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Multiple Emulsions for Anti-Inflammatory Treatment of Chemoradiotherapy-Induced Skin Damage

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INTRODUCTION & AIM

Oncological therapies (radiotherapy/chemotherapy), though effective, often damage the skin barrier, causing erythema, dryness, inflammation, and fragility. Conventional topical formulations may then worsen irritation or allow uncontrolled drug penetration, leading to toxicity or insufficient exposure. This highlights the need for safe, well-tolerated dermal delivery systems tailored to therapy-damaged skin. Multiple water-in-oil-in-water (W/O/W) emulsions represent an innovative approach to this challenge. Their complex architecture („droplets in drops") creates a natural barrier that allows fine modulation of drug transport across impaired skin. This structure provides multiple advantages: sustained and controlled release of active substances, improved drug stability, reduced irritation potential, and enhanced tolerability for compromised tissue.

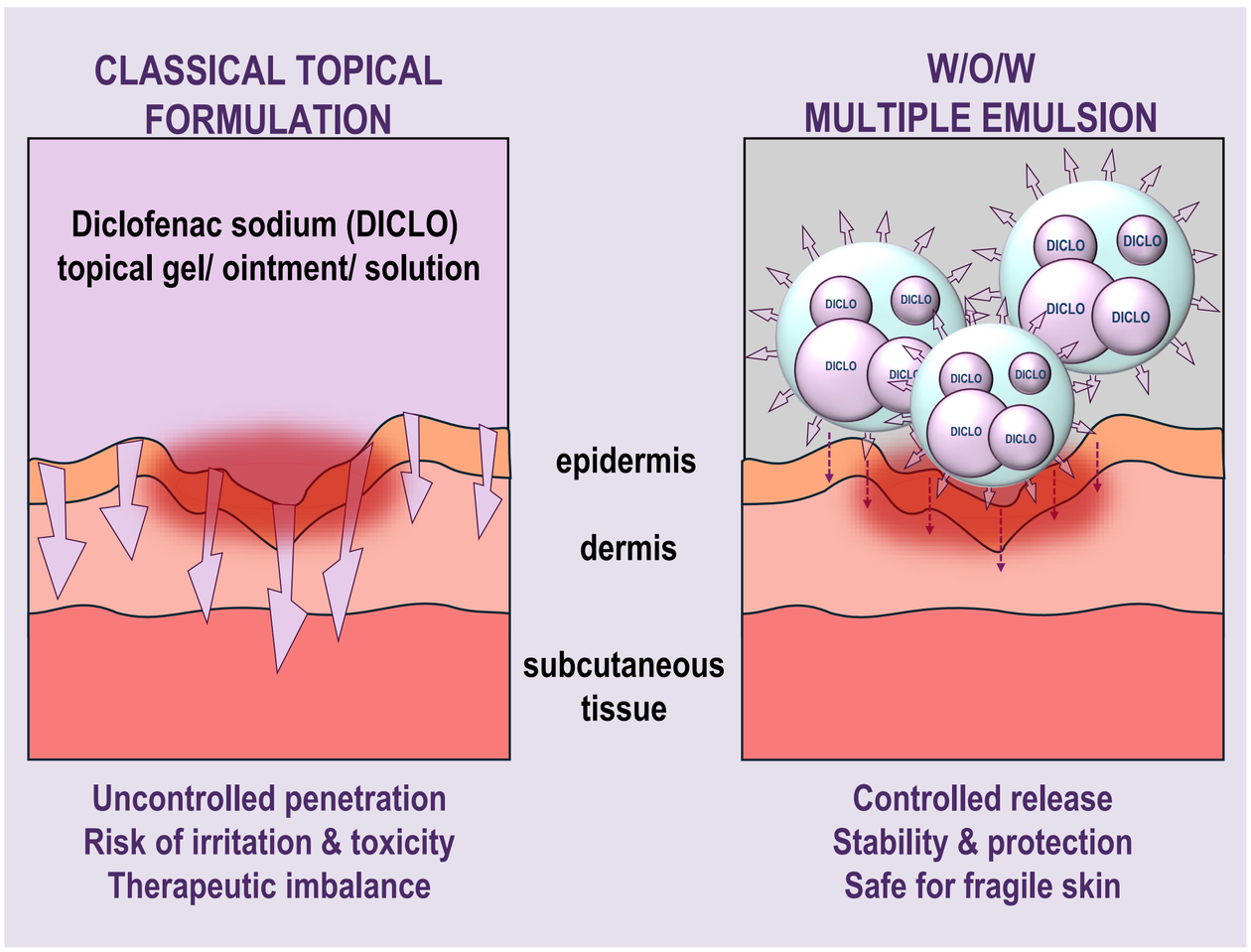

Fig. 1. *Conventional vs. W/O/W formulations: uncontrolled penetration versus controlled release and skin protection.*

The aim of this study was to design and evaluate W/O/W emulsions as carriers for sodium diclofenac, assessing their physicochemical properties, stability, rheological behaviour, drug release profile, and biological performance in models simulating post-oncological skin damage. We aimed to validate emulsions as a safe and effective topical therapy for oncology patients.

METHOD

Multiple W/O/W emulsions were prepared using a Couette–Taylor Flow (CTF) contactor. The system consisted of two coaxial cylinders (inner-rotating, outer-stationary) [1]. Streams of internal (W1), membrane (O), and outer (W2) phases were introduced into the annular gap of the contactor. Phase composition: W1: sodium alginate (1.9 wt%), Pluronic P-123 (0.24 wt%), methanol (0.041 wt%), diclofenac sodium (final DICLO concentration: 1 mM in emulsion), water; O: soybean oil + Span 83 (2 wt%); W2: poloxamer 407 (0.25 wt%), sodium CMC (0.20 wt%), Pluronic P-123 (0.25 wt%), Tween 80 (0.25 wt%), water. Operating parameters: gap size 1.5 mm, length 40 cm, inner cylinder rotation frequencies: 925–1264 rpm. Flow rates: W1: 20 mL/min, O: 40 mL/min, W2: 60 mL/min. Emulsion morphology was monitored over 60 days by optical microscopy (Olympus BX-60, SC50 camera). Internal and membrane phase drop sizes were measured using Image-Pro Plus. Rheology properties were examined using a rotational rheometer (Anton Paar RheolabQC). Release kinetics of diclofenac were evaluated using dialysis membranes (MWCO 14kDa) and PBS buffer (pH 7.0, 37°C). DICLO concentration was analysed spectrofluorimetrically (Jasco FP-6500). Drug release was expressed as a cumulative fraction over time**.** In vitro therapeutic effect: Human fibroblast K21 cells were cultured under standard conditions and irradiated with UV (15 J/m²≈2 Gy) or diclofenac sodium solution (0.1 μM) to mimic post-therapy damage. Cells were treated with either diclofenac solution or emulsion and incubated for 72h. Viability was assessed at 24, 48, and 72 h using PrestoBlue assay (fluorescence 535/590 nm). Emulsions significantly improved fibroblast survival compared to free diclofenac.

RESULTS & DISCUSSION

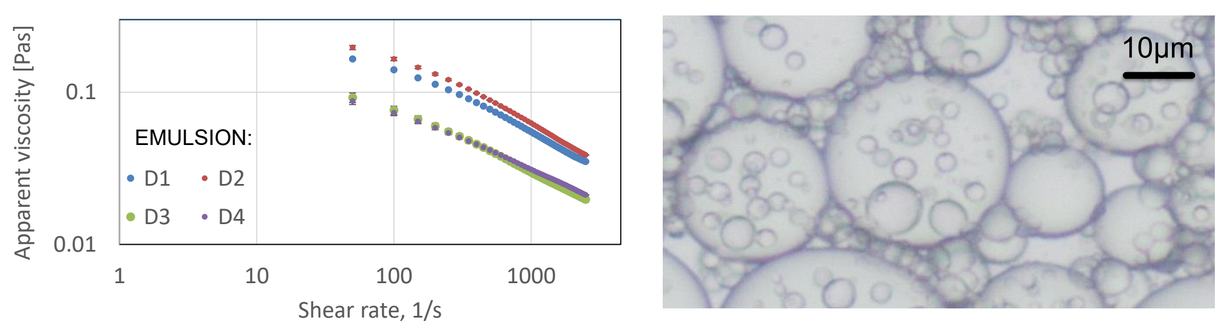

Fig. 2. *Rheological behaviour and microstructure of multiple emulsions (D1–D4).*

Table 1. *Emulsion stability assessments for samples stored at temperatures of 24°C and 4°C.*

Storage conditions		Stability of emulsions			
Temp., °C	Time, days	D1	D2	D3	D4
24	1	++	++	++	++
	7	++	++	++	++
	30	++	++	++	++
	60	++	++	++	++
4	1	++	++	++	++
	7	++	++	+	+
	30	++	+	+	+
	60	+	+	-	-

++ stable structure (change in droplet size less than 15% from initial size)
+ medium stable (change in droplet size of 15-25% from initial size)
- unstable (change in droplet size of more than 25% from initial size)

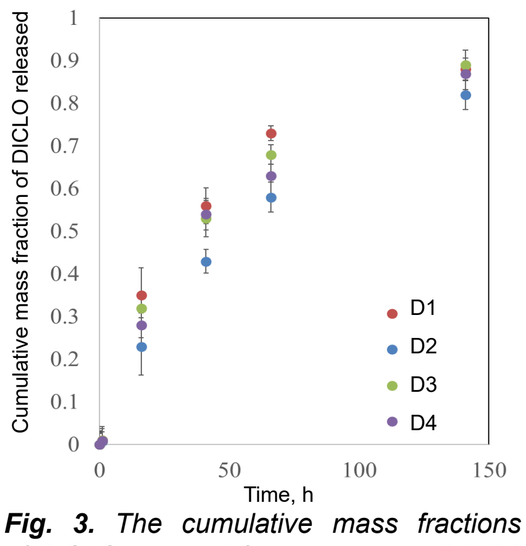

Fig. 3. *The cumulative mass fractions of DICLO released from emulsions D1–D4*

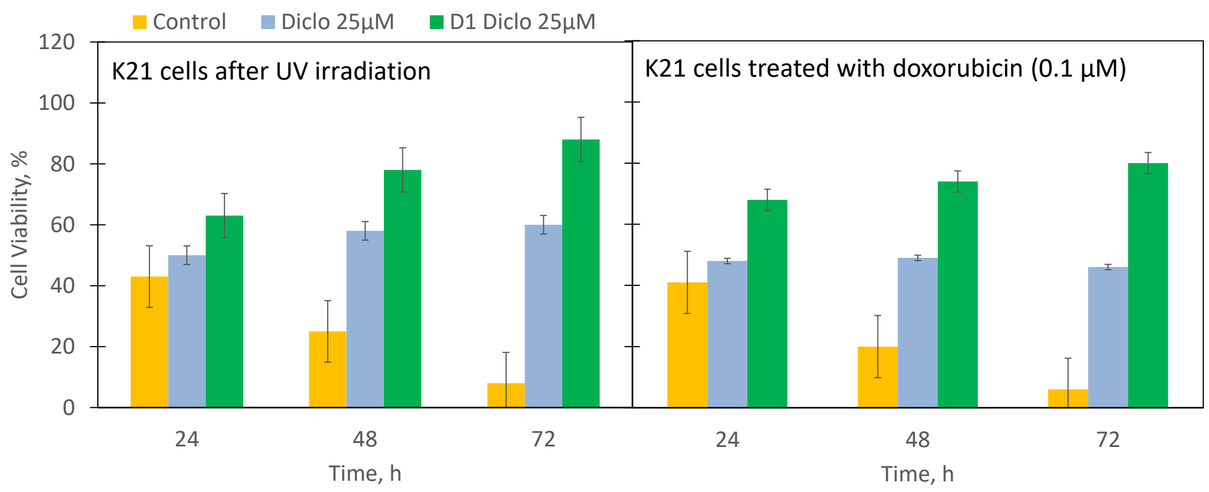

Fig. 4. *Viability of K21 cells treated with diclofenac after exposure to UVB irradiation or doxorubicin-induced damage (0.1 μM). Cell viability (%) was evaluated after 24, 48, and 72 hours of incubation with a diclofenac solution (25 μM) or the D1 emulsion containing diclofenac (25 μM). Data are presented as mean ± SD (n = 3).*

Optical microscopic observations of emulsion droplets confirm the presence of a complex multiple W/O/W morphology. The release study demonstrated that the rate of diclofenac diffusion can be effectively modulated by adjusting the emulsion structure, which is influenced by its composition and preparation conditions. All formulations exhibited pseudoplastic, shear-thinning behaviour, with kinetic stability maintained for 60 days at 24 °C, while at 4 °C, only formulation D1 remained stable. K21 cells subjected to UVB-induced/cytostatic injury displayed ~25–30% higher survival when treated with diclofenac-loaded emulsions than standard solutions, confirming their protective and regenerative potential.

CONCLUSION

These findings demonstrate that multiple emulsions constitute a rational strategy for transdermal delivery of anti-inflammatory drugs in patients with skin barrier damage following oncological therapies. By combining controlled release with improved tolerability, W/O/W emulsions mitigate the risks of uncontrolled permeation and support the development of safer, patient-tailored formulations for mitigating cutaneous side effects of cancer treatment.

FUTURE WORK

Future research will focus on refining the 3D human skin model and optimising multiphase emulsion carriers to improve the efficiency of transdermal delivery of bioactive compounds. Emphasis will be placed on understanding how emulsion composition and interfacial properties affect diffusion and release kinetics. Advanced analytical and imaging techniques will be applied to quantify substance transport and to develop predictive models correlating physicochemical parameters with biological response. The outcomes will support the design of transdermal formulations for therapeutic and regenerative applications.

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