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Short Communication

Design and development of Unani anti-inflammatory cream

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ABSTRACT

Inflammation is the symptom of many diseases like rheumatoid arthritis and osteoarthritis. Many side effects are associated with the Non-Steroidal Anti-inflammatory Drugs (NSAIDs) used as conventional treatment for these conditions. In Unani, there are large number of single and compound drugs for inflammatory conditions. One dosage form of Unani system of medicine is named as Zimad in which paste is formed by mixing powder in oil, water, herbal extract. Zimadat is prepared just before application and used in many disease conditions as resolving, styptic, astringent, and antiseptic. As the pre-application procedure is difficult and also complicated for patients, hence, the present study attempted to modify the form of Zimad into cream. Various batches of cream of *Zimad Mohallil* were prepared by using extracts of the formulation and by adding additives. Various physicochemical parameters of prepared cream were carried and compared with market cream. The optimized cream of *Zimad Mohallil* (F_4) was selected after preliminary tests and evaluated further. The optimized cream showed good results in physicochemical parameters equivalent to market sample. *Zimad Mohallil* was converted into convenient cream form by adding minimum additives and benefits could be achieved without any hassle and cumbersome work, which is encountered in crude or paste form. The optimized cream was equivalent to standard market cream.

1. Introduction

There are large number of single and compound drugs in Unani system of medicine, which have been described as analgesics and as anti-inflammatory. Some of them such as *Suranjan* (*Colchicum luteum*) [1], *Khulanjan* (*Alpinia galanga*) [2], *Babuna* (*Matricaria chamomilla*) [3], *Nakhuna* (*Astragalus hamosus*) [4], *Rewand chini* (*Rheum emodi*) [5], *Asgandh* (*Withania somnifera*) [6], *Arand* (*Ricinus communis*) [7], *Chobchini* (*Smilax china*) [8], *Muqil* (*Commiphora mukul*) [9], *Zanjabeel* (*Zingebar officinale*) [10], *Dhatura* (*Datura stramonium*) [11] have been scientifically proven to possess anti-inflammatory action. Apart from single drugs given above, some drugs are used as combination of different ingredients (compound formulation). Compound formulations are used either externally such as *Roghan surkh*, *Zimade naana*, *Roghan babuna*, *Roghan haft barg*, *Marham daakhilyoon* or internally such as *Habb suranjan*, *Habb muquil*, *Majoon yograj goggul*, *Majoon chobchini*, *Habb suranjaan*, *Habb hudaar*, *Habbe asgandh* [12–14]. In the present study, an attempt was made to modify the form of one compound formulation from above mentioned different formulations which is *Zimad*. *Zimad* is an important dosage form of Unani system of medicine.It is a powder preparation and always used in a paste form after mixing in any of the specified oils, water etc. at the time of use [15–17]. It is generally prepared with the drugs having *Mohallil* (resolving), *Habis* (styptic), *Qabiz* (astringent), and *Dafe Taffun* (antiseptic) properties. Different types of oils are used in the preparation of *Zimad* like *Roghane gul*, *Roghane zard*, *Roghane badam*, *Roghane kunjad* and sometimes *arqiyat* are also used or any other specified oil mentioned in text [18]. Drugs which are mostly used for the preparation of *Zimadat* and their indication is specially for *awraam baaridah* (Inflammation) such as *Babuna* (*M. chamomilla*), *Nakhuna* (*A. hamosus*), *Marjanjosh* (*Origanum vulgare*), *Soya* (*Anethum graveolens*) [19].

The primary aim of the present research work is to explore new alternatives for the treatment of inflammatory conditions which are commonly associated with many diseased conditions like

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rheumatoid arthritis and osteoarthritis. The conventional treatment for these conditions comprises of oral medication which includes the tablets of NSAIDs. However there are many side effects associated with these conventional NSAIDs therapy. In India, Unani system of medicine has been practised since ancient times and many medicinal plants are used in the form of their powders, extracts to treat many diseases and claimed to have lesser side effects than the drugs of modern system of medicine available in the market. Though the above mentioned dosage form, *Zimad* is very much helpful in treating anti-inflammatory conditions, but the pre-application procedures and application is difficult and sometimes not suitable for the patients. Therefore in the present study, an attempt was made to modify the form of *Zimad Mohallil* (Z.M.), an ancient classical preparation mentioned in Unani literature for anti-inflammatory action into a cream based semi-solid preparation to improve the patient's compliance. The composition of Z.M. is mentioned in the National Formulary of Unani Medicine [Part I]. The ingredients of the preparation are *Iklilul malik* (*A. hamosus* Linn.), *Babuna* (*M. chamomilla* Linn.), *Asgandh* (*W. somnifera* Dunal.), *Rewand chini* (*R. emodi* Wall), *Tukhme khatmi* (*Althea officinalis* Linn.), *Mako* (*Solanum nigrum* Linn.) and *Muqil* (*C. mukul* Hook.) (Table 1) [15]. The formulation design of Unani anti-inflammatory cream exploiting the composition of Z.M. may improve the efficacy and patient compliance of this Unani classical preparation.

2. Materials and methods

2.1. Procurement and identification of herbal drugs

The ingredients of the anti-inflammatory cream formulation were procured from the market and were identified and certified by Senior Asst. Professor, C-RMR, TransDisciplinary University (TDU) FRLHT-IAIM, Bengaluru. The specimens were preserved in the Repository of Medical Resources Herbarium and the Accession numbers are *Iklilul malik* – 3817, *Babuna* – 3812, *Asgandh* – 3818 and *Mako* – 3814, *Rewand chini* – 3816, *Tukhme khatmi* – 3813, *Muqil* – 3815. The additives were procured from a reputed chemical dealer of good standard.

2.2. Extraction of herbal drugs

All the crude drugs/ingredients of *Zimad Mohallil* were cleaned to remove the impurities present, and allowed to dry in shade. Thereafter all the ingredients were separately put in electrical grinder to make a coarse powder. This coarse powder was then mixed together in required proportion as in Z.M. except *Muqil* (Table 1) after that hydroalcoholic extracts of all drugs were collected through Soxhlet apparatus in the ratio of 1:5:5 (Drug:-Distilled water:Ethanol) at 50 °C till the drugs got exhausted. Extracted material was first filtered and then dried in water bath. After drying, percentage of extractive value of Z.M. was calculated. This extract was ground in mortar and pestle and stored in an air tight glass container at room temperature for further use. *Muqil* (*C. mukul*) was taken in 1/4th proportion of all drugs and macerated with hydroalcohol 1:5:5 (*Muqil*:Distilled water:Ethanol) and after 24 h filtered dried and stored well.

2.3. Preparation of Unani anti-inflammatory cream

The formula of Z.M. used in inflammatory disease was taken from reference book *National Formulary of Unani Medicine Part 1*. Ingredients of Z.M. were *Iklilul malik*, *Babuna*, *Asgandh*, *Mako*, *Rewand chini*, and *Tukhme khatmi* in equal quantity and *Muqil* in 1/4th quantity. Z.M. is recommended to be applied in paste form on affected area, which is prepared by mixing the powder of ingredients as given above with water or arq-e-mako. Z.M. was selected for conversion into an anti-inflammatory cream. Anti-inflammatory cream composed of same ingredients as in Z.M. was prepared with some additives. Cream was formulated by preparing multiple batches and final batch was selected by analysing those different batches.

First heat Polyethylene glycol (PEG) 4000 and Polyethylene glycol (PEG400) on a water bath at 65 °C. Extracts were mixed with deionised water and then mixed with PEG 400. Thereafter PEG 4000 was poured gradually in this solution and stirred continuously until cool and congealed [20]. Different batches of anti-inflammatory cream were prepared by optimizing the concentration of PEG 400 and PEG 4000 as shown in Table 2.

2.4. Phytochemical analysis

The hydroalcoholic extract obtained was subjected to various phytochemical screening as per the standard procedures to reveal the presence of various active phytoconstituents like alkaloids, carbohydrates, flavonoids, glycosides, phenols, proteins, resins, saponins, steroids and tannins [21,22].

2.5. Development of anti-inflammatory cream

Different batches prepared were tested for organoleptic properties like appearance, odour, homogeneity, physical stability, pH, spreadability, extrudability and total residue. Best optimized formula was selected on the basis of analysis of different batches on the above mentioned parameters. Thereafter final batch was further evaluated. One final batch and one market cream were tested on various parameters mentioned below [23–25]. Same type of market cream was selected which is made up of herbal ingredients as in the in-house preparation. The composition of market cream is Linseed oil (3.0%w/w), Methyl salicylate (15.0%w/w), Menthol (2.0%w/w), Turpentine oil (3.0% w/w) and gel base (q.s).

2.5.1. Extrudability

Two different samples (one in house & one marketed) were filled into collapsible aluminium tubes and sealed by crimping the

Table 1
Ingredients of *Zimad Mohallil*.

S. No.	Ingredients	Scientific name	Parts used	Quantity
1.	*Iklilul malik*	*Astragalus hamosus* Linn.	Pods	1 kg
2.	*Babuna*	*Matricaria chamomilla* Linn.	Flowers	1 kg
3.	*Asgandh*	*Withania somnifera* Dunal.	Roots	1 kg
4.	*Mako*	*Solanum nigrum* Linn.	Fruits	1 kg
5.	*Rewand chini*	*Rheum emodi* Wall	Roots	1 kg
6.	*Tukhme khatmi*	*Althea officinalis* Linn.	Seeds	1 kg
7.	*Muqil*	*Commiphora mukul* Hook.	Resin	250 g

Table 2
Formulation composition (%w/w) of different batches of anti-inflammatory cream.

S. No.	Ingredients	F_1	F_2	F_3	F_4
1.	Extract	6.25	6.25	6.25	6.25
2.	Polyethylene glycol 400	56.14	44	40	48.72
3.	Polyethylene glycol 4000	37.44	38	43.6	30.72
4.	De-ionised water	0	14	10	14
5.	Methyl paraben	0.1	0.1	0.1	0.1
6.	Propyl paraben	0.05	0.05	0.05	0.05
7.	Perfumes	q.s	q.s	q.s	q.s

end. The tubes were pressed to extrude the material and the extrudability of the formulations was checked. The comparative extrudability of the formulations is shown in Table 5 [25].

2.5.2. Spreadability

Two grams of sample of cream was placed on this ground slide. The cream was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. 1 kg weight was placed on top of the two slides for 5 min to expel air and to provide a uniform film of the cream between the slides. Excess of the cream was scrapped off from the edges. The top plate was then subjected to pull of 80 g. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 6 cm was noted.

Spreadability was then calculated using following formula:

$$S = M \times L/T$$

where, S = Spreadability, M = Weight in the pan (tied to the upper slide), L = length moved by the glass slide and T = represents the time taken to separate the slide completely from each other [26].

2.5.3. Total residue

Five grams of the cream was accurately weighed and placed in a tared, weighed, clean and dry petri dish and dried to constant mass at 105 °C. It was cooled in a desiccator and weighed again. The quantity of residue was calculated as follows [24].

$$\text{Residue present by mass} = 100M_1/M_2$$

where M_1 = mass in gm of the residue, and M_2 = mass in gm of the material taken for the test.

2.5.4. Viscosity

Viscosity of cream was determined by Brookfield viscometer. The viscosity measurements were done using Brookfield DV-II + Pro viscometer using Spindle no. 7 at different RPM at different percent of torque [27].

2.5.5. Moisture content

The water content of the drug was determined by distilling the cream with toluene. Ten gram of cream was taken in a flask of Dean Stark apparatus and 75 ml of distilled toluene added to it. Distillation was carried out for five hours. The volume of water collected in receiver tube was noted and the percentage of moisture calculated with reference to the weight of the cream taken [22].

2.5.6. Acid value

Ten grams of cream was dissolved in 50 ml of equal mixture of alcohol and solvent ether, the flask was connected to reflux condenser and slowly heated, until sample was dissolved completely. 1 ml of phenolphthalein was added to this and titrated with 0.1 N NaOH, until faintly pink colour appeared after shaking for 30 s [27,28].

$$\text{Acid value} = n \times 5.61/w$$

n = number of ml of NaOH required; w = weigh of substance.

2.5.7. Saponification value

About two grams of substance was refluxed with 25 ml of 0.5 N alcoholic KOH for 30 min. 1 ml of phenolphthalein was added to this and titrated immediately, with 0.5 N HCL. [27,28].

$$\text{Saponification value} = (b-a) \times 28.05/w$$

The volume in ml of titrate = a; The volume in ml of titrate = b.

2.5.8. Thermal stability

The humidity chamber/incubator controlled at 60% relative humidity and 45 °C was used for the study. Clean glass bottles of around 30 ml capacities with plug and screw on cap for proper closure were used. With the help of a spatula, the cream was inserted into the glass bottle and tapped to settle it to the bottom. The bottle was filled up to 2/3rd capacity and plug was inserted and the cap was tightened. The filled bottle was kept erect inside the incubator at 45 °C for 48 h. The sample was taken to have passed the test, if on removal from the incubator showed no oil separation or any other phase separation [24,29].

3. Observations and results

3.1. Extraction and phytochemical analysis

The percentage yields of the hydroalcoholic extract of all drugs were found to be 15.81% w/w and *Muqil* was 18.95% w/w. Phytochemical screening of hydroalcoholic extracts of all drugs confirmed the various phytoconstituents like alkaloids, carbohydrate, glycosides, phenols, proteins, saponin, steroids and tannins as shown in Table 3.

3.2. Development of Unani anti-inflammatory cream

Four different batches of cream were prepared by taking 6.25% extract of all drugs and de-ionized water and varying concentrations of PEG 400 and PEG 4000 for optimizing the best batch. The prepared different batches were characterized by organoleptic properties like appearance, odour, homogeneity, physical stability, pH 1% and 10%, spreadability, percent of total residue and extrudability as shown in Table 4. Batch F_4 was selected after analysing the results of all prepared batches on appearance, odour, homogeneity, physical stability, pH, spreadability, total residue and extrudability, thereafter this final batch was further evaluated and comparison was also done with market cream as shown in Table 5.

Viscosity of cream was done by Brookfield viscometer as shown in Table 6.

3.3. Thermal stability

Both in-house cream and market cream were found to be thermally stable. There was no separation found in these samples.

Table 3
Phytochemical analysis of hydro-alcoholic extracts of ingredients of Z.M.

Constituents	Phytochemical test	Results
Alkaloids	Dragendroff's test	+
	Mayer's test	+
	Wanger's test	+
Carbohydrates	Benedict's test	+
	Fehling's test	+
Flavonoids	Flavonoids test	+
Glycosides	Keller–Killiani test	+
Phenols	Ferric chloride test	+
Proteins	Biuret's test	+
	Millon's test	+
Resin	Resin test	–
Saponins	Froth test	+
	Foam test	+
Steroids	Liebermann–Burchard's test	+
	Salkowski reaction	+
Tannins	Ferric chloride test	+
	Lead acetate test	+

Table 4
Characterization of prepared formulations and market cream.

Parameters	F_1	F_2	F_3	F_4
Appearance	Dark brown	Dark brown	Dark brown	Dark brown
Odour	Pleasant	Pleasant	Pleasant	Pleasant
Homogeneity	Homogeneous and smooth	Homogeneous and smooth	Homogeneous and smooth	Homogeneous and smooth
Physical stability	Cracking	Cracking	Average	Stable
pH (1% w/w)	5.53 ± 0.04	6.26 ± 0.06	5.10 ± 0.03	5.49 ± 0.09
pH (10% w/w)	4.87 ± 0.14	6.13 ± 0.04	4.71 ± 0.07	5.53 ± 0.06
Spreadability (g cm/s)	9.18 ± 0.21	5.33 ± 0.06	27.33 ± 1.39	34.4 ± 1.42
% total residue	93.63 ± 0.42	89.42 ± 0.39	87.54 ± 0.32	89.47 ± 0.35
Extrudability	+	+	++	+++

+++ Excellent, ++ Good, + Satisfactory.

Table 5
Characterization of optimized formulation and market cream.

Parameters		Final in house cream	Market Cream
Organoleptic properties	Appearance	Dark brown	White
	Odour	Pleasant	Pleasant
	Homogeneity	Homogeneous and smooth	Homogeneous and smooth
	Physical stability	Stable	Stable
Extrudability		+++	+++
pH	pH 1%	5.49 ± 0.09	6.31 ± 0.03
	pH 10%	5.53 ± 0.06	5.41 ± 0.10
Spreadability		34.4 ± 1.42	69.33 ± 5.81
% total residue		89.47 ± 0.35	73.26 ± 0.32
Moisture content		13.22 ± 0.17	15.37 ± 0.13
Acid value		1.88 ± 0.07	1.46 ± 0.10
Saponification value		34.08 ± 0.10	73.70 ± 0.21

+++ Excellent, ++ Good, + Satisfactory.

4. Discussion

Different batches of cream were prepared and subjected to physico-chemical characterization to assess the various characteristics. All formulated creams were dark brown in appearance which was mainly due to the presence of phyto-constituents added in the form of extracts. Odour of formulated batches was found to be pleasant. However market cream chosen as standard was found to be white in appearance and having a smell of menthol. Consistency of F_1, F_2 were found not optimum, due to non-homogeneity in nature. However, F_3 formulation was also found not optimum, due to lack of perfect consistency. Formulation F_4 was found to be homogenized, smooth and complete absence of any grittiness particle on texture analysis. Cracking in phase was found in batch F_1 and F_2 and physical instability was observed in the form of oozing in the batch F_3. However, formulation F_4 was found to be physically stable and any sign of phase separation was not found in this batch. pH of 1% and 10% solution of all formulations were found to be in range of 4.95–6.37 and comply with the pH of market cream. pH value of the cream is an important parameter because drop in pH (become more acidic) value during storage of creams is an early indication of bacterial growth. According to Bureau of Indian Standards (BIS) specification skin cream should have pH value 4.0 to 9.0. The pH of all formulations was in range [24]. Extrudability is a useful empirical test to measure the force required to extrude the material from a tube, since the packing of cream has gained a considerable importance in delivery of desired quantity of cream. The formulation F_4 showed excellent extrudability. However, formulation F_3 showed less extrudability. Formulation F_1 and F_2 showed very least extrudability, when they were extruded from the metallic collapsible tube. The spreadability is used to denote the extent of area to which a cream is readily spread on application to the skin on affected part. The therapeutic and bioavailability efficiency of a cream also depends on its spreading value. Lagexbuchers and Lange described spreadability as a measure of viscosity correlated to the subjective preference [30]. F_1 and F_2 were very less spreadable, F_3 was good, F_4 was very good spreadable, its spreadability was 34.4 ± 1.42 and market cream was 69.33 ± 5.81, its spreadability was very high because most of the constituents of this cream were oils. Total residue indicates the water content present in formulation. In all formulations total residue was 3.63 ± 0.42–73.26%. Total residue value was found more in F_1 formulation and less in market sample, but all were within range; according to BIS, percentage of total residue by mass should not be less than 10% [24]. Value of F_4 was found in standard range or more close to the standard values. Therefore this F_4 batch was optimized as a final batch. Thereafter, further evaluation was done in F_4 batch. The moisture content was determined by distilling the creams with toluene. The moisture content of in-house final batch and market cream were 13.22 ± 0.17 and 15.37 ± 0.13. Acid value of in-house final batch and market cream were 1.88 ± 0.07 and 1.46 ± 0.10, which is less. If acid value is more, then it will cause irritation to the skin after application. Saponification value of in-house final batch and market cream were 34.08 ± 0.10 and 73.70 ± 0.21. Thermal stability of both optimized cream and market cream were found to be stable. There was no oil separation or any other type of phase separation observed.

Table 6
Viscosity of optimized cream.

Sample	Model	Spindle	RPM	Dial reading % Torque	Viscosity cP	Temperature °C
1.	Brookfield viscometer DV II + Pro	S_7	100	30	12,000	28.9
			60	22.3	14,867	28.9
			50	20.3	16,240	28.9
			30	16.2	21,600	28.9
			20	14.0	28,000	28.9
			12	11.8	39,333	28.9
			10	11.3	45,200	28.9

5. Conclusion

This study showed that the classical formulation of *Zimad Mohallil* which is in powder form, mixed with some oleaginous base before application and used in various inflammatory conditions was converted into cream dosage form. It is elegant, convenient, easier in application and provides better patient compliance.

A clinical comparative study can be carried out to assess the efficacy of formulated optimized cream in comparison with classical Unani *nuskha* in future studies.

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Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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