FORMULATION OF CREAM CONTAINING IBUPROFEN 5%

Huynh Thi My Duyen*, Le Thi Minh Ngoc
Can Tho University of Medicine and Pharmacy
**Corresponding author: htmduyen@ctump.edu.vn*

ABSTRACT

Background: *Non-steroidal anti-inflammatory drug (NSAID) is a group of drugs commonly used to treat musculoskeletal diseases. However, according to statistics, up to 25% of long-term NSAID users had peptic ulcer disease, and 2-4% had gastrointestinal bleeding or perforation. Therefore, it is necessary to study preparations for external use to minimize these undesirable effects.* ***Objectives:*** *The cream containing ibuprofen 5% has been formulated with good physical characteristics and high bioavailability in the in vitro test based on the support of design and optimization software.* ***Methods:*** *According to the D–Optimal model, the formula models of cream containing ibuprofen 5% were designed with the different concentrations of oil phase, water phase, and emulsifier. The formulas of medicinal cream were prepared by direct emulsification method, then evaluated and compared to the criteria consisting of the phase separation, spreadability, and release of the active ingredient through cellulose nitrate membrane with a 0.45 µm pore size.* ***Results:*** *The formulation of the cream containing ibuprofen 5% with various components consisting of ibuprofen (5 g), cetyl alcohol (3.85 g), stearyl alcohol (1.54 g), beeswax (3.85 g), paraffin oil (10.77 g), span 80 (11.70 g), sodium lauryl sulfate (3.30 g), propylene glycol (59.90 g), and nipagin M (0.10 g). The results also showed that the product had good physical characteristics with no separation between the oil and the water phases, a spread area of 618 mm^2, and the release of the active ingredient through the cellulose nitrate membrane at 0.209 mg/mL.* ***Conclusion:*** *The cream containing ibuprofen 5% was researched based on excipients of oil and water, making an emulsion structure stable and helping meet the foundational criteria according to the medicinal cream regulations.*

Keywords: *cream, ibuprofen, spreadability, diffusion through the membrane.*

I. INTRODUCTION

Osteoarthritis is quite common in Vietnam. In addition, there have been more and more young people who have it. WHO ranked Vietnam in the group of countries with the highest rate of the population suffering from osteoarthritis all over the world [10]. The disease causes discomfort, making patients' daily activities more difficult. Many groups of drugs are effective against the disease, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, etc. are popular. However, oral use of NSAIDs for a long time may cause many side effects, especially on the gastrointestinal tract such as peptic ulcer disease and its complications. In that case, the most serious one can be gastro-intestinal bleeding and even gastrointestinal perforation [6]. Products containing NSAIDs for external use help limit unexpected effects and achieve therapeutic efficiency. There-fore, preparing analgesic products for external use needs to be researched and developed more and more.

In the world, cream preparations containing ibuprofen are produced a lot, but the price is still high compared to the average income of Vietnamese people. At the same time, there are still few domestic pharmaceutical companies producing preparations containing ibuprofen for external use. Therefore, it is necessary to research the preparation of our nation's analgesic products containing ibuprofen for external use. This study aims at determining the formula (of the cream containing ibuprofen 5%) that meets the foundational criteria for the quality of the ointment form and has high bioavailability in the in vitro test with the support of intelligent software.

The study was carried out with the following specific objectives:

1. To design and optimize the cream containing ibuprofen 5% with intelligent soft-ware.
2. To investigate the incompatibility of the active ingredient and excipients in the optimal formula in storage conditions (4oC and 40oC, and 75% humidity for 4 weeks).
3. To evaluate the finished product quality.

II. MATERIALS AND METHODS

2.1. Materials

Ibuprofen (India), propylene glycol, white beeswax, stearyl alcohol, sodium lauryl sulfate, cetyl alcohol, paraffin oil, span 80, and nipagin M (China) met pharmaceutical standards. Standard ibuprofen (Institute of Drug Quality Control Ho Chi Minh City), methanol, potassium dihydro phosphate (Merck), and distilled water (Vietnam) met testing standards.

2.2. Methods

2.2.1. Design and optimization of the formula of cream containing ibuprofen 5% with intelligent software

Design of formula model

We designed the formula model for the cream containing ibuprofen 5% with Design-Expert software 11.0 based on the D–Optimal model:

- The concentrations of the oil phase, the water phase, and the emulsifier were investigated at different concentration ranges.
- The concentrations of ibuprofen and the preservative were kept steady.

Table 1. Recipe ingredients

Ingredient	Percentage (%)
Ibuprofen	5
Oil phase	20 – 30
Emulsifier	5 – 15
Water phase	49.9 – 69.9
Preservative	0.1

Preparation method

Determination of the formula of the cream containing ibuprofen 5%

The ratio and the weight of each emulsifier in the formula were calculated based on the RHLB (Required Hydrophilic Lipophilic Balance) and HLB (Hydrophilic Lipophilic Balance) values [2], [4].

The creams containing ibuprofen 5% were formulated (700 g of each) through the following steps [4]:

Oil phase: we weighed paraffin oil (53.84%), cetyl alcohol (19.23%), stearyl alcohol (7.7%), beeswax (19.23%), and span 80 on a beaker. Then, we made them melt completely, stirred, continued to cook to about 65 °C, and maintained this temperature.

Water phase:

We weighed sodium lauryl sulfate on a beaker, stirred, heated it to about 70 °C, and maintained this temperature.

Active ingredient solution: we weighed propylene glycol on a beaker, added ibuprofen, heated it to around 60°C, stirred it until dissolution, and maintained this temperature.

Mix two phases: the oil phase was slowly added into the solution containing sodium lauryl sulfate, then we stirred until the temperature was approximately 50°C. Next, we added the active ingredient solution and 10% of nipagin M alcohol into it, continued to stir for about 02 minutes, and let it cool naturally.

We packed the complete preparations in tubes of 30 g.

Criteria for formula optimization

Phase separation

We prepared the medicinal cream products based on 16 formulas in the same conditions and procedures. Then they were preserved in natural conditions for 60 days.

They were observed with unaided eyes to determine whether or not there was any separation.

Requirements: cream had no phase separation.

Spreadability [4]

The spread of a medicinal cream is illustrated as the area in which a given amount of medicinal cream spreads out when different weights are put onto the sample. The tools used are two smooth glass plates.

Procedure: we put a certain amount of medicinal cream (about 0.5 g) on a glass sheet with a certain diameter, then we continued to put the other glass plate on. After one minute, we read the spreading diameter of the sample. The following formula was used to calculate the area of spread:

$$S = \frac{d^2\pi}{4} \qquad (2.1)$$

where,

S: the area of the spread of the medicinal cream (mm^2).

d: the spreading diameter of the medicinal cream (mm).

Requirements: the larger the area was, the better the cream was.

Release of the active ingredient

Use Franz diffusion method as follows [8]

- We filled the chamber of the test apparatus with phosphate buffer (pH 7.2).
- We weighed approximately 400 mg of medicinal cream on the cellulose nitrate membranes with a 0.45 µm pore size.
- We heated it with a water bath at 37 ± 0.5°C.
- After 20 minutes, the absorbance of the sample was measured at wavelength 221 nm by the UV-VIS spectroscopy method.
- We measured the absorbance on 16 formulas. Then, we measured 03 times for each formula, and then we took the average values.

Requirements: the more the active ingredient released, the better the cream was.

The formulas' results were considered input data for the optimization software BCPharSoft OPT by Mr. Do Quang Duong. This software was verified by the Department of Science and Technology of Ho Chi Minh City in 2011 to optimize and predict the optimal formulas. Then, we made 03 lots (700 g of each) to confirm the optimal formula.

2.2.2. Investigation of incompatibility between the active ingredient and excipients in the optimal formula

The incompatibility of the active ingredient and excipients in the formula of cream containing ibuprofen 5% was evaluated as ICH guidelines:

The finished cream containing ibuprofen 5% was contained in a glass jar with a punctured LDPE cap, then it was stored at 4 °C and 40 °C and 75% humidity for 04 weeks, and we helped the mixture expose to storage conditions well. We observed the finished product after 04 weeks, evaluated organoleptic changes (color, texture, odor, etc.), phase separation, and pH, then compared them to control samples stored in normal conditions of 25 °C and 75% humidity.

2.2.3. Quality evaluation of the finished medicinal cream containing ibuprofen 5%

Physical characteristics

The final cream was smooth, uniform, white, soft, and had no separation between the oil and the water phases. Also, it did not melt at 37°C.

Mass uniformity

We followed Appendix 11.3, Vietnamese Pharmacopoeia V [7].

pH

We weighed 5 g of medicinal cream on a beaker, added 50 mL of distilled water, boiled at 70 °C, stirred well, and let it cool. Then, we measured the pH. Requirements: pH from 5.5 to 6.5.

Qualitative method

The sample with UV-VIS spectrum had the same spectral form and absorption peak as the standard one.

Quantitative method

We used the UV-VIS spectroscopy method at a wavelength of 264 nm. Ibuprofen content must be from 4.5 to 5.25 g per 100 g of medicinal cream [7].

Release of active ingredients *across membranes using Franz diffusion cells:*

After 20 minutes, at least 0.2 mg/mL of active ingredients was released.

III. RESULTS

3.1. Design and optimization of the formula of cream containing 5% of ibuprofen with intelligent software

3.1.1. Determination of the ratio of substances in the emulsifying system

Table 2. RHLB value of oil phase

Compositions of the oil phase	RHLB	Percentage (%)
Cetyl alcohol	15.5	19.23
Stearyl alcohol	15.5	7.70
Beeswax	12	19.23
Paraffin oil	10.5	53.84

Total HLB value of oil phase: 12.13.

The ratio of emulsifier: sodium lauryl sulfate had an HLB value of 40, and the span had an HLB value of 4.3.

We let z be the ratio of the span used. We had:

$$4.3 \times z + 40 \times (1-z) = 12.13 \Rightarrow z = 78\%.$$

So Span 80 accounted for 78%, and sodium lauryl sulfate contributed 22%.

3.1.2. Test results of the formulas for optimization

Table 3. Compositions and test results of the formulas for optimization

	x_1	x_2	x_3	$\bar{y}_1$	$\bar{y}_2$	$\bar{y}_3$
1	20.00	5.00	69.90	yes	1625.15	0.152
2	26.22	5.00	63.68	yes	1537.08	0.123
3	30.00	15.00	49.90	no	671.62	0.105
4	30.00	5.00	59.90	yes	1287.60	0.098
5	20.00	11.86	63.04	no	848.40	0.207
6	20.00	8.27	66.63	yes	1808.64	0.164
7	23.00	8.65	63.25	yes	1287.60	0.092
8	30.00	5.00	59.90	yes	1319.59	0.115
9	22.88	15.00	57.02	no	604.50	0.097
10	30.00	15.00	49.90	no	604.50	0.150
11	20.00	5.00	69.90	yes	1468.39	0.100
12	25.79	9.29	59.81	no	920.85	0.220
13	20.00	11.86	63.04	no	907.46	0.086
14	30.00	9.68	55.22	no	803.84	0.136
15	22.88	15.00	57.02	no	572.27	0.126
16	26.44	15.00	53.46	no	770.70	0.209

where,

- Oil phase (x_1): 20% - 30%.
- Emulsifier (x_2): 5% - 15%.
- Water phase (x_3): 49.9% - 69.9%.
- $\bar{y}_1$: the average phase separation (yes or no).
- $\bar{y}_2$: the average spreadability (mm^2).
- $\bar{y}_3$: the average release of active ingredient (mg/mL).

The optimal parameters and predictive results were performed by BCPharSoft OPT software for the following prediction formulas:

Optimal parameters	Predictive properties
x_1: 20 %	$\bar{y}_{1:}$ no
x_2: 15 %	$\bar{y}_2$: 590.83 (mm^2)
x_3: 59.9 %	$\bar{y}_3$: 0.219 (mg/mL)

Table 4. Experimental results of 03 lots and predictive results

Product Features	Experiment				Prediction
	Lot 1	Lot 2	Lot 3	Average	
$\overline{y_1}$	no	No	no	no	no
$\overline{y_2}$	615.44	637.62	601.02	618.03	590.83
$\overline{y_3}$	0.211	0.214	0.202	0.209	0.219

The experimental averages were compared to the predictive values by the T-test. Result: experimental t-value < theoretical t-value. Therefore, the experimental results obtained were consistent with the results predicted by the software BCPharSoft OPT.

So the formula for preparing 100 g of cream containing ibuprofen 5% included:

Ibuprofen	5 g
Cetyl alcohol	3.85 g
Stearyl alcohol	1.54 g
Beeswax	3.85 g
Paraffin oil	10.77 g
Span 80	11.70 g
Sodium lauryl sulfate	3.30 g
Propylene glycol	59.90 g
Nipagin M	0.10 g

3.2. Investigation of incompatibility between the active ingredient and excipients in the optimal formula

Table 5. Evaluation of the finished medicinal cream containing ibuprofen 5% in various conditions

Criteria	4ºC	25ºC	40ºC
Physical characteristics	Smooth, uniform, white, not hard, and not runny	Smooth, uniform, white, not hard, and not runny	Smooth, uniform, white, not hard, and not runny
pH	5.9	5.9	6.0
Phase separation	No	No	no

The results indicated that the active ingredient and excipients in the formula of cream containing ibuprofen 5% were incompatible [5].

3.3. Quality evaluation of the finished cream containing ibuprofen 5%

Table 6. Evaluation results of 03 batches of the finished cream containing ibuprofen 5%

Criteria	Quality level	Result		
		Lot 1	Lot 2	Lot 3
Physical characteristics	Smooth, uniform, white, not hard, no phase separation, and does not melt at 37°C	Passed	Passed	Passed
Mass uniformity	Weight from 27.6 to 32.4g	Passed (30.2g)	Passed (30.8g)	Passed (29.7g)
pH	pH from 5.5 to 6.5	Passed (5.9)	Passed (6.0)	Passed (5.8)
Qualitative method	The sample with UV-VIS spectrum had the same spectral form and absorption peak as that of the standard one	Matched	Matched	Matched
Quantitative method	Content from 4.5 to 5.5 g per 100 g of medicinal cream	Passed (5.06)	Passed (5.08)	Passed (5.02)

Criteria	Quality level	Result		
		Lot 1	Lot 2	Lot 3
Release of active ingredient	After 20 minutes, at least 0.2 mg/mL of active ingredient should be released	Passed (0.211)	Passed (0.214)	Passed (0.202)

IV. DISCUSSION

The preparation of medicinal cream by direct emulsification is applied in case of liquid or solid active ingredients soluble in water or oil, and excipients used are complete emulsions. During the preparation process, the water phase cools down faster than the oil phase, so it is necessary to heat the water phase about 3-5^{o}C higher than the oil phase so that when mixing them, the temperature of the two phases will balance to make the form of emulsion stable. We chose an oil/water emulsion for two reasons. First of all, ibuprofen dissolves in water well. Secondly, we wanted to create a pleasant feeling when applying the cream. Especially, when combining two phases, the oil phase should be slowly added to the water one.

Several studies demonstrated that propylene glycol had an important effect on the permeability of ibuprofen through the skin. More precisely, absorption through the skin would increase when raising the concentration of propylene glycol [3], [9]. However, suppose the ratio of any phase is excessively increased. In that case, it will be hard to unbalance the structure of the emulsion, making the product physicochemically unstable and easy to separate phases. Therefore, the formula in Table 2.1 was designed to balance the different ingredients to help the drug penetrate the skin as much as possible. Moreover, the combination of paraffin, cetyl alcohol, stearyl alcohol, and beeswax in the oil phase would help adjust the texture of the cream that was soft and had good adhesion to the skin.

Emulsifiers have an important influence on the structure of the emulsion. Furthermore, a combination of water-based emulsifiers and oil-based ones will work better than just using a single emulsifier [2]. In this research, Tween 80 was initially selected as a water-based emulsifying excipient, because it is widely used and safe when applied to the skin. However, Tween 80 significantly affected the sample's absorbance in the validation of the UV-VIS quantitative procedure for specificity. Therefore, Tween 80 was replaced with sodium lauryl sulfate. The mixture of Span 80 and sodium lauryl sulfate did not affect the quantitative process of the medicinal cream and created a good texture for the cream [1].

The bioavailability of drugs for skin application is evaluated by the characteristic parameters including spreadability and release of active ingredients. When the spreadability of drugs is better, the contact area will be larger and the absorption will be better. The release of active ingredients was the priority in the evaluation of the selection of the optimal formulas. The use of Franz cells to evaluate the release of active substances in the in vitro test only provides a reference because the structure of the membranes for drugs' penetration is not the same as that of the skin (both healthy and damaged skin). However, this method can help compare the release of active ingredients of soft drugs with different excipients or various preparation methods. In addition, the methods used in this study were simple, and had quick results, serving as a guide before proceeding with complicated and expensive in vivo methods. The survey time was 20 minutes. The reason is that the 20-minute interval was appropriate to show the difference in the release of the active ingredient of formulas after probing at intervals of 5 minutes, 10 minutes, 20 minutes, and 30 minutes.

The first stage of researching the formulas of soft drugs always involves the incompatibility to assess whether or not the active ingredients and the excipients can be combined [5]. Through investigation, there were no significant changes in physical characteristics, pH, and phase separation of the cream containing ibuprofen 5% in storage conditions after 4 weeks, showing that the active ingredient and excipients in the formula of cream containing ibuprofen 5% were incompatible with each other.

V. CONCLUSIONS

The medicinal cream containing ibuprofen 5% has been formulated with a good release of the active ingredient, high spreadability, and no separation between the oil and the water phases at room temperature. Furthermore, this formula has qualified for the foundational quality criteria of the medicinal cream.

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