

ENHANCED ANTIINFLAMMATORY ACTIVITY OF DICLOFENAC IN JOJOBA OIL SUBMICRON EMULSION CREAM

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Synopsis

Jojoba liquid wax is a stable highly lipophilic, non-irritative and non-toxic "oil", obtained from desert plant Jojoba (*Simmondsia chinensis*). The potential use of Jojoba oil as excipient for the preparation of submicron emulsions (SME) for topical use was investigated. Submicron oil-in-water emulsion containing 20% Jojoba oil and the antiinflammatory drug Diclofenac Diethylammonium (1.16%) was prepared by a *proprietary* high pressure homogenization technique (mean droplet size about 150 nm). The effectiveness of the 1.16% Diclofenac Diethylammonium in the Jojoba SME topical cream was evaluated in carrageenan paw edema model. Diclofenac in Jojoba SME vehicle demonstrated significantly greater antiinflammatory activity than marketed Voltaren[®] Emulgel[®] cream (Ciba-Geigy). The unique penetrative properties of the SME delivery technology makes this novel topical vehicle attractive for development in cosmetic formulations. Water-insoluble substances used in personal care products as antioxidants and vitamins such as tocopherols (vitamin E), retinoids (vitamin A) have been successfully incorporated in SME formulations. The solvent-free SME technology can be also considered for use in cosmetic preparations to replace alcohols used as solvents and coolants (e.g. after-shaves and antiseptic solutions). Additional potential cosmetic uses of interest for SME lipoidal vehicle in the form of lotions, gels, or creams might include hair-lotions, sunscreens, after-sun gels, and encapsulation of fragrances and perfumes.

Riassunto

La cera liquida di jojoba é un olio altamente lipofilo, non irritante e non tossico, ottenuto dalla pianta desertica *Simmondsia chinensis*.

Si é voluto studiare il comportamento dell'olio di jojoba come eccipiente per la preparazione di submicro emulsioni (SME) di uso topico.

É stata perciò preparata una submicro emulsione O/W (con micelle di una grandezza media dell'ordine di 150 nm) contenente il 20% di olio di jojoba ed il farmaco antinfiammatorio Diclofenac dietilammonio (1,16%). L'efficacia dell'attività svolta dal Diclofenac all'1,16% nella jojoba SME é stata valutata sul modello dell'edema indotto dalla carragenina.

Il Diclofenac nel veicolo jojoba SME ha dimostrato una attività antinfiammatoria più marcata del

Voltaren® Emulgel® in crema (Ciba-Geigy). Le notevoli proprietà di penetrazione dimostrate da questa nuova tecnologia SME rendono tale veicolo interessante anche per l'uso cosmetico. I principi attivi idrosolubili usati nei prodotti di igiene personale come antiossidanti e le vitamine quali i tocoferoli (vit. E) ed i retinoidi (vit. A) sono stati incorporati con successo in questo nuovo veicolo. Il veicolo SME privo di solventi può essere utilizzato in cosmetica per rimpiazzare l'uso dell'alcool come solvente e come agente rinfrescante (dopobarba e soluzioni antisettiche). Altri potenziali usi cosmetici del veicolo SME sotto forma di lozioni, geli o creme può essere nei prodotti solari nelle lozioni per capelli e nei profumi incapsulati.

Jojoba oil, also known as Jojoba liquid wax, is a non-toxic and non-irritative oil, which is now widely used in cosmetics (1). It is a highly lipophilic compound, consisting almost entirely of wax esters of high molecular weight monounsaturated acids and alcohols, mainly C₁₈ - C₂₂ (2,3). Jojoba oil is stable to oxidation and remains chemically unchanged for years (3, 4). The skin irritation potential of Jojoba oil in different preparations was evaluated by various methods and the material was classified as non-irritating (5). Acute and sub-chronic toxicity,

skin sensitization and mutagenicity assessments of jojoba oil also show lack of undesirable effects. Additionally, jojoba oil was found to be non-comedogenic in topical formulations even at high concentrations (5). The excellent safety profile of Jojoba oil makes it a promising component for topical preparations. Emulsions play a critical role in the cosmetic field and they are of widespread importance in the cosmetic industry. They offer many advantages to the cosmetic chemist allowing compounding immiscible ingredients into single formula-

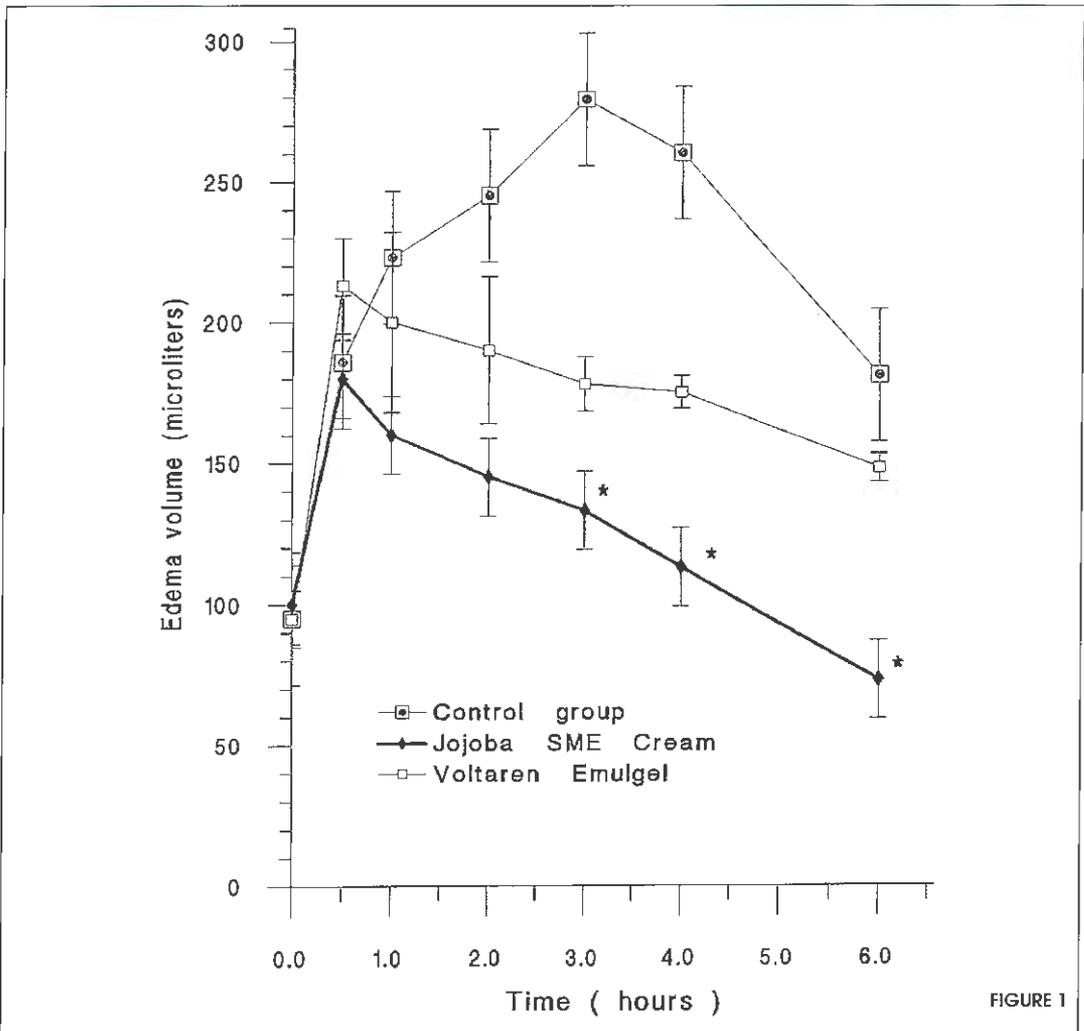


FIGURE 1

tions. We have developed a novel emulsion-based lipoidal vehicle consisting of stable, submicron particles of oil-in-water emulsions, termed Sub-Micron Emulsions or SME. SME droplets are characterized by a mean droplet size of less than one micron (generally in the range of 0.1-0.2 μm) uniformly dispersed in an aqueous phase. The droplet size reduction is essential to generate preparations with high stability. The uniqueness of the large internal hydrophobic oil core of the SME droplets provides high solubilization capacity for water insoluble compounds compared to other lipoidal vehicles such as liposomes (Figure 1).

Recently we demonstrated that submicron emulsions (SME) exhibit enhanced topical and transdermal delivery of several drugs, included into SME creams, prepared with different types of oil phase components, such as capric/caprylic triglycerides, soybean oil, isopropylmyristate and paraffin oil.. Drug activity increase up to 1.5 - 3 fold was demonstrated for antiinflammatory drugs (steroidal and non-steroidal), diaepam, atropine and local anesthetics (6-10). The extended drug activity might be attributed to increased penetration of submicron oil droplets through the stratum corneum of the skin and improved association of the drug with increased surface of the SME particles (9).

SME cream comprised of 20% Jojoba oil phase and containing 1.16% Diclofenac (Diethyl ammonium salt) was prepared by a proprietary high pressure homogenization process. Diclofenac was dissolved in the oil phase, consisted of 85% Jojoba oil (Jojoba Israel Ltd., Israel) and 15% purified egg lecithin (Lipoid E-80, Lipoid AG, Germany). After drug dissolution, the oil phase was mixed with the water phase containing 2% Cremophor EL (Polyoxyl-35 castor oil, BASF, USA) as surfactant to obtain a 20% oil-in-water emulsion. The mixture was homogenized using a high shear homogenizer (Polytron K3000, Kinematica, Switzerland) at 20,000 rpm (1-2 min.) and then sized by a high pressure homogenizer (Micron Lab 70, APV Gaulin Inter-

national SA, Netherlands), 8 cycles at 800 bar. The resultant submicron emulsion was cooled and filtered through a 0.45 μm nylon filter (Schleicher and Shuell, Germany), and particle size distribution was determined by quasielastic light scattering, using a Coulter N4MD Particle Size Analyzer, (Coulter Electronics, USA). The Jojoba oil SME formulation containing Diclofenac showed a narrow size distribution (156 ± 56 nm), and 100% of the particles were below 215 nm. Diclofenac-Jojoba oil SME cream topical emulsion was prepared by thickening with Carbopol 940 (BF Goodrich, USA) to a 0.8% w/w final concentration and adjusting the pH to 6.0 - 6.5 with triethanolamine (Merck, Germany). Carbopol was added to the SME as preswollen gel (10% in water), by mixing with the help of a high shear homogenizer (Polytron K3000, 5,000 rpm, 2 min). The viscosity of the Jojoba oil SME cream with Diclofenac, determined by a Brookfield rotor viscometer DV II+ (spindle LV4, 6 rpm) was about 100,000 cP.

The antiinflammatory activity of Diclofenac in Jojoba SME cream was investigated using the carrageenan induced paw edema model in rats (11, 12). Voltaren[®] Emulgel[®] (Ciba-Geigy, Switzerland), a marketed antiinflammatory cream with identical active component content (1.16% Diclofenac Diethylammonium) was used as a comparative formulation. Edema volume changes after topical application of the creams were tested using a plethysmometer (Ugo Basile, Italy).

Rats (Wistar, 230-250 g bodyweight, 6 animals in each group, Anilab-Israel) were anesthetized during the experiment by sodium diethylbarbiturate (120 mg/kg S.C., Fluka, Switzerland) and Rompun[®] (10 mg/kg I.P.) injections. One hundred microliters of 1% iota-Carrageenan (Fluka, Switzerland) solution in saline was injected subplantar into the hind paw of the rat. Sixty μl of topical preparation (Diclofenac dose 2.5 mg/kg) was applied on the hind paw and gently rubbed into the skin, and edema volume changes were tested at 0, 0.5, 1, 2, 3, 4 and 6

Table I

**RELATIVE ANTIINFLAMMATORY ACTIVITY OF DICLOFENAC
IN JOJOBA SME CREAM AND IN VOLTAREN® EMULGEL®**
(Mean data \pm S.D., AUC - area under curve for edema volume; for Control group - 100%)

GROUP	AUC, $\mu\text{l} \cdot \text{hr}$	RELATIVE ACTIVITY, %
Control	981 \pm 154	100 \pm 16
Voltaren® Emulgel®	774 \pm 107	79 \pm 14
Jojoba SME cream	456 \pm 83	46 \pm 18

hours time intervals. No signs of skin irritation were observed during the experiment in any group. A control group of animals did not receive any antiinflammatory treatment. The results obtained are presented in Fig. 1.

The onset of antiinflammatory activity for Diclofenac in Jojoba SME vehicle is about 1 hour, and at 3, 4 and 6 hour paw edema volumes were significantly ($p < 0.05$) lower than for Voltaren® Emulgel®. Antiinflammatory activities, presented in terms of area under the curve (AUC, $\mu\text{l} \cdot \text{hr}$), were calculated using the trapezoid method with the help of SigmaPlot® program, (see Table 1).

It is evident from the Table 1 and Fig. 1 that Diclofenac Diethylammonium in Jojoba SME topical vehicle demonstrates enhanced antiinflammatory activity compared to Voltaren® Emulgel® with identical drug content. In contrast to Voltaren® Emulgel® formulation, which contains propylene glycol and isopropyl alcohol, the Jojoba SME vehicle does not include any organic solvent or other irritative penetration enhancer.

In conclusion, Jojoba oil as a non-toxic and non-irritative lipophilic compound is very suitable for preparation of submicron emulsion for topical and transdermal drug delivery. Incorporation of Diclofenac into SME Jojoba oil cream provides a highly effective antiinflammatory topical preparation. The unique penetrative pro-

erties of the SME delivery technology makes this novel topical vehicle attractive for development in cosmetic formulations. Emollients and lubricants are used in cosmetics to improve consumer acceptance of the product by providing skin-care preparations with the appropriate slip, tactile feel, and rub-in properties to encourage the consumer to use the product more liberally and more frequently. Since emollients and lubricants can be easily incorporated in SME formulations, topical preparations of SME lipoidal vehicle in the form of lotions, gels, or creams may have potential applications in cosmetics to deliver moisturizing agents and lipids to skin.

The solvent-free SME technology can be also considered for use in cosmetic preparations to replace alcohols used as solvents and coolants (e.g. after-shaves and antiseptic solutions). Additional potential cosmetic uses of interest for SME might include hair-lotions, sunscreens, after-sun gels, and encapsulation of fragrances and perfumes. Water-insoluble substances used in personal care products as antioxidants and vitamins such as tocopherols (vitamin E), retinoids (vitamin A) have been successfully incorporated in SME formulations.

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