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PRODUCTION OF CREAM PREPARATION CONTAINING RUXOLITINIB PHOSPHATE ACTIVE INGREDIENT WITH WATER IN OIL SYSTEM

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ABSTRACT

The aim of this study was to develop a formulation of a topical cream dosage form containing the active ingredient ruxolitinib phosphate, which is used effectively in non-segmental vitiligo disorders by specifically blocking JAK1 and JAK2, two enzymes involved in various cytokine pathways that contribute to inflammation, pruritus and skin barrier function in the skin, using the water in oil system within the scope of the patent overrun study. The present study describes the formulation, manufacturing method and the optimized formulation and manufacturing process of the Opzelura Cream product containing the active ingredient Ruxolitinib Phosphate, which has the targeted specification features, with the water in oil system, which is the reverse process of the oil in water system specified in the formulation patent number EP2574168B9.

KEYWORDS: Ruxolitinib phosphate, water oil, water in oil, cream, opzelura.

1. INTRODUCTION

Cream

Creams are emulsions, usually containing more than 20% water and less than 5% and/or 50% hydrocarbons, waxes or polyols as carriers.[1] It is defined as a semi-solid dosage form containing one or more drug substances, usually consisting of an oil and water phase, dissolved or dispersed in a base suitable for external application to the skin or mucous membranes. There are two types basedon phase.

a. Oil-in-water (o/w) type cream
b. Water-in-oil (w/o) type cream

a. Oil-in-Water (O/W) Type Cream

A cream system consisting of small oil droplets, mostly dispersed in a water phase. They are more comfortable and cosmetically acceptable because they are less oily and more easily washed off using water. They can be produced using natural emulsifiers (beeswax, wool alcohols, wool grease).

b. Water in Oil (W/O) Type Cream

It is an oil-in-water (W/O) cream system consisting of small water droplets dispersed in a mostly oily phase. It is more difficult to use, however, many of the active ingredients included are hydrophobic and are more easily released in a W/O cream system than in an O/W cream. It is therefore more moisturising because it provides an oily barrier that reduces water loss from the stratum corneum, the outermost layer of the skin.[2]

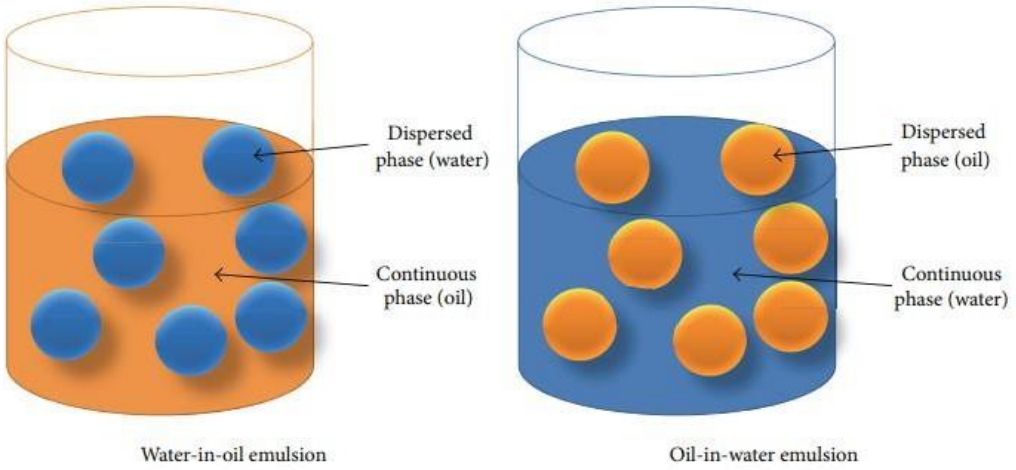


Figure 1: Oil in water and water in oil system.[3]

Substances Used in Cream Ingredients

Ruxolitinib, formerly known as INCB018424 or INC424, is an anticancer drug and a Janus kinase (JAK) inhibitor. It is a potent and selective inhibitor of JAK1 and JAK2, tyrosine kinases that play a role in cytokine signaling and hematopoiesis. By inhibiting JAK1 and JAK2, it blocks unregulated cell signaling pathways and prevents abnormal blood cell proliferation. Due to the large number of myeloproliferative neoplasm patients with JAK2 mutations, ruxolitinib is the first ATP-competitiveJAK1 and JAK2 inhibitor ever developed.[4]

Ruxolitinib was first approved by the FDA in 2011 for the treatment of adult patients with myelofibrosis, followed by EMA approval in 2012. In 2014, it was approved for the treatment of polycythemia vera in adults who have had an inadequate response to or are intolerant to hydroxyurea, and in 2019, ruxolitinib was approved for use in adults and children for steroid- refractory acute graft-versus-host disease.[4] The topical formulation of ruxolitinib is used to treat atopic dermatitis and vitiligo. The FDA has approved Opzelura cream, which contains the active ingredient ruxolitinib, for the treatment of non-segmental vitiligo in adult and pediatric patients 12years of age and older. Opzelura is a topical Janus kinase (JAK) inhibitor currently approved for thetopical short-term and discontinuous chronic treatment of mild to moderate atopic dermatitis in immunocompromised patients 12 years of age and older whose disease is not adequately controlledby topical prescription therapies or when such therapies are not recommended.[5,6]

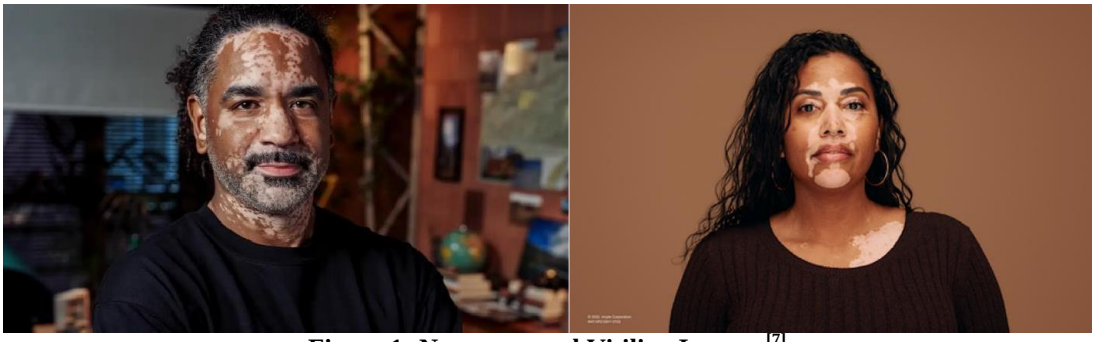


Figure 1: Nonsegmental Vitiligo Images.[7]

In addition to the active ingredient or ingredients, there are various auxiliary raw materials used to obtain the cream product. These raw materials have various functions and purposes.

1. **Water:** It is the most important and widely used raw material in any cream formula. It is the cheapest and most readily available. In skin creams, it is used as a solvent to dissolve other ingredients. Water can also form emulsions, which depend on how much water is used in the formulation and are sometimes called water-in-oil emulsions and sometimes oil-in-water emulsions depending on the amount of oil phase and water phase used.[8]
2. **Oils and Waxes:** Oils and waxes, their derivatives, form an essential part of creams. Waxes actas emulsifiers, oils as thickeners and, depending on their function, as perfumes, preservatives, etc. Different types of oils are used in the preparation of creams. These materials can be of animal, vegetable or mineral origin. Glyceride oils and fats can be of animal or vegetable origin. They are composed of combinations of higher fatty acids and glycerin. When saponified, they form soap or fatty acid and glycerin, depending on the process used. The most common of these fatty acids are lauric, palmitic, stearic, saturated group. Oleic acid is a liquid and the most popular unsaturated fatty acid.[9]

a. **Mineral oil:** Mineral oil is composed of hydrocarbons derived from petroleum oil. Mineral oil is a clear, odorless, and highly refined oil that is widely used. It is light and inexpensive, helps reduce water loss from the body, and keeps the body moist. A number of mineral oils areused in cream formulations.

b. **Glycerine oil:** Glycerine oil is mostly vegetable oil. Examples of glycerine oils include almond oil, peanut oil, castor oil, coconut oil, olive oil, etc.

c. **Vegetable oil:** It forms a barrier on the skin's surface and helps the skin maintain its fullnessby slowing water loss. Vegetable oils can also be used to increase the thickness of the lipid or oil portion of creams or personal care products. For example, almond oil, seed oil, avocado oil,sunflower oil, etc.[10]

d. **Waxes:** Those used in cream preparation include beeswax, etc. Waxes help prevent the separation of the oil and liquid components of a cream dosage form. These waxes also increasethe thickness of the lipid part and adhere to the surface of the skin.

e. **Lanolin:** It is obtained from the wool fat of sheep. There are two types of lanolin. Hydrous lanolin contains 25% - 30% water. Anhydrous lanolin has a temperature point of 38°C - 42°C and has a mild odor. These components act as lubricants on the skin surface, giving the skin a soft and smooth appearance. Lanolin helps form emulsions and mixes well with other ingredients used in cosmetics and personal care products.[11]

3. **Colors:** Before the development of modern technology, colors primarily came from naturally occurring substances such as turmeric, saffron, indigo, etc. They could also be produced without the use of plants harvested from the wild.[12]
4. **Emollients:** Emollients, also commonly referred to as moisturizers, are products that help softenskin or treat dry skin.

5. Humectants: These are important multifunctional ingredients found in most skin care formulas. Humectants are hydroscopic organic compounds. They are materials that can absorb or retain moisture. Examples include glycerin, Hydroxyethyl urea, betaine, sodium PCA, Sodium-L- Lactate, etc.[13]

6. Fragrances: A fragrance is a substance that imparts a scent or a pattern, including a sweet and pleasant smell. Examples of natural fragrances used in creams are: rose oil, jasmine flower oil, orange blossom, etc.

7. Vitamins: Vitamins play an important role in maintaining the physiological function of the entire body and skin. Vitamins A, B, C, E, etc. are generally used in the formulation of creams.

8. Preservatives: The use of preservatives is important to prevent conditions that will affect product quality due to microorganisms and contamination during product formulation, storage, and consumer use. Antioxidants can also be used to protect against conditions caused by exposure to oxygen.

2. MATERIALS AND METHODS

2.1 Materials

The ingredients in the formulation were: Ruxolitinib Phosphate (MSN Laboratories Private Limited., India), Cetyl Alcohol (BASF, Germany), Stearyl Alcohol (CRODA International Plc, UK), Dimethicone (RIOCARE INDIA), Disodium Ededate (MERCK, Germany), Glyceryl Monostearate SE (IOI Oleochemical GmbH, Germany), White Paraffin (SONNEBORN, Germany), Xanthan Gum (CP KELCO, India), Light Liquid Paraffin (SAVITA Oil Technologies Limited, India), Medium Chain Triglyceride (IOI Oleochemical GmbH, Germany), Methyl Paraben (CLARIANT, Switzerland), Propyl Paraben (CLARIANT, Switzerland), 2-Phenoxyethanol (SHARON Personal Care, Israel), Polyethylene Glycol 200 (CLARIANT, Switzerland), Polysorbate 20 (CRODA International Plc, UK), Propylene Glycol (SHELL Chemicals, USA), Butyl Hydroxy Toluene (MERCK, Germany).

2.2 Methods

In this study, it was aimed to analyze the topical cream dosage form containing Ruxolitinib Phosphate active ingredient physically and chemically, to evaluate it rheologically by developing itwith the water in oil system and to exceed the oil in water system formulation patent of Opzelura Cream product.

The raw materials and unit formula used in the formulation patent numbered EP2574168B9 of Opzelura Cream product are given in Table 1.

Table 1: Opzelura Cream Product Formulation Patent Formula No. EP2574168B9.[14]

Active Substance	Function	Unit Formula (%)
RUXOLITINIB PHOSPHATE(EQUIVALENT TO 1.5% RUXOLITINIB)	Active Substance	1,98
Yardımcı Maddeler		
CETYL ALCOHOL	Hardening Agent	3,00
STEARYL ALCOHOL	Hardening Agent	1,75
DIMETHICONE	Skin Protector	1,00
DISODIUM EDETAT	Chelator	0,05
GLYCERYL STEARATE SE	Emulsifier	3,00
WHITE SOFT PARAFFIN	Softening Agent	7,00
XANTHAN GUM	Suspending, Viscosity Agent	0,40
LIQUID PARAFFIN	Solvent	4,00
MEDIUM CHAINTRIGLYCERIDE	Softening Agent	5,00
METHYL PARABEN	Antimicrobial Preservative	0,10
PROPYL PARABEN	Antimicrobial Preservative	0,05

2-PHENOXYETHANOL	Antimicrobial Preservative	0,50
POLYETHYLENE GLYCOL 200	Plasticizer, Solvent	7,00
POLYSORBATE 20	Emulsifier	1,25
PROPYLENE GLYCOL	Solvent	15,00
DEIONIZE WATER	Solvent	48,92

The steps given in the patent content as a production method are given below.

1. A paraben phase is prepared by mixing methyl and propyl parabens with some of the propylene glycol.
2. Next, a xanthan gum phase is prepared by mixing xanthan gum with propylene glycol.
3. Next, an oil phase is prepared by mixing light mineral oil, glyceryl stearate, polysorbate 20, whitepetrolatum, cetyl alcohol, stearyl alcohol, dimethicone, and medium-chain triglycerides. The phaseis heated to 70-80 °C to melt and form a homogeneous mixture.
4. Then, an aqueous phase is prepared by mixing pure water, polyethylene glycol, and disodium EDTA. The phase is heated to 70-80 °C.
5. The aqueous phase of step 4, the paraben phase of step 1, and the phosphate salt of the API are combined to form a mixture.
6. The xanthan gum phase from step 2 is then added to the mixture from step 5.
7. The oil phase from step 3 is then combined with the mixture from step 6 under high mixing to form an emulsion.
8. 2-phenoxyethanol is then added to the emulsion from step 7. Mixing is continued and then the product is cooled to volume and mixed at low rpm.

Since it is a production method consisting of multiple steps, this multi-step method is not a desiredsituation as it will affect mass production and create production difficulties. Considering this situation, the development of this patented formulation and production method has been madewithin the scope of patent overrun.

2.3 Studies Conducted

Trial 1: In this study, firstly, a trial was conducted in the water in oil system by reversing the oil inwater system without changing the multiple steps obtained in the production method. In the patent formula, the production method consisting of adding all phases to the water phase in order is appliedand the product is obtained by adding all phases to the oil phase in order without any change in quantity. As a result of the production, when a 20-hour aging at 40^{o}C is performed in the Turbiscandevice, it is seen that there is a phase separation problem.

Table 2: Trial 1 Turbiscan Results.

Global	Bottom	Middle	Top
0.8	1.0	0.6	1.6

As a result, the product was found to be unsuitable as a result of reversing the oil in water system, which is the production method, without making any changes in quantity.

Trial 2: In light of the studies conducted and the results obtained, a study was conducted to developa production method and overcome the patent with a formulation that does not have a multi-step production method, using the main steps that make up the cream dosage form, and where permeability is within the confidence interval criterion.

First, multiple production steps are removed and a production method draft consisting of only waterphase and oil phase is created. For this purpose, raw materials that can dissolve in water and oil, mix and form emulsion are separated. The

following formulation and production method are designed to obtain a product with similar properties to the Opzelura Cream product taken as a reference.

Table 3: Water in Oil System Formula Developed for Patent Exceeding.

Active Substance	Function	Unit Formula (%)
RUXOLITINIB PHOSPHATE (EQUIVALENT TO 1.5% RUXOLITINIB)	Active Substance	%1,98
Yardımcı Maddeler		
CETYL ALCOHOL	Hardening Agent	%1,0-10,0
STEARYL ALCOHOL	Hardening Agent	%1,0-5,0
DIMETHICONE EP	Skin Protector	%1,0-5,0
DISODIUM EDETAT	Chelator	%0,01-0,5
GLYCERYL STEARATE SE	Emulsifier	%1,0-10,0
WHITE SOFT PARAFFIN	Softening Agent	%3,0-15,0
XANTHAN GUM	Suspending, ViscosityAgent	%0,05-1,0
LIQUID PARAFFIN	Solvent	%1,0-10,0
MEDIUM CHAIN TRIGLYCERIDE	Softening Agent	%1,0-15,0
METHYL PARABEN	Antimicrobial Preservative	%0,05-0,2
PROPYL PARABEN	Antimicrobial Preservative	%0,01-0,2
2-PHENOXYETHANOL	Antimicrobial Preservative	%0,1-1,0
POLYETHYLENE GLYCOL 200	Plasticizer, Solvent	%1,0-15,0
POLYSORBATE 20	Emulsifier	%0,5-2,0
PROPYLENE GLYCOL	Solvent	%5,0-20,0
BUTYL HYDROXY TOLUENE	Antioksidant	%0,0005-0,0001
DEİYONİZE WATER	Solvent	%30,0-60,0

Production Method

1. Water Phase: Methyl and propyl parabens are dissolved in heated water. Disodium edetate is added and dissolved. Polyethylene glycol 200 is added. Finally, xanthan gum is added to the clear mixture and mixed.
2. Oil Phase: Liquid paraffin, glyceryl stearate SE, propylene glycol, polysorbate 20, white vaseline, cetyl alcohol, stearyl alcohol, dimethicone and medium chain triglyceride are melted to prepare an oil phase.
3. Combination Phase: The water phase is combined by adding the oil phase to it. Ruxolitinib Phosphate, the phosphate salt of the API, is added to it to form the mixture.
4. Then, 2-phenoxyethanol and butyl hydroxy ethanol are added to the emulsion. Mixing is continued and then the product is cooled under low speed mixing.

The obtained products are compared with the reference product physically, chemically and rheologically.

Table 4: Comparative Results.

	Opzelura Cream	Trial 2
Appearance	White-off-white cream	White-off-white cream
Viscosity	18.976 cp	19.885 cp
pH	3.44	3.25
Related Compounds Amide Impurity Sem Pyrimidine Impurity Acrylo Pyrimidine ImpurityAny Unknown Impurity Total Impurity	 <NL**ND***ND <NL <NL	 <NLND ND %0,08 %0,08
Assay Ruxolitinib Phosphate 15.0 mg/g ± %5 (14.25 mg/g-15.75 mg/g)	14.87 mg/g	14.53mg/g

* Viscosity could not be measured because there was phase separation.
** Neglect limit
*** Not Detected

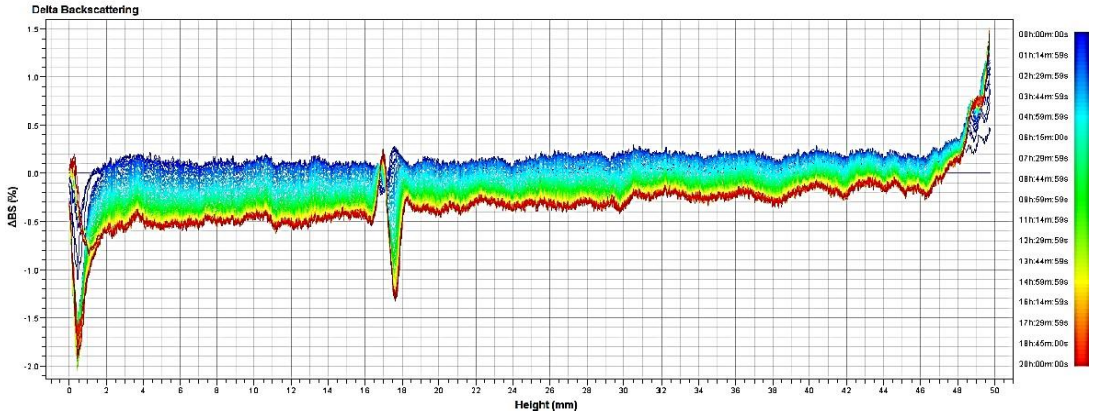
After the visual and analysis results of the trial 2 were found to have similar properties, the aging process was carried out in the Turbiscan device at 40°C for 20 hours. The results are given in Table 5.

Table 5: Trial 2 Turbiscan Result.

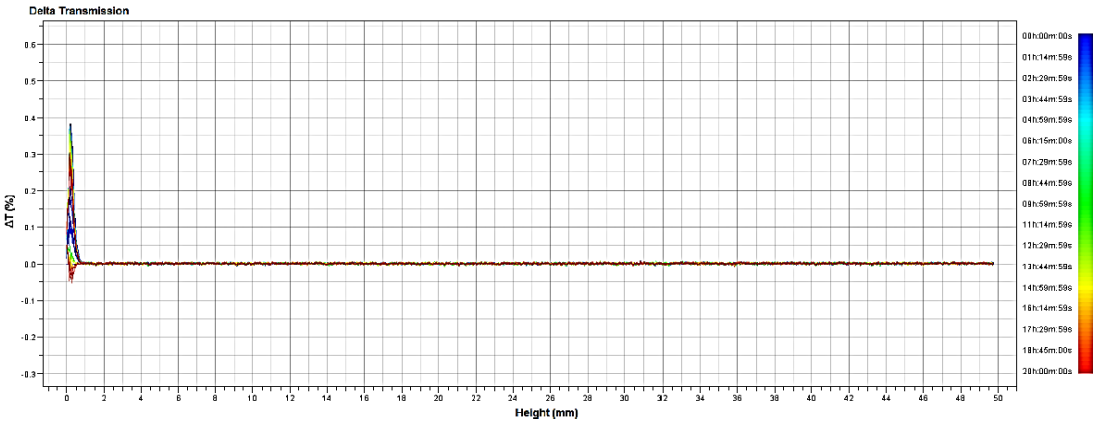
Global	Bottom	Middle	Top
0,7	1,0	0,7	0,7

Table 6: Graphical Representations of Trial 2 Turbiscan Results.

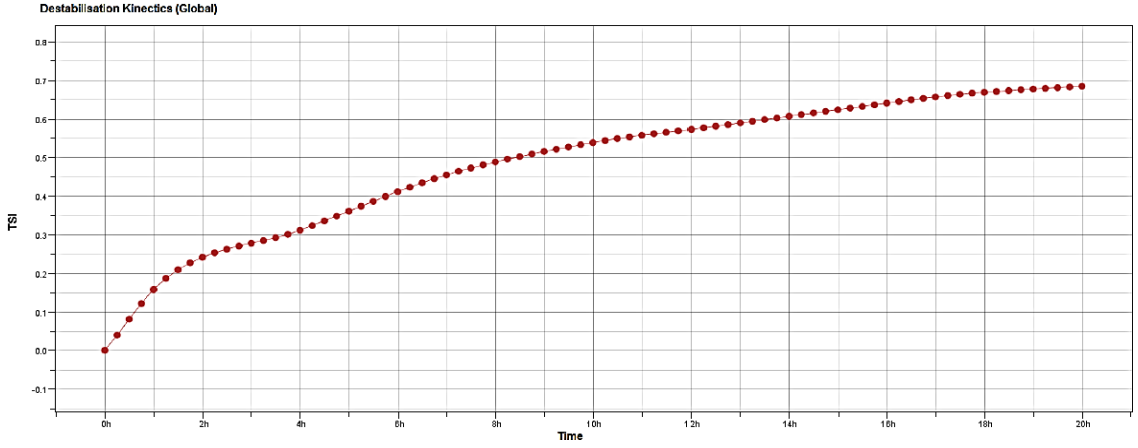
Raw Data - Delta BS



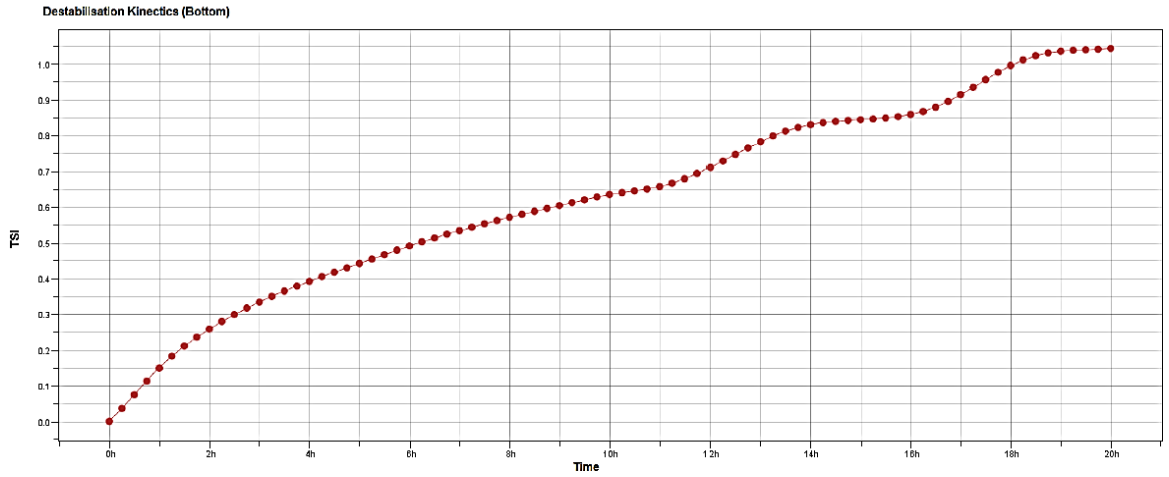
Raw Data - Delta T



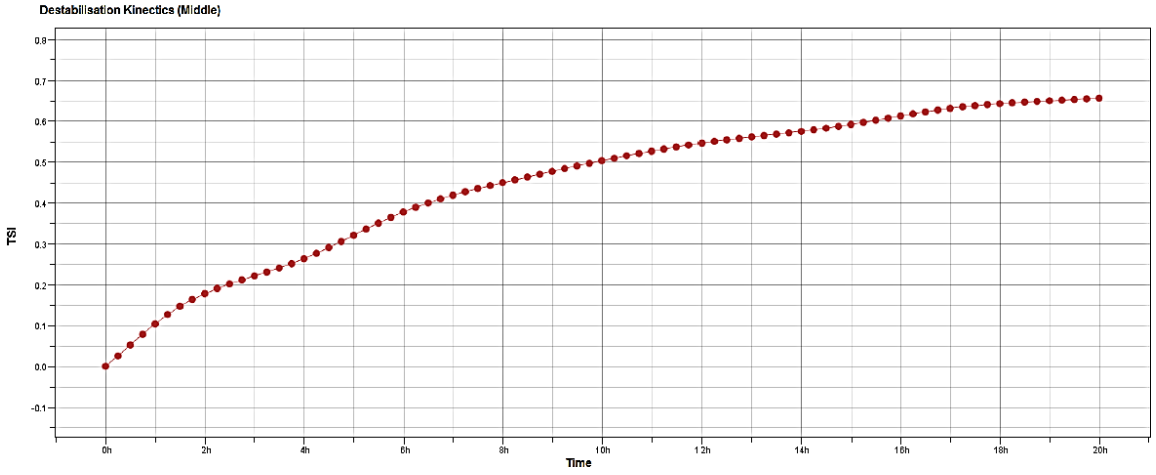
Destabilisation - TSI (global)



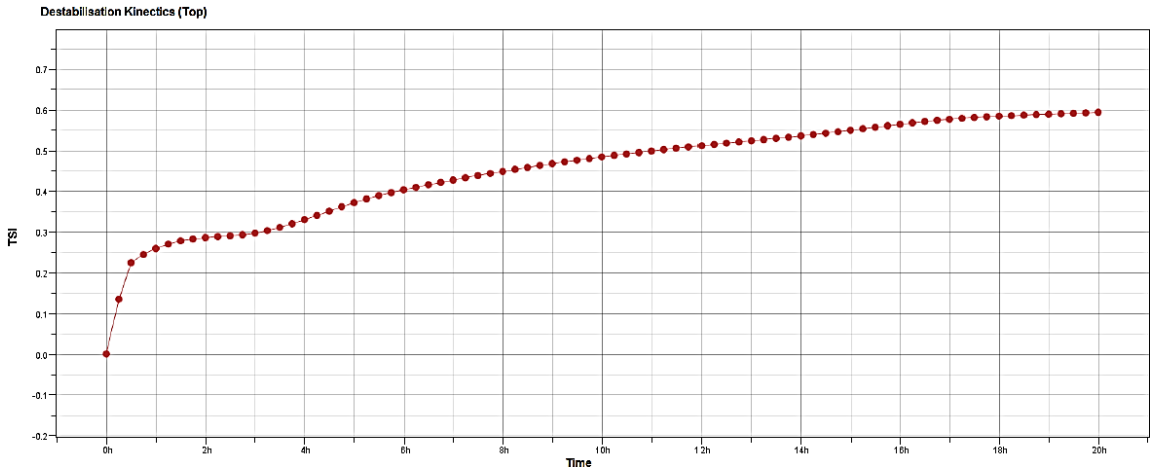
Destabilisation - TSI (bottom)

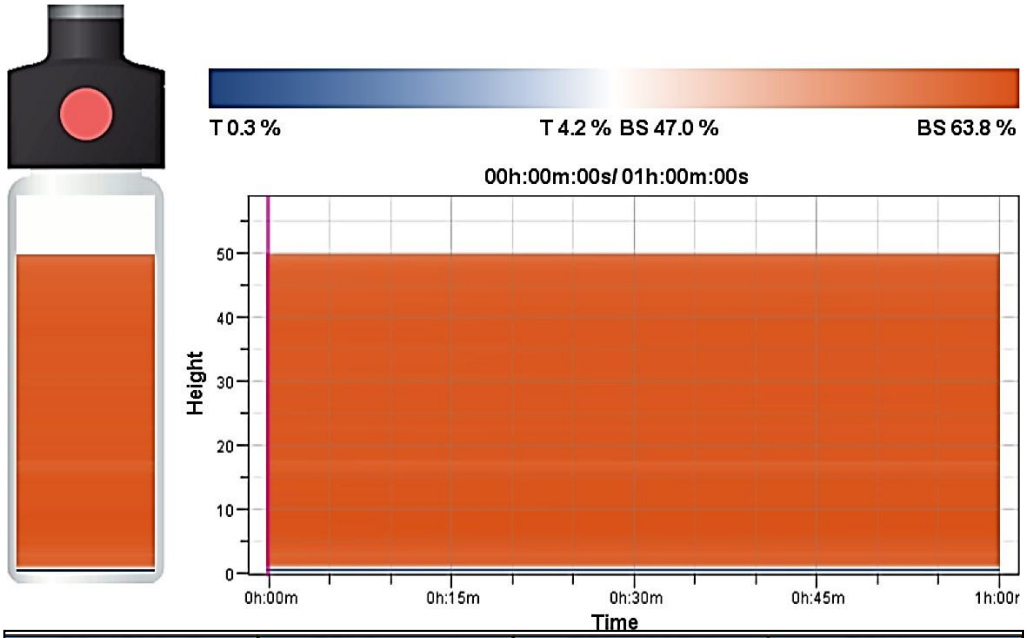


Destabilisation - TSI (middle)



Destabilisation - TSI (top)





TSI (Global) 20h	TSI (bottom) 20h	TSI (middle) 20h	TSI (top) 20h
0.7	1.0	0.7	0.6

Table 7: Trial 2 Franz Diffusion Cell Results.

Trial	**Result** %90 Confidence İnterval Criterion %75-%133.33
Trial 1	%1.79-%3.03
Trial 2	%104.61-%117.58

As a result of the analysis, the suitability of the product developed with the water in oil system has been proven. The stability of the product has been monitored and the results are as follows.

3. CONCLUSION AND DISCUSSION

In the study, instead of a multi-step production method, a single-step system consisting of the combination of the water phase and oil phase, which are the main phases of the cream dosage form, was developed and a product with similar properties to the reference product Opzelura Cream was obtained. As a result of the studies, it was observed that Opzelura Cream, which contains the active ingredient Ruxolitinib Phosphate (equivalent to Ruxolitinib) with a formulation patent with the oil in water system and is used in the treatment of non-segmental vitiligo by blocking the JAK1 and JAK2 enzymes, obtained positive results using the water in oil system and could be developed withthe single-step production method. The product obtained with this developed method constitutes an alternative to the reference product in pharmacy and health services.

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