EFFECT OF CHAMOMILE OIL AS A PERCUTANEOUS ABSORPTION ENHANCER

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Article Received on: 19/08/13 Revised on: 01/09/13 Approved for publication: 19/09/13

DOI: 10.7897/2230-8407.04914

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ABSTRACT

The aim of this study was to investigate the ability of Chamomile oil as absorption enhancers for cutaneously administered Silver Sulfadiazine by comparing it with a penetration enhancer Dimethyl Sulfoxide. Silver sulfadiazine is used in burn infection. Gel was selected as the vehicle for Silver Rat' skin samples were placed in a continuous flow diffusion cell, with Silver Sulfadiazine gel on top. Receptor fluid samples were analyzed using high-performance liquid chromatography. The quantity of gel remaining on the skin surface after completion of each test was weighed and the amount of drug in the skin was analyzed. Addition of chamomile oil or Dimethyl Sulfoxide to the gel increased the percutaneous absorption of the drug. 5 % Chamomile oil was found to be the most efficient absorption enhancer in this comparison.

Keywords: high-performance liquid chromatography; percutaneous absorption enhancer; Chamomile oil; Dimethyl Sulfoxide; Silver Sulfadiazine.

INTRODUCTION

The improvement of topical administration through skin biological barriers is always a difficult problem due to its complex structure and its protection role against exogenous substances¹. Therefore, to increase the absorption rate through the skin, many factors should be considered such as selection of a safe penetration enhancer, lipophilicity of the base type and solubility of the drug itself. Proper enhancers should specifically enhance drug penetration across the skin without altering its properties² or inducing undesirable effects such as severe skin irritation³. Moreover, it has been reported that penetration enhancers can disrupt skin function by altering its lipid structure. Optimally, the testing of topical delivery system should be performed *in vivo*, this is often impossible. Therefore, *in vitro* percutaneous absorption procedures have become increasingly important for the absorption of topical compounds⁴. Generally, for a drug to penetrate the stratum corneum and lower layers of the skin, it should diffuse and release from its vehicle, then into the skin. *In vitro* experimental procedures for drug release have multitude of benefits associated with this field. Many different types of penetration enhancers have been investigated for potential usefulness in this effect using these techniques. To this end, data obtained from receptor fluid levels measurements have become insufficient for most experiments⁵. These procedures now accurately accomplished till the end of the experiment to measure the amount of compound diffusing into the receptor fluid and the absorbed material remaining in skin. The sum of these values is determined after removal of unabsorbed material, and it serves as the real amount absorbed of the drug in the skin. Proper selection of safe and natural drug release enhancer have been investigated for accomplishing this goal. Extensive research during the past two decades had revealed considerable information on several classes of drug release enhancers, including surfactants and terpenes⁶. Surfactants are synthetic chemicals, rapidly losing their value when used topically due to reports of their absorption into the systemic circulation and subsequent possible toxic effect upon long term application⁷. Efforts have been directed at identifying

safe and effective enhancers from both natural products and synthetic chemicals. In particular, terpenes from natural sources have attracted great interest⁸. Terpenes are generally considered to be less toxic with low irritancy potential compared to surfactants and other synthetic skin penetration enhancers. Further, quite a few terpenes are included in the list of Generally Recognized as Safe (GRAS) agents issued by US FDA⁹. Terpenes can increase drug release by one or more of the mechanisms interacting with subcutaneous (SC) lipids as well as increase the solubility of the drug into SC lipids. However, the interaction of terpenes with SC in presence of various solvents may not be similar due to differences in the physico-chemical properties of these solvents and their interactions with SC¹⁰ Lipids. *Matricaria recutita* (*Matricaria chamomilla*) family Asteraceae is commonly known as German chamomile, blue chamomile, Hungarian chamomile and single chamomile. German chamomile flowers contain 0.24- to 2.0 percent volatile oil that is blue in color. The two key constituents of *Matricaria chamomilla* oil (MCO) are (-)-alpha-bisabolol and chamazulene, account for 50 - 65 percent of total volatile oil content. Other components of the oil include (-)-alpha-bisabolol oxide A and B, (-)-alpha-bisabolone oxide A, spiroethers (cis- and trans- en-yn-dicycloether), sesquiterpenes (antheotulid), cadinene, etc. Preliminary *in vitro* studies on the antimicrobial activity of chamomile oil had yielded promising results. Chamomile oil, at a concentration of 25 mg/ml, showed antibacterial activity against gram-positive bacteria as well as some fungicidal activity against *Candida albicans*. These activities may be attributed to alpha-Bisabolol. Natural alpha-Bisabolol, a monocyclic unsaturated sesquiterpene alcohol, is nontoxic and nonirritating to the skin, has been shown to possess anti-inflammatory and wound healing properties, as well as antimycotic and antibacterial effects although the precise mechanism of action remains unclear^{11,12}. Silver Sulfadiazine (SSD) is widely used in third and fourth degree burn¹³. SSD is a highly lipophilic substance with a tendency to concentrate in the skin¹⁴. Previous studies had shown that SSD penetrates the stratum corneum rapidly and remains in

the skin for a long time after treatment, possibly because SSD is bound to a slow-release reservoir, such as fat in the subcutis¹⁵. Fatty acids or lipid soluble carrier are relatively insoluble in water, making it difficult to remove from the burn wound, in addition to its tendency to form pseudo eschar, which impede SSD penetration¹⁶. Silver sulphadiazine has less solubility in water and readily release in water soluble gel due to low affinity between them. The aim of this *in vitro* study was to monitor and to investigate whether *Matricaria chamomilla* oil (MCO), compared to Dimethyl Sulfoxide (DMSO), increases the percutaneous absorption of SSD.

MATERIALS AND METHODS

Chemicals

SSD was a gifted sample from Julphar Company, Ras Elkeimah, UAE. Dimethyl sulfoxide and ethanol were purchased from Sigma Aldrich Co., Ayrshire, UK. German Chamomile oil was purchased from Esoteric essential oils, Sallamander, Lynnwood, South Africa. All ingredients used were of analytical grade.

Preparation of gels

Gels were prepared by various polymers as shown in Table 1. The polymer and purified water were taken in a mortar and allow soaking for 24 h. Solid dispersion containing required amount of drug was dissolved in ethanol and other additives were added. The trituration was continued to get homogenous dispersion of drug in the gel¹⁷. All formulations prepared protected from light by storing the containers in dark place and wrapped in aluminum foil.

Permeation Enhancer for DMSO and MCO

The permeation enhancer dimethyl sulfoxide (DMSO) and *Matricaria chamomilla* oil (MCO) were incorporated in different concentration as shown in Table 2.

Animals

Five healthy Wistar albino rats weighing 150 - 180 g were used. The experiment was carried out per the guidelines of research and ethical Committee in Dubai Pharmacy College. The dorsum of each rat was shaved. Samples of skin were collected while the animals were under anesthesia.

Skin Samples Preparation

Samples from the skin (3 × 6 cm in area and 300 – 400 µm in thickness) were taken from anesthetic animals. The skin was stored in cold buffer (7.4), for a maximum of one hour after being surgically removed until the start of the experiment.

HPLC analysis

HPLC method was developed for analysis of silver sulfadiazine, based on the USP method¹⁸. All samples were analyzed by HPLC with absorbance detection at a wavelength of 254 nm, on a Genesis C18 column (3.9 × 300 mm), Sorbent AB, Göteborg, Sweden). 0.5 ml of triethylamine (TEA) was added to 1000 ml of water, pH was adjusted to 3 with phosphoric acid to use as a mobile phase. The mobile phase fluid, Water : Acetonitrile mixture (90 : 10), was filtered through a 0.22 µm membrane filter (GV membrane filters, Millipore, Billerica, USA) at a flow rate of 1.5 ml/min. Inj. Volume 20 µL and ambient temperature.

Preparation of Standard

50 mg of Silver Sulfadiazine reference standard was weighed accurately and transferred in 100 ml volumetric flask. About 60 ml of diluents was added and shaken well to dissolve, made up to volume with diluents and mixed well. 5 ml of this solution was diluted to 50 ml with mobile phase and mixed well. Then, the solution was passed through 0.45 µm filter before injecting to HPLC. 20 µl of each Standard preparation having concentration approx. 5 mg% of Silver Sulfadiazine was Injected until replicate chromatograms identical.

Preparation of Test sample

2 g of test gel (equivalent to 20 mg of Silver Sulfadiazine) was weighed accurately and transferred in a 100 ml beaker. 30 ml of ethanol was added, heated on a water bath and then 30 ml of diluents were added and mixed well. The content of the beaker was transferred to a 100 ml volumetric flask, cooled to 10°C temperature and completed to volume with diluent. 5 ml of this solution were diluted to 20 ml with mobile phase and mixed well then filtered through 0.45 µm filter paper. 20 µl of each test sample preparation having concentration approx. 5 mg% of Silver Sulfadiazine was injected until replicate chromatograms identical.

In vitro SSD diffusion through the skin

One square centimeter of the skin piece was placed in a continuous Franz diffusion cell (Laboratory Glass Apparatus Inc., Berkley, USA) with the stratum corneum upper-most. A 50 mg quantity of the test gel was applied on the top of each skin sample. Phosphate buffer (7.4 PBS (30:70)) was degassed in an ultrasound bath (Branson 2200, Hayward, USA) before being used as receptor fluid. The fluid was pumped through the cell at a flow rate of 2 ml/h. Fractional sampling was started immediately and continued for 60 h and one fraction was sampled every 30 minutes. The test gel that did not absorbed was removed carefully and weighed. The proportion of the test substance that diffused through the skin was analyzed using HPLC method. The test substance absorbed into the skin was extracted using 0.5 ml ethanol and shaken for 10 minutes. The supernatant was decanted and the procedure was repeated three times. The supernatants were pooled and evaporated with nitrogen gas at 37°C, dissolved in 0.5 ml mobile phase fluid, filtered through a 0.45 µm syringe filter and analyzed using HPLC. All experiments were repeated five times.

Assay calculation for silver sulfadiazine

The percentage L.A. of Silver Sulfadiazine in SSD 1% gel was calculated by the formula:

$$\text{Silver Sulfadiazine (\% L.A.)} = \frac{P A_T \times C_s}{P A_s \times C_T} \times P$$

Where, $P A_T$ is the peak area of Silver Sulfadiazine peak in test solution, $P A_s$ is the peak area of SSD peak in standard solution as is the final, C_s is the final concentration of Silver Sulfadiazine in standard solution, C_T is the final concentration of Silver Sulfadiazine in test solution, P is the potency of Silver Sulfadiazine reference standard in % w/w

SSD gel evaluation

Physical appearance

The prepared gel formulations containing silver Sulfadiazine 1% (w/w) were inspected visually for their colour, consistency and phase separation.

Consistency

The cone attached to holding rod was dropped from the fix distance of 10 cm such that it should fall on the centre of measuring cylinder filled with SSD gel. The distance travelled by cone was noted down after 10 seconds.

Measurement of pH

One gram of gel was dissolved in 100 ml distilled water and stored for two hrs and pH measured with digital pH meter.

Drug content

The amount of solid dispersion equivalent to 10 mg drug was weighed accurately. Then it was dissolved in 100 ml of water, suitably diluted and UV absorbance was measured at 254 nm.

Spread ability

One gram of SSD gel was placed between the two glass slides and load of 500 g was applied¹⁹. The time required to slip off the slides was measured and Spread ability was calculated using formula

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

Where M = wt. tied to upper slide, L = length of glass slides,
T = time taken to separate the slides.

Rheological Study

The viscosity of different gel formulation was determined at 37°C using a Brook field viscometer (Brookfield DV-E viscometer) with helipath spindle no F at three different rpm (10, 50, 100)¹⁹.

Swelling index

The swelling index can be calculated by placing 1 g of SSD gel formulation on porous aluminium foil¹⁹. It was placed in petriplate containing 0.1N NaOH. The sample was weighed after specific time interval and swelling index was calculated using formula.

$$\% S_w = [(W_t - W_0) / W_0] \times 100$$

W_t = weight of swollen gel after time t.
 W_0 = original weight of gel at zero time.

Extrudability

The Extrudability was measured by application of force to the aluminium collapsible tube (weight in grams) containing SSD gel¹⁹. The area of ribbon of gel was measured and Extrudability was measured by formula

$$\text{Extrudability} = \frac{\text{Applied weight to extrude gel from tube (in gm)}}{\text{Area (in cm}^2\text{)}}$$

Antimicrobial activity

Antimicrobial activity was determined by ditch plate technique²⁰. This technique has been used for evaluation of bacteriostatic and fungistatic activity of compounds especially in semisolid preparations. Agar plates were prepared and sterilized as per standard procedure. A cup (2.5 X 0.5 cm²) was made in the center of agar plates. (0.5 g) of each formulation was mixed with 1 ml of sterile water using a whirl mixer until a slurry was formed. One hundred µl of each slurred cream was placed into pre labeled cups filled in the cup. The prepared culture loops were streaked across the agar at right angle from ditch to the edge of the plate. The formulations containing different penetration enhancers were allowed to diffuse for 1 h before incubating the bacteria

plates at 37 °C for 24 h, and the fungal plates were incubated at 25°C for a minimum of 48 h. The diameter of zone of inhibition was measured after the incubation period for each formulation, compared with control. The percentage inhibition was calculated as follow²⁰:

$$\text{Percentage Inhibition} = L_2 / L_1 \times 100,$$

where L_1 = Total length of streaked culture, L_2 = length of inhibition.

Skin irritation test

The SSD cream containing drug was applied on the skin²¹. The test cream and cotton swab covering it were secured firmly on the applied surface with the help of adhesive tapes. Then observations were made for any sign of erythema and ranked as follows as per the state of the applied site: +++ = Severe erythema, ++ = Moderate erythema, + = Slight erythema, - = No irritation.

RESULTS AND DISCUSSION

Investigation of the prepared SSD formulations containing different concentrations of MCO and DMSO indicated that they are white, smooth, and homogenous of semisolid consistency without sticky skin feel. The drug content of all the formulations was found to be in good agreement with the theoretical value, indicating the stability of the drug in the formulations. pH of all the formulations was found to be between 5.7 and 7.2, which indicated suitability of the formulations for application on the skin; As show in Table 1. Rheological properties (spread ability and Extrudability) of the SSD semisolid formulations were found to be equivalent to silver sulfadiazine cream USP. The Flow patterns of all samples were nearly similar as the commercial product. SSD formulation containing 20 % MCO showed better *in vitro* release profile and gave larger zones of inhibition in comparison to commercial SSD cream, indicating the synergistic activity of MCO when combined with the drug. In creams, owing to their biphasic nature, partitioning of the drug occurs in 2 phases, resulting in slower release of drug, while in the case of increasing the oil phase in addition of MCO the release of drug is more due to in affinity of the drug, the drug diffusion occurs through the oil phase and hence they offer a greater drug diffusion and release²². The results for the amount of SSD absorbed into the skin are shown in Table 5. For all samples SSD was found in the receptor fluid within 5 h. The amount of SSD in the receptor fluid was approximately the same for both percentages of MCO compared with the result from the control gel, which is 10 % of that value. When analyzing the amount extracted from the skin at the end of the experiment there was about five times more SSD in the skin when 5 % MCO was used as enhancer compared with 20 % MCO and the control. For SSD left on the skin, the control and 5 % MCO gave approximately similar values and the amount for 20 % MCO was five times greater. The profile in Figure 2 for 5 % MCO describes a fast penetration through the skin at first that rapidly declines after a peak at approximately 15 h. After this time-point most of the SSD is absorbed into the skin. This profile also matches the control curve (Figure 2), but with a much higher maximum value. The profile of the curve for 20 % MCO shows continuing penetration of SSD into the receptor fluid and thus an even release over time. These results indicate that the most efficient absorption enhancer in this comparison is 5 % MCO. Table 5 shows quite small differences between the two percentages of DMSO.

Table 1: Formulation of SSD Gels with Permeation Enhancer (DMSO) and (MCO)

Content	Gel 1	Gel 2	Gel 3	Gel 4
SSD	1 %	1 %	1 %	1 %
Carbopol 940	1.0 %	1.0 %	1.0 %	1.0 %
Triethanol amine	0.50 %	0.50 %	0.50 %	0.50 %
Propylene glycol	10 %	10 %	10 %	10 %
Ethanol	2.5 %	2.5 %	2.5 %	2.5 %
Water (ml)	100	100	100	100
DMSO	5 %	20 %	1 %	1 %
MCO	-	-	5 %	20 %
Control	The plain gel with 1% SSD (without DMSO or MCO)			

Table 2: Physical Appearance of Various Formulations

Parameter	SSD + 20 % DMSO	SSD + 5 % DMSO	SSD + 20 % MCO	SSD + 5 % MCO	SSD gel only (control)	commercial
Colour	white	white	white	white	white	white
pH	5.66	5.3	5.7	5.8	5.6	5.8
Drug content (%)	95.19 ± 0.09	97.4 ± 2.8	93.1 ± 3.7	99.7 ± 4.8	95.3 ± 4.7	100.7 ± 4.8
Homogeneity	+++	+++	+++	+++	+++	+++
Consistency(mm)*	5	6	9	7	7	5

Table 3: Rheological Properties of SSD Gel with DMSO and MCO Formulations

Parameter	SSD + 20 % DMSO	SSD + 5 % DMSO	SSD + 20 % MCO	F4 SSD + 5 % MCO	SSD gel only (control)	commercial
Spreadability gcm/sec*	30	60	52	48	70	50
Extrudability* (g/cm ²)	22	10	18	13	26	17
Viscosity (cps)* 10 rpm	605	705	460	510	920	810

Table 4: Antimicrobial activity of m topical drug delivery systemSSD fro

Formulation base	inhibition zone diameterin mm*				
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Bacteroides fragilis</i>
SSD + MCO%20	56.82	55.82	56.32	53.33	54.33
SSD + MCO%5	49.72	55.33	50.22	46.32	49.21
DMSO %20 + SSD+	36.32	33.33	31.21	32.33	35.21
DMSO %5 +SSD	32.13	31.33	30.23	30.21	30.11
(control)SSD only	28.52	29.23	28.5	28.43	19.62
SSD .Comm	45.33	51.22	48.31	44.72	47.12

*Values are average of 3 determination

Table 5: Percutaneous Absorption of Gel Containing 1% SSD in the Presence of DMSO and MCO*

Enhancer	SSD absorbed in skin (µg)	SSD receptor fluid (µg)	Non-absorbed gel (µg)
Control	7.9	0.37	11.5
DMSO 20 %	21.5	2.4	19.7
MCO 20 %	11.6	3.2	76.2
DMSO 5 %	19.1	2.6	34.1
MCO 5 %	51.8	2.9	14.2

*Results are shown for percutaneous absorption in the skin, passage through the skin (receptor fluid) and non-absorbed SSD gel. All results are mean values of five samples

Figure 1: Chromatogram of silver sulfadiazine 1 % cream of the standard sample

Figure 2: Percutaneous absorption of 1 % SSD gel formulation with different concentration of DMSO and CMO

There was seven times more SSD in the receptor fluid than in the control gel and twice as much was found in the skin. A slightly larger amount of gel remained on the skin surface for the 5 % DMSO, about three times more than for the control gel. The amount left on the skin for 20 % DMSO was almost twice the amount for the control gel. These data are interesting in comparison with the curves for 5 % and 20 % DMSO. Although the results in Table 5 are similar, the profiles in the above-mentioned figure are quite different. The higher percentage of DMSO appears to have more of a depot effect, whereas the lower amount of the DMSO releases a larger amount of SSD into the receptor fluid at the beginning and then almost stops. Figure 2, which describes the results from the gel with 5 % DMSO, shows a similar profile as the curves for the control and for 5 % MCO, but the maximum is reached more than 20 h later, although it is almost as high as for 5 % MCO. When the percentage of enhancer is increased to 20 % DMSO the curve agrees with the result for 20 % MCO, but the SSD is found in the receptor fluid from the start of the experiment and reaches its peak later. The curves for 5 % added enhancer show a profile that is more desirable in this case than those for 20 % added enhancer because the active substance should be absorbed into the skin and not pass through it. It is also favorable if the absorption starts as soon as possible, as is the case for 5 % MCO. This indicates that MCO in low concentration can be used as penetration enhancer, with the advantages of its biological activities. All these indicate the ability of MCO as penetration enhancer; therefore it can be used as enhancer. That agreed with the previously published results concerning the terpenes. Terpenes are generally considered to be less toxic with low irritancy potential compared to surfactants and other synthetic skin penetration enhancers. Further, quite a few terpenes are included in the list of generally recognized as safe (GRAS) agents issued by US FDA⁹. The aim was to investigate for a safe and natural substance such as MCO to penetrate and absorb into the skin, without causing systemic effects. The combination of too high a concentration of MCO with a lipophilic substance such as SSD may result in percutaneous penetration rather than percutaneous absorption. With a lower amount of MCO the SSD can interact with the enhancer as well as the lipophilic regions of the skin, which results in a high amount of drug absorbed and a slower and less efficient transportation of active substance through the skin. DMSO is a less lipophilic substance and, as such, is less suitable as an enhancer in this particular case.

CONCLUSION

From the *in vitro* studies carried out in this work, it can be concluded that in comparison to the Commercial cream (1 % SSD), 5 % MCO is superior in terms of antimicrobial and percutaneous activities. The superiority of MCO may be attributed to the high content of (-)-alpha-bisabolol and chamazulene content in the oil, which gives a synergistic effect with SSD in antimicrobial as well as anti-inflammatory activities. The antimicrobial, anti-inflammatory and percutaneous properties are beneficial in burn management products. Extension of this work is planned to include *in vivo* and clinical studies.

ACKNOWLEDGMENT

The authors express gratitude to the DPC undergraduate students Heba Basam and Mina for their support in lab work.

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Cite this article as:

Ali Heyam Saad, Shehab Naglaa Ahmed and El-ahaj Babiker Mohamed. Effect of chamomile oil as a percutaneous absorption enhancer. *Int. Res. J. Pharm.* 2013; 4(9):66-71 <http://dx.doi.org/10.7897/2230-8407.04914>

Source of support: Nil, Conflict of interest: None Declared