International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2017; 5(3): 93-97
Received: 05-03-2017
Accepted: 06-04-2017

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Exploring the role of Mahua oil as potent emulsifier in cream formulations

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Abstract
The research endeavors at investigating the role of Mahua oil (MO), obtained from *Madhuca longifolia* as an emulsifier for formulating the w/o cream. Utilizing; erythromycin stearate, stearic acid, potassium hydroxide, glycerine, MO, and methylparaben, four different cream formulations were prepared. The formulations were characterized in terms of pH, viscosity, spreadability, extrudability, skin irritability test, drug content, accelerated stability studies and *in vitro* drug diffusion. The evaluation parameters highlighted that batch F4 exhibited the best formulation characteristic (highest drug release of 94.33% in 300 minutes) as compared to other formulations. The range of drug content (85.69–95.72%), pH (5.98-6.42), viscosity (880-1040 cps), and spreadability (2.69-3.5 g/sec) were observed. The accelerated stability study expressed no substantial alteration and skin irritation test showed no significant signs and symptoms. MO was found to be chemically inert, non-toxic, economic, biodegradable, good emulsifying ability, widely available and may be utilized as excipients in cream formulations.

Keywords: Cream, Emulsifier, Formulation, Oil, *Madhuca longifolia*, Mahua.

1. Introduction
Nature based products, either in form of active pharmaceutical ingredient (API) or the excipient are gaining citadel fame in the century owing to their diverse promising pharmacological activities [1-4]. In early years, for developing formulations which have the ability to exhibit better therapeutic activity, new drug entities were preferred. In contrast, the modern rational design of formulations which deliver drug into the skin, excipients play a major role. An excipient is a substance, may be either of natural or synthetic origin, used primarily for formulating a product along with the API. Over the years, the status of excipients as “non-active agents” has changed to “key determinant” in dosage form fabrication [5]. In formulations, it has been found to enhance the activity of API by facilitating drug absorption or solubility; or may impart imperative role(s) in designing any dosage form. Today numerous natural pharmaceutical excipients such as acacia, agar, alginates, cellulose, gelatin, guar gum, pectin, starch, tragacanth, xanthan gum, etc. have come into limelight for their therapeutic supplementary properties as well as pharmaceutical applications like bases in suppositories, binding agent, coating material, disintegrating agent, gelling agent, stabilizer, sustaining agent, thickening agent, and many more [6]. In the global market, there is an emerging need for the complete herbal based formulations which must be free from any kind of harmful chemical excipients. Due to the belief that natural products are quite safe as compared to that of compounds of synthetic origin, a trend has come in this decade for a 100% natural formulation with less toxicity [7]. Many products have already come into existence due to strategic marketing by multiple pharmaceutical companies, where they claim their product to be 100% safe by virtue of the natural origin [8]. Mahua or butternut tree (family, Sapotaceae) known scientifically as *Madhuca longifolia* is a large multipurpose forest tree found throughout the Indian subcontinent and other South Asian countries. It is a well-known popular plant in India having traditional uses like antidiabetic activity, itching, swelling, fractures snake-bite poisoning, antibacterial activity, rheumatism, bleeding and spongy gums, skin diseases, epilepsy, pneumonia, anti-ulcer, and piles [9]. In traditional practice, it is utilized for making alcoholic beverages and as cooking oil in villages, and this practice is well known for centuries. Mahua extract is now branded as nutraceutical product across many nations in form of jam, jelly, biscuit, and liquid formulations, due to its nutritional values like amino acids, enzymes, organic acids, sugars, vitamins, and miscellaneous compounds. The long shelf life characteristic of the oil and technological advancements has played crucial role in product commercialization [10]. Mahua Oil (MO) is extracted from the seeds of Mahua plant. This ingredient possesses emollient, laxative, emetic, illuminant, and hair fixing properties.

With several attributes like chemically inert, non-toxic, less expensive, and biodegradable, it is a well-known for its traditional use that is in skin disease, rheumatism, and headache. The oil is commercially available under various brands and is beneficial for patients with habitual constipation, piles, and hemorrhoids [11]. However, to the best of our knowledge and from the data obtained by searching many databases, the application of MO as an emulsifier in formulating any w/o based cream is not yet studied. Another key factor that promoted the initiation of this research is that this product (MO) is widely acceptable in the society for decades and its standard specifications are also available by the Government. The present research endeavors at investigating the role of MO as an emulsifier for formulating the w/o cream. Utilizing; erythromycin stearate, stearic acid, potassium hydroxide, glycerine, MO, and methylparaben, four different cream formulations were prepared. The formulations were characterized in terms of pH, viscosity, spreadability, extrudability, skin irritability test, drug content, accelerated stability studies and *in vitro* drug diffusion.

2. Materials and Methods

2.1 Chemicals

Erythromycin Stearate was obtained as a generous gift from Flamingo Pharmaceutical Ltd., Mumbai. Mahua oil was purchased from Gondwana Herbs, Gadchiroli, Maharashtra, India. Stearic acid, potassium hydroxide, glycerine, and triethanolamine were procured from Loba Chemie Pvt. Ltd., Mumbai. Rose oil and methylparaben were obtained from Fine Chem Industries Ltd., Mumbai.

2.2 Instruments

Spectroscopic analysis was carried out using double-beam Shimadzu® Ultraviolet-Visible Spectrophotometer (Model UV-1800, Kyoto, Japan) connected to a computer having a spectral bandwidth of 1 nm and wavelength accuracy of ±0.3 nm with a pair of 10 mm path length matched quartz cells was used. All weighing were performed using Shimadzu® electronic balance (Model AUW220D, Kyoto, Japan). Sonication was performed using Transonic Digital S (Sonicator), USA. Stability chamber (Bio-Technics, India) was employed for accelerated stability studies.

2.3 Pre-formulation and standardization

2.3.1 Determination of acid value

10 gm of MO was dissolved in a 50 mL mixture of ethanol (95%) and ether, previously neutralized with 0.1 M KOH. In presence of 1 mL of phenolphthalein solution, the content was titrated with 0.1 M KOH until the solution becomes faintly pink permanently. The acid value was calculated as per the formula: Acid Value = 5.61 n/w; where, n = volume of KOH required, and w = weight of the sample (in g) [12].

2.3.2 Determination of saponification value

2 g of weighed MO was taken in a flask fitted with a reflux condenser. 25 mL of 0.5 M ethanolic KOH solution and little pumice powder were added and the content was refluxed for the duration of 30 min. 1 mL of phenolphthalein solution was added and titration was performed immediately with 0.5 M HCl. Alongside, a blank titration was carried out omitting the MO. The saponification value was calculated as per the formula: Saponification Value = 28.05 (b- a)/w; **w**here, w = weight (in g) of MO, b = volume of HCl utilized in blank titration, and a = volume of HCl consumed [12].

2.3.3 Determination of iodine value

An accurately weighed quantity of MO was placed in a dry iodine flask. To it, 10 mL of CCl_4 and 20 mL of iodine monochloride solution were added. The content was allowed to stand in the dark at a temperature between 15°-25 °C for 30 min. 15 mL KI solution was placed in the cup top and the stopper was carefully removed. From the side of the flask, 100 mL water was added and titrated with 0.1 M sodium thiosulphate using starch solution indicator. The amount required was noted. A blank titration was also performed sidewise. The iodine value was calculated as per the formula: Iodine Value = 1.269 (b –a)/w; where, w = weight (in g) of the substance, b = volume of titrant utilized in blank titration, and a = volume of titrant consumed [12].

2.4 Preparation of Formulations

Erythromycin stearate, stearic acid, and potassium hydroxide were dissolved in water at the temperature of 70 °C in a china dish. Separately; glycerine, MO, methyl paraben in water were prepared by heating at 70°C in a second china dish. The content of the second china dish was added to the first with continued stirring. The perfume was added when the temperature attained 30 °C. The content was milled further using suitable procedures. Table 1 describes the formulation chart.

2.5 Evaluations of Creams

2.5.1 Determination of pH

The pH of the cream formulations was determined using the calibrated digital type pH meter which was calibrated before each use with buffered solutions at pH 4 and 7. The pH was measured by dipping the glass electrode and the reference electrode completely into the cream [13].

2.5.2 Determination of viscosity

The apparent viscosity values of the cream formulations were measured using a Brookfield DV-II + viscometer with spindle no. 64 at 50 rpm [14].

2.5.3 Determination of spreadability

Spreadability was determined by the apparatus consisting of a wooden block which was provided by a pulley at one end. By this method, the spreadability was measured on the basis of slip and drag characteristics of the creams formulations. An excess of cream (about 2 g) was placed on the ground slide of the apparatus. The cream was then sandwiched between this glass slide and another glass slide having the dimension of the fixed ground slide and provided with the hook. A 1 kg weight was applied over the top of the two slides for 5 minutes to expel the entrapped air and to form a uniform film of the gel between the slides. The excess of cream was scrapped off from the edges. Subsequently, the top plate was subjected to a pull force of 50 g. With the aid of string attached to the hook and the time (in second) required by the top slide to cover a distance of 7.5 cm was noted. A shorter interval indicates better spreadability and the vice-versa. The spreadability was calculated using the following formula: $S = M \times L/T$; where, S= spreadability coefficient, the M= weight applied, L = length moved by the glass slides, and T = time taken to separate the glass slides completely from each other [15].

2.5.4 Determination of extrudability

Extrudability is defined as the weight in grams required for extruding 0.5 cm long ribbon of formulation in 10 sec. The cream formulations were filled in a standard capped collapsible aluminium tubes and sealed by crimping to the end. The tubes were placed between two slides and were clamped. 500 g weight was placed on the slides and then the

cap was removed. The length of the ribbon of the formulation that came out in 10 sec was recorded [16].

2.5.5 Skin irritation test

0.5 g of the cream formulation was applied to 6 cm^2 of the area of skin and subsequently covered with a gauze patch, held loosely in contact by a semi-occlusive dressing for a period of 1 hr and the gauze was removed. After 1 hour, the residual test substance was removed without changing any other conditions, and examination was performed after patch removal. The protocol was conducted for the period of 7 days. The signs of rash and other sensitivity characteristics were detected and if reaction occurs, were reported as per grades [17].

2.5.6 Creaming and cracking

Creaming may be defined as the formation of a layer of relatively concentrated emulsion and this condition favors breakdown of the interface and consequent coalescence of the oil globules. The cracking involves coalescence of the dispersed globules and separation of the disperse phase as a separate layer. In both the cases, the emulsion may eventually crack. Simple visual observation technique (of the storing the sample for about 1 month) was the method adopted here to determine the creaming and cracking [18].

2.5.7 Determination of drug content

1 g of cream formulation was accurately weighed and dissolved in phosphate buffer (pH 6.4). The content was further sonicated for a period of 10-15 min and volume was made up to 100 mL. 10 mL of the content was pipetted out and diluted further to 100 mL with phosphate buffer (pH 6.4) and the final dilution was made to get a concentration within Beer-Lambert's range. The absorbance was measured spectrophotometrically at 225 nm against blank cream treated in the same manner as the sample.

2.5.8 Determination of *in vitro* drug diffusion study

In vitro drug diffusion study of creams was carried out across the parchment paper. The receptor compartments were filled with phosphate buffer (pH 6.4). The entire setup was placed on a thermostatic magnetic stirrer and the temperature was maintained at 37 °C throughout the study. The drug diffusion study carried out over a period of 6 hrs at regular intervals. The samples were withdrawn and analyzed spectrophotometrically at 225 nm.

2.5.9 Accelerated Stability Studies

The optimized cream formulation (F4) was selected and studied for stability under accelerated conditions of temperature (40 °C ±2 °C) and moisture (75%±5% RH) for the duration of 3 months. The cream formulation was placed in a PVC container and wrapped with an aluminum foil. After 3 months, the formulation was retested for physical appearance, pH, viscosity, spreadability, extrudability, and drug content [19].

3. Result and Discussion

The standardization of MO by variously reported techniques like saponification value, acid value, and iodine value represented that the MO exhibit the desired authenticity and purity as indicated by the values in the specified range (Table 2).

The formulations were elegant in look, free from any grittiness, soft to touch, free from any defects like creaming or cracking or coalescence of dispersed globules, and non-irritancy was observed for any of the prepared formulations. However, in appearance, the formulations F3 and F4 looked relatively elegant as compared to F1 and F2. In skin irritation test, no signs and symptoms of erythema or edema were detected after of cream application for 7 days.

From the above study, the formulation F4 exhibited the best performance as compared to other prepared formulations. The evaluation of the cream formulations showed satisfactory results in terms of the physical parameters such as pH, viscosity, spreadability and extrudability. All the prepared formulations containing the emulsifier MO demonstrated pH in the range of 5.98-6.42. The observations reflect the pH which is quite compatible with that of the skin. Most of the synthetic cosmetics are petroleum based which causes irritation to the skin while MO-based formulations did not show any irritation to the skin and could compete with available synthetic excipients.

The drug content in cream formulations was observed in the range of 85.69–95.72% (Table 3). The highest drug content of 95.72% was determined in formulation F4 in which the concentration of MO was highest (0.5%), presenting better emulsification and drug loading as compared to the formulation F1 which contained no MO.

The rheological parameters of viscosity were detected in the range of 880-1040 cps (Table 3). The formulation F4 displayed the lowest viscosity as compared to F1, which may be correlated with the fact that as the concentration of the emulsifier gets increased, the viscosity decreases simultaneously. Also, it has been observed that as the torque increases, the sheer stress increases, and as a result, the viscosity decreases. The spreadability of the prepared batches was found to be in the range 2.69-3.5 g/sec. Several studies have indicated that as the viscosity of the fabricated formulation decreases, the spreadability increases concurrently. The extrudability of the batches was found to highest for the formulation F4, this may be due to decreased viscosity and increased spreadability of the prepared formulation.

The *in vitro* drug diffusion study revealed that formulation F4, containing 0.5 g of MO in the cream illustrated the highest drug release of 94.33% in 300 minutes (Figure 1) as compared to the formulation F1 which do not contain MO (83.5%). Table 4 depicts the *in vitro* drug diffusion of formulations.

The accelerated stability study expressed no substantial alteration in physical appearance, pH, viscosity, spreadability, and extrudability of the optimized batch F4 after subjecting the formulation at 40 °C±2 °C and 75%±5% RH for 90 days. A little alteration in drug content (0.28%), pH (0.39), and viscosity (25 cps) was detected after 90 days. The fall in pH may be due to generation of some acidic principles in MO under accelerated conditions. Table 5 describes the differences observed in optimized formulation before and after stability study. Hence, the prepared cream formulation was found to be highly stable.

Table 1: Formulations Chart.

Ingredients	F1	F2	F3	F4
Erythromycin Stearate	0.5	0.5	0.5	0.5
Mahua Oil	-	0.05	0.25	0.5
Stearic acid	10	10	10	10
Pottassium Hydroxide	0.7	0.7	0.7	0.7
Glycerine	2	2	2	2
Water	36.5	36.45	36.25	36.0
Methylparaben	0.3	0.3	0.3	0.3
Preservative	q.s	q.s	q.s	q.s

Table 2: Observed standardization results for Mahua oil.

Properties	Standard value	Observed value
Acid value	20	26.92
Saponification value	187 – 197	190
Iodine vale	55 - 70	63.45

Table 3: Evaluation of cream formulations.

Formulation	pH	Viscosity (cps)	Spreadability (gm.cm/sec)	Extrudability	Drug Content (%)	Creaming	Cracking
F1	6.41	1040	2.69	+	85.69	+	+
F2	6.42	970	2.91	++	90.17	- -	- -
F3	6.33	930	3.18	++	92.33	- -	- -
F4	5.98	880	3.50	+++	95.72	- - -	- - -

Table 4: *In vitro* drug release of cream formulations.

Time(min)	F1	F2	F3	F4
0	0	0	0	0
30	16.68	17	17.62	18.56
60	21.55	24.38	25.05	26.67
90	30.72	34.68	35.39	36.18
120	41.98	48.37	49.12	50.9
150	45.42	52.53	53.32	54.88
180	52.06	58.33	59.47	62.06
210	57.85	65.06	66.54	68.27
240	66.79	72.32	74.77	77.41
270	75.68	80.89	83.77	86.52
300	83.5	89.47	91.85	94.33

Table 5: Accelerated stability studies of optimized formulation (F4).

	pH	Viscosity (cps)	Spreadability (gm.cm/sec)	Extrudability	Drug Content (%)
0 day	5.98	880	3.50	+++	95.72
90th day	5.59	855	3.86	+++	95.44

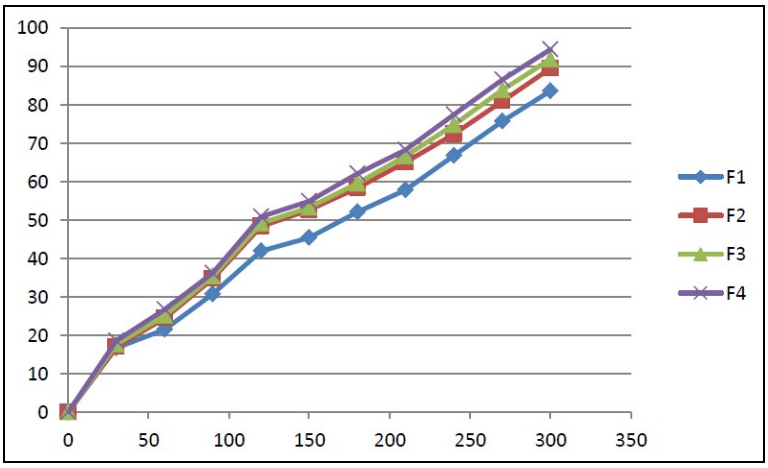

Fig 1: Graph depicting i*n vitro* drug release from cream formulations.

4. Conclusion

The present study indicated that Mahua oil obtained from the *Madhuca longifolia* (family Sapotaceae) served as a good emulsifier for formulating the w/o cream formulation. In the global market where there is an emerging need for complete herbal based formulations which must be free from any kind of harmful chemical excipients which generally have attributes of making the skin rough, hyperpigmentation, darkening, and other associated damage. Mahua oil was found to be chemically inert, non-toxic, less expensive, biodegradable, demonstrated comparable properties with that of synthetic excipients, have the good emulsifying ability, and widely available. It may be beneficial to adopt such uncomplicated natural excipient to be utilized in the commercial production of cream formulations in the future.

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