micelles that are formed, leading to a higher drug loading capacity. When increasing the concentration of the polymer, the drug loading increased until a plateau is reached and the micelle is fully saturated.[40]

A possible explanation of why the concentration of H-Ibp in Cream 208 (5% H-Ibp, 3g SP) was determined to be lower when compared to Cream 207 (5% H-Ibp, 0g SP) could be that the hydrophilic portion of the PS60 (the ethoxylated sorbitan) is interacting with the SP, rendering less available from both SP and PS60 to dissolve the drug. Also, it could be that SP is entrapping PS60 into the core, and leading to less PS60 to dissolve the drug.

In my study, the numbers of moles of H- and Na-Ibp that might be inside one mole of SP core were estimated using simple calculations. The calculations included finding the molarity of H- and Na-Ibp in the water phase of the creams with and without SP, along with the molarity of SP. To do that, the average concentration of the H- and Na-Ibp in the water phase converted to molarity using the following equation:

$$avg\,\frac{g}{ml} * \frac{1mol}{206.29g} * \frac{1000mL}{1L} = \frac{mol}{L}$$

The molarity of H- and Na-Ibp in creams without SP was subtracted from the molarity of H- and Na-Ibp in cream with SP. The results of the subtraction were divided by the molarity of SP in the cream. Throughout all the study, the concentration of SP in the cream formulation was consisted as 3g/100mL, and the molarity (based on a molar mass of 118,000 g/mol; Section 1.3) was found to be 0.000254mol/L for all the

calculations. The final results gave us the "excess" number of moles of H- and Na-Ibp that were made soluble by the presence of SP core. Tables 10 and 11 give the molarities and the number of moles of Ibp per 1 mole of SP.

Table 10. Calculation series and number of mole of Ibp per one mole of SP in

Cream Code	M Ibp w/o SP	M Ibp w/ SP	Difference	M of SP	1 mol Ibp / 1 mol SP
103	0.0086				
104		0.011	0.0026		10
105	0.055				
106		0.059	0.0037	0.00025	14
107	0.060				
108		0.074	0.014		56

Table 11. Calculation serious and number of mole of Ibp per one mole of SP in BC2

Cream Code	M Ibp w/o SP	M Ibp w/ SP	Difference	M of SP	1 mol Ibp / 1 mol SP
203	0.0030				
204		0.010	0.0073		29
205	0.053				
206		0.059	0.0056		22
207	0.052			0.00025	
208		0.031	-0.022		-85
209	0.25				
210		0.26	0.011		43

The results from Tables 10 and 11 show that the number of mole of H- and Na-Ibp per one mole of SP increases with increasing the percentage of the drug inside the cream (Cream 107/108 compared to 103/104). This is consistent with data found in the literature – higher concentrations of drugs lead to a larger drug loading capacity.[40]

Polysorbate 60 (PS60), macrogol cetostearyl ether 20 (CS 20) and SP were the emulsifiers in this study. PS60 contains a C18 group as the hydrophobic tail, and an ethoxylated sorbitan as the hydrophilic head (Figure 29).

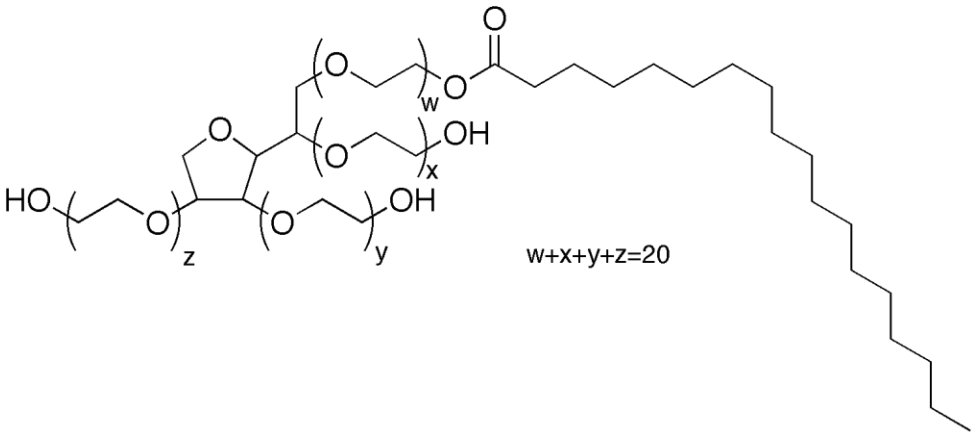

Figure 29. Polysorbate 60 structure. Contains C18 as the hydrophobic tail, and an ethoxylated sorbitan as the hydrophilic head.[41]

Macrogol cetostearyl ether 20 (CS20) is a polyethoxylated (PEG 20 chain) esterified to a range of C16s and C18s. Overall, the structures of the two emulsifiers are fairly similar, especially when comparing the hydrophobic chains. Moreover, in half of the cases, the CS20 is going to also have a C18 saturated lipid chain. This will anchor the inside of the oil droplet in both emulsifiers, leaving the ethoxylated portions exposed to the water. Another comparison between the PS60 and CS20 is the hydrophilic-lipophilic balance (HBL) values, which are 14.9 and 15 respectively. These values suggest that functionally the two emulsifiers have roughly the same balance of hydrophobic to hydrophilic character and will function similarly.

There were slightly higher concentrations of 1% and 5% H-Ibp in creams that contain CS20 compared to creams that contained PS60. A possible explanation for this result is that when SP was absent, Ibp was dissolve slightly more into the CS20 polymeric micelles in the water phase, particularly with 1% H-Ibp concentrations. With higher API concentrations, this effect is essentially washed out. Since Na-Ibp is already an order of magnitude more soluble, the effect is minimal. The presence of SP assist in the solubilization of mainly H-Ibp and has an additive effect to the CS20 solubilization. Also, the amount of H-Ibp observed decreased in the oil phase in creams with SP as was expected. This is because there is more SP in the aqueous phase, and SP solubilizes more Ibuprofen when taken from the oil phase.

5 CONCLUSION & FUTURE WORK

5.1 Conclusions

Since SP has shown to help the solubility of API in oral application, the long term goal of this project is to show that SP can also increase the solubility of API in topical creams and gels. Another goal of this project is to characterize the physical properties of SP, due to SP being a new product on the market.

My thesis is pioneer work that was done on physical properties of SP and the current topical applications. The cloud and the gel points of SP were found using UV-Vis and hot water bath with digital thermometer, respectively. The results of the curves matched the curves from polymers containing the individual building blocks of SP.

For the current application, it was found that the presence of SP in H-Ibp and Na-Ibp increased the partitioning of API into the water phase due to a significantly increased solubilzation capacity; this would result in improved API concentration in contact with the skin for oil in water emulsion.

5.2 Future work

The studies describes in my thesis could be followed by future investigation in a number of possible directions.

Physical Properties. The gel points were found in a standard method, but can be performed more accurate. A better, more scientific way to measure the gel points is to measure the viscosity of SP in different concentration in aqueous solutions. To do that, a

rheometer instrument and viscosity studies will be needed. This is currently another branch of this project.

My thesis focused on the cloud and gel points of SP as a whole. But, to evaluate which part of the copolymer is responsible for the cloudiness and the gelation of SP, each of the building blocks will have to evaluate separately. The cloud points method in section 2.3.1 is an accurate method and should be used in the future. For the gel points, the viscosity of SP and each of its building block should be evaluated using rheometery.

Current Applications. Each emulsion required oil phase, water phase, and emulsifier. The formulations are common formulations that are used in the industry. For a future study, it will be interesting to see if different compositions of oil phase, water phase, and especially emulsifier can contribute to the solubility of the APIs.

Moreover, this research was checking the solubility of API in skin creams only. Another future study could be applying SP as emulsifier also in gels and lotions.

Micelle Characterizations. The theory behind the results that were observed in my study related mostly to the formation of polymeric micelle between the polymers and the drugs. Future in depth studies could be used to verify the results in my thesis. Currently some work is being done to observe if there is a change of the micelle' size due to temperature change or concentration change. Also, some work was done on a mixture of API with emulsifier and SP to see the change in the micelles size. This work is done by using a dynamic light scattering (DLS) instrument.

Moreover, the micelles should be characterized not only when mixing an API with emulsifier and SP, but actual characterizing the micelle inside the oil phase and the water phase of the creams after centrifugation.

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