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Mahua Oil, an Ayurvedic Product Demonstrated Permeation Enhancing Attribute in Topical Gel Formulations

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ABSTRACT

The current study aims at examining the role of Mahua Oil (MO) as a permeation enhancing agents in gel formulation. Employing, erythromycin stearate, triethanolamine, ethanol, MO, DMSO, and water; two different gel formulations were fabricated. One formulation comprise of MO whereas the other contained DMSO as the permeation enhancer. Both the formulations were characterized in terms of viscosity, pH, extrudability, spreadability, skin irritability test, drug content, in vitro drug diffusion, and accelerated stability studies. The evaluation of formulation F2, which contain the MO, exhibited pH of 5.92, viscosity of 4090 cps, spreadability of 3.88 g.cm/sec, drug content of 98.11%, in vitro drug release of 95.64%, along with good extrudability. The accelerated stability study expressed no substantial alteration and skin irritation test showed no significant signs and symptoms. MO was relatively non-toxic, chemically inert, economic, widely availability, biodegradable, and demonstrate analogous attributes as compared to that of synthetic permeation enhancers. Therefore, a move towards utilizing excipients of natural origin represents a novel approach in formulating gel products in the future.

Keywords: Mahua, Madhuca longifolia, Gel, Formulation, Permeation, Enhancer.

INTRODUCTION

Natural products, in the form of excipient or active pharmaceutical ingredient (API), are well known across the globe for their safety, diverse applications, ethnobotanical and traditional usage, multiple pharmacological activities, and social acceptance [1-4]. In initial stages of research, the secondary metabolites were considered as active products owing to their ability to exhibit therapeutic activity and were a preferred class of medicines for treating several ailments [5]. As the science progressed, a need for the herbal formulations rose due to the appearance of numerous side and adverse effects. The demand for the safe formulation for prolonged use revived the traditional and ethnopharmacological principles [6]. By the end of last decade, several products arrived in the market which had herbal active ingredients. But, the presence of synthetic excipients again became a challenge in due course of time. Excipients were once considered as the inactive materials which supplement the API, but as the knowledge advances, they were found to be the decisive factor. These components elevate the activity of API by promoting drug absorption or solubility and play a vital role in formulation development [7].

In rational designing of topical formulations, excipients play a critical role. In gel formulations, the permeation enhancers are the decisive factor in effective drug release and subsequent absorption. A permeation enhancer is a class of chemical that increases the penetration of the drug into the skin by reducing the barrier resistance of the stratum corneum without damaging the living cells [8]. These compounds promote fast absorption of the drug from the skin by either disrupting the lipids, or interaction with intracellular proteins or by improving the partition of the drug [9]. In today's situation, numerous natural permeation enhancers are available such as fixed oils (corn, jojoba, groundnut, sunflower, and sesame) and essential oil (basil, eucalyptus, ginger, clove, and citronella) [10,11].

Mahua Oil (MO) is extracted from the seeds of Mahua or butternut tree, known scientifically as Madhuca longifolia (family: Sapotaceae). It is a large forest tree found right through the Indian subcontinent to South Asian nations [12]. MO is a well-known, widely socially acceptable natural ingredient used as a nutraceutical product due to its nutritional values. As the component is economic, non-toxic, chemically inert, and biodegradable; it is employed traditionally for treating skin disease, rheumatism, headache, constipation, piles, and hemorrhoids. Apart from these properties, it is widely utilized as laxative, emollient, illuminant, emetic, and as hair fixer [13]. The long shelf life of MO and easy extraction processes has revolutionized the commerciality of this oil. From the literature survey and the data obtained from traditional databases, it has been found that till date the application of MO as a permeation enhancer in gel formulation have not been exploited. Several essential factors like the utility of MO as cooking oil in villages and employing MO in various traditional and social practices for several centuries have provided the thrust for initiating the gel based product formulation [14].

The current study aims at examining the role of MO as a permeation enhancing agent in gel formulation. Employing, erythromycin stearate, triethanolamine, ethanol, MO, DMSO, and water; two different gel formulations were fabricated. One formulation comprises of MO whereas the other contained DMSO as the permeation enhancer. Both the formulations were characterized in terms of viscosity, pH, extrudability, spreadability, skin irritability test, drug content, in vitro drug diffusion, and accelerated stability studies.

METHODS AND MATERIALS

Chemicals

Erythromycin Stearate was obtained as a gift from Flamingo Pharmaceutical Ltd., Mumbai. Mahua oil was obtained from Gondwana Herbs, Gadchiroli, and Maharashtra, India. Caropol 940 and DMSO were procured from HiMedia India Ltd., Mumbai. Triethanolamine and ethanol were purchased from LobaChemie Pvt. Ltd., Mumbai.

Instruments

The UV-Vis spectroscopic analysis was performed using double-beam Shimadzu® Ultraviolet-Visible Spectrophotometer (Model UV-1800, Kyoto, Japan). Weighing was 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.

Preformulation and Standardization

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) [15].

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; where, w = weight (in g) of MO, b = volume of HCl utilized in blank titration, and a = volume of HCl consumed [15].

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 [15].

Preparation of Formulations

The gel was formulated using erythromycin stearate (1% w/w), carbopol 940 (1% w/w), triethanolamine (0.4% w/w), ethanol and distilled water. Erythromycin stearate was dispersed in a mixture of 24.1% w/w distilled water and 18.72% w/w ethanol, which was added dropwise into the hydrated carbopol 940 containing 6.25 % w/w ethanol

and 49.3% w/w distilled water. The content was stirred continuously until to form the gel. As the gel started forming, DMSO or MO (as a permeation enhancer) was added immediately, and further, the gel was allowed to set (Table 1).

Table 1: Describes the formulation chart

Ingredients	F1	F2
Erythromycin Stearate	1	1
Carbapol 940	1	1
Triethanolamine	0.4	0.4
Ethanol	24.5	24.5
Mahua oil	-	2
DMSO	2	-
Water	74.1	74.1

Evaluations of Gel Formulation

Determination of pH

The calibrated digital type pH meter was employed for determining the pH of the gel formulations. The pH meter was calibrated before the application with buffered solutions of pH 4 and pH 7. The protocol involved dipping the glass electrode and the reference electrode completely into the gel formulation [16].

Determination of viscosity

The viscosity of the gel formulations were determined by Brookfield DV-II+ viscometer with spindle number 7 at 100 rpm [17].

Determination of spreadability

The spreadability was determined on the principle of slip-drag attribute of the gel formulations. 2 g of gel was taken and placed over the ground slide, which was followed by sandwiching the test material by another glass slide with similar length and comprise of a hook. 1 kg of mass was applied over the slides to drive out the entrapped air and to promote the formation of a uniform film between the slides. The excess of gel materail was swiped off from the edges and then the top slide was subjected to a drag of 50 g intensity. The time (in sec) needed by the top slide to cover a distance of 7.5 cm was determined. The spreadability was concluded 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 [18].

Determination of extrudability

Extrudability may be defined as the weight (in g) required extruding 0.5 cm length ribbon of gel formulation in 10 sec. The conducted protocol was slightly modified where the weight was kept constant (500 g) and the length of ribbon of gel was determined. The gel formulation was fill up into the capped collapsible aluminium tubes and sealed suitably. The tube was placed in between two slides and clamped properly. 500 g of weight was placed on the slide and after that the cap was opened. The extruded ribbon length of the gel formulation was recorded after 10 minutes [19].

Skin Irritation Test

The gel formulation of quantity (0.5 g) was applied to the skin area of 6 cm^2 and the area was then covered using a gauze patch. The area was held loosely by a semi-occlusive bandage for the duration of 1 hr. Afterwards, the bandage was removed and the applied gel was scrapped off. After patch removal of patch, the area was inspected. The skin irritation test was performed for the duration of 7 days. The test results were expressed in terms of grades [20].

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.

Determination of in vitro Drug Diffusion Study

The *in vitro* drug diffusion study of gel formulations were carried out across the parchment paper. Initially, the receptor compartments were filled with phosphate buffer of pH 6.4. The total system was positioned over a thermostatic magnetic stirrer, maintaining the temperature at 37°C during the study. The drug diffusion study was performed for the period of 6 hr. The samples were withdrawn at every 30 minutes and analyzed spectrophotometrically at 225 nm.

Accelerated Stability Study

The accelerated stability study (40°C±2°C, 75%±5% RH) for the duration of 90 days was performed for formulation F2. The gel formulation was put inside the PVC container and duly covered with an aluminum foil. After the desired period of time, the gel formulation was evaluated for physical appearance, drug content, spreadability, pH, viscosity, and extrudability [20,21].

RESULT AND DISCUSSION

The parameters like saponification value, acid value, and the iodine value substantiate that MO had the preferred authenticity and purity as specified by the values in the pharmacopoeial range (Table 2).

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

The gel formulations appeared quite attractive in look-wise, no solid particles or grittiness were found, and was pretty soft to touch between the fingers. After the application of gel for the 7 days, the skin irritation test highlighted no striking signs and symptoms of rashes, edema, erythema or any inflammation. The formulation F2, containing MO, demonstrated a satisfactory outcome in the terms of the physical parameters like pH, viscosity, extrudability, spreadability, and drug content.

Both the formulations; F1 and F2 presented pH of about 6, which is somewhat similar with that of pH of the human skin, and hence the formulations are compatible for use on skin. In today's scenario, several synthetic components are employed in topical formulations which are often toxic on prolonging use. MO as a permeation enhancer or excipients is a product of natural origin which is well known for its beneficial effects over the decades and may be safe for formulating topical products like gel.

The drug content in gel formulations was found to be quite similar and not much significant difference was detected. The formulation F2 where MO was added, high drug content was noticed (98.11%) as compared to formulation F1 which contain DMSO (97.34%) (Table 3). The reason may be due to the fact that polymer carbopol 940 promoted good gelation in the case of formulation F2 which influenced better drug loading as compared to the formulation F1. The viscosity of the formulation F2, which contained MO, was found to be notably higher (4090 cps) than that of formulation F1 (3850 cps) (Table 3). The reason for the higher viscosity of the formulation F2 may be attributed due to MO, which might have promoted gelation in the polymeric matrix, causing an increase in the viscosity of the formulation. From the experiment, it was also observed that as the torque decreases, the sheer stress decreases, and accordingly the viscosity increases. The spreadability of both formulations F1 and F2 was observed to be 4.76 g.cm/sec and 3.88 g.cm/sec, respectively. It was analyzed that as the viscosity of the prepared formulation increases, the spreadability decreases alongside. The extrudability of formulation F2 was noticed to be less as compared to the formulation F1. The scientific basis may be, as the viscosity of the prepared formulation increases, the extrudability decreases.

Table 3: Evaluation of gel formulations

Formulation	pH	Viscosity (cps)	Spreadability (g.cm/sec)	Extrudability	Drug Content (%)
F1	6.39	3850	4.76	+++	97.38
F2	5.92	4090	3.88	++	98.11

The permeation enhancement attributes of the MO holds true as reflected by the observations of in vitro drug diffusion study. The formulation F2, containing 2 g of MO in the gel formulation exhibited higher drug release of 98.11% in 300 minutes (Figure 1) as compared to the formulation F1 which contains DMSO (97.38%). Table 4 highlighted the in vitro drug diffusion of formulations F1 and F2.

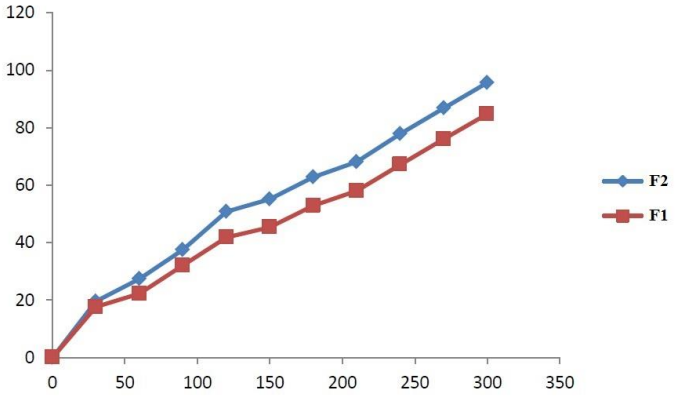

Figure 1: Graph depicting in vitro drug release from gel formulations

Table 4: *In vitro* drug release of gel formulations

Time(min)	F1	F2
0	0	0
30	17.62	19.5
60	22.23	27.36
90	32.07	37.53
120	41.85	50.77
150	45.28	55.05
180	52.83	62.85
210	57.97	68.10
240	67.18	77.81
270	76.02	86.85
300	84.89	95.64

Table 5: Accelerated stability studies of gel formulation (F2)

	pH	Viscosity (cps)	Spreadability (g.cm/sec)	Extrudability	Drug Content (%)
0 day	5.92	4090	3.88	++	98.11
90th day	5.67	4050	3.52	++	97.54

After subjecting the gel formulation F2 at 40°C ± 2°C and 75% ± 5% RH for 90 days, no considerable variation in the physical appearance, spreadability, pH, extrudability, and viscosity were noticed. Under accelerated conditions, a minor fall in pH (0.25), viscosity (40 cps), spreadability (0.36 g.cm/sec), and drug content (0.57%) was observed. In conclusion, the fabricated gel formulation containing MO was found to be stable for the duration of 90 days. Table 5 describes the parameters of gel formulation F2 before and after the stability study.

CONCLUSION

The current research concluded that Mahua oil, a key ingredient obtain from Madhuca longifolia served as a brilliant permeation enhancer for formulating gel formulation. In today's scenario, a complete herbal formulation, which will be free from every kind of unsafe synthetic excipients, is the global need. Some permeation enhancers like DMSO are often associated with making the skin rough; some people are idiosyncratic to reactions, and other associated damages. The study revealed that Mahua oil was relatively non-toxic, chemically inert, economic, widely availability, biodegradable, and demonstrate analogous attributes as compared to that of synthetic permeation

enhancers. Therefore, a move towards utilizing excipients of natural origin represents a novel approach in formulating gel products in the future.

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