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Development And Characterization Of Diacerin Loaded Niosomes For Improved Transdermal Delivery In Osteoarthritis

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Abstract

General Background: Osteoarthritis is a chronic degenerative joint disease, while oral diacerein has limited dissolution and low bioavailability. **Specific Background:** Niosomes may provide a vesicular approach for transdermal diacerein delivery while addressing limitations associated with oral administration. **Knowledge Gap:** An optimized diacerein niosomal formulation requires appropriate surfactant, cholesterol ratio, and sonication conditions. **Aims:** This study aimed to develop and optimize diacerein-loaded niosomes using the thin film hydration method. **Results:** Formulation F8 showed a vesicle size of 164.92±0.41 nm, entrapment efficiency of 91.52±1.0%, PDI of 0.16±0.015, and zeta potential of −33.94 mV. Increasing Span 60 reduced vesicle size and increased entrapment efficiency, whereas higher cholesterol increased vesicle size and reduced entrapment efficiency. Longer sonication reduced vesicle size but decreased entrapment efficiency. **Novelty:** F8 combined favorable vesicle characteristics with high drug entrapment. **Implications:** F8 may serve as a candidate for further transdermal development, requiring ex vivo permeation and in vivo anti-inflammatory studies.

Key Findings Highlights

- Span 60 increased drug entrapment while reducing vesicle size.
- Higher cholesterol produced larger vesicles with lower entrapment.
- Extended sonication reduced vesicle size but lowered drug entrapment.

Keywords : Diacerein, Niosomes, Transdermal Drug Delivery, Osteoarthritis, Nanovesicles

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Introduction

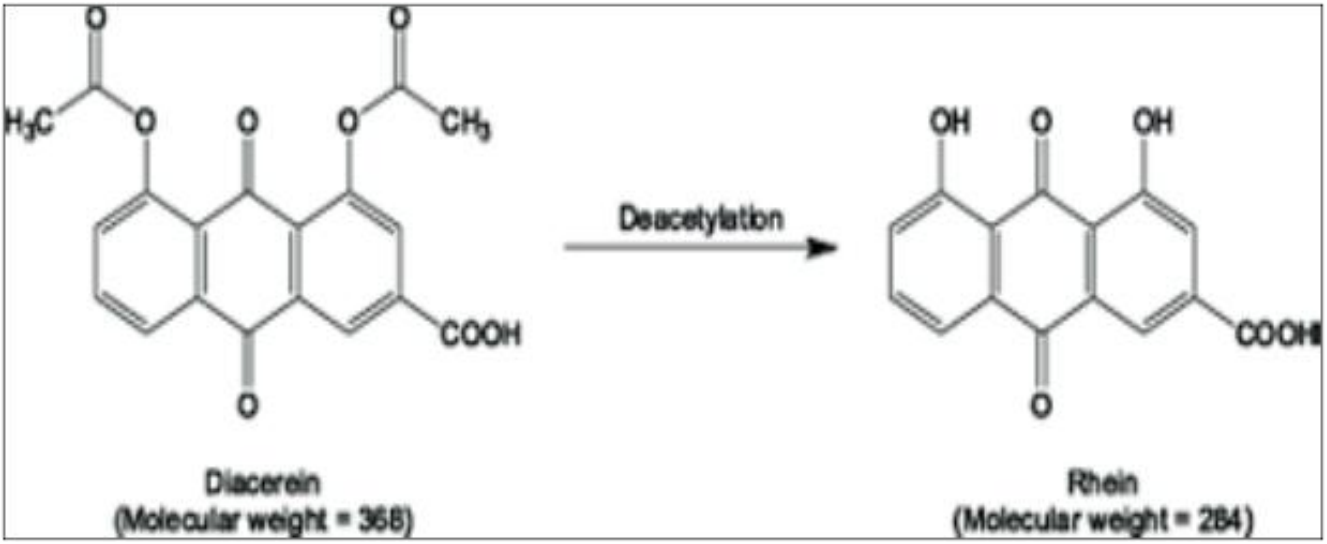
One of the most prevalent degenerative joint diseases, osteoarthritis (OA) is a major contributor to global impairment, especially among the elderly. This is a complex, multifaceted disease that causes articular cartilage to steadily worsen, subchondral bone to change, osteophytes to grow, and the synovial membrane to become inflamed [1].

Gender, obesity, musculoskeletal trauma, athletic participation, and occupation are some of the primary reasons of OA [2]. Although paracetamol and NSAIDs are often used to relieve OA symptoms, they are ineffective in halting the illness's progression [3]. Because OA is a chronic condition, using these medications for a long time has a number of negative effects, including kidney and gastrointestinal issues with nonselective COX inhibitors and cardiovascular problems with selective COX-2 inhibitors [4]. Diacerein (DCN) is a non-steroidal anti-inflammatory medication derived from anthraquinone. It is safe and efficient for treating osteoarthritis. It has anti-catabolic and pro-anabolic actions on cartilage, serves as an antioxidant, and protects subchondral bone remodeling. Recent studies have found that it has beneficial effects [5].

Through deacetylation, diacerein is transformed into Rhein, its active metabolite [6]. Diacerein's active metabolite and chemical structure are depicted in Figure 1 [7]. The medication operates by obstructing the enzyme IL-1 converting enzyme, which transforms Pro-IL-1 into IL-1, therefore preventing the IL-1 biosynthetic route. Therefore, diacerein inhibits IL-1's negative effects on osteoarthritis. Additionally, diacerein indirectly blocks the formation of inflammatory cytokines like tumor necrosis factor-alpha (TNF-) and interleukin-6 (IL-6) by decreasing IL-1 activity [8].

Because of its poor dissolving in the GIT fluid, Diacerein, a BCS class II medication, has a low oral bioavailability of 35-50% [9]. In addition, colonic microorganisms convert unabsorbed rhein into rhein-9-anthrone, which results in soft stools or diarrhea and promotes poor compliance and treatment termination [10]. Transdermal delivery appears to be a good technique. For the treatment of osteoarthritis, a transdermal delivery device that crosses the stratum corneum needs to be created [11].

Figure (1): Structure of rhein and diacerein (7)



Some limitations of transdermal delivery systems include the stratum corneum's (the skin's outermost layer) poor permeability, which can make it harder for bigger or hydrophilic molecules to be absorbed. To promote drug absorption, this barrier frequently requires the usage of penetration enhancers or specialized delivery systems. Several hypotheses have been put forth to account for niosomes' ability to improve permeation. Niosomes can either enter the stratum corneum intact or undergo structural changes to create smaller vesicles within the skin, depending on the amount of local hydration [12]. Through activities like adsorption or fusion, they might also talk with the stratum corneum directly. Adsorption can allow substances to pass directly from the vesicle to the skin either by forming receptor-ligand bonds or by physically interacting nonspecifically [12]. The self-assembly of nonionic surfactants that produce lipid bilayers around an aqueous core creates colloidal carriers called niosomes, which may contain medications with a variety of solubilities. Their makeup and characteristics, including their size, lamellarity, and surface charge, may be modified to suit a specific goal [13].

The present study aimed to create an ideal DCN niosomal carrier that could deliver DCN across the skin while minimizing oral administration's issues of bad dissolution and diarrhea.

Materials and Methods

Lee Chemicals, China, provided the diacerin. Direvo Industrial Biotechnology in Germany provides cholesterol. Tween 60, Tween 40, Span 60, and Span 40 were bought from Himedica Laboratories in India. Other chemicals and other solvents, including water, were purchased from various sources and were of analytical quality.

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Preparation of Diacerin Niosomes

Using the thin film hydration technique described in the literature, niosomes of DCN were synthesized for this investigation with minor changes. Drug, cholesterol, and surfactant were dissolved in 10 mL of chloroform in the round bottom flask. After that, the chloroform was rotary evaporated (100 rpm, 60 ◦C) in 25 minutes or when a thin film appeared. Using 15 ml of phosphate buffer saline (pH 7.4), the dried thin films were hydrated about 30 minutes at 100 rpm, 60 ◦C, with no vaccum vacuum. Finally, the niosomal suspension was sonicated for the predetermined time with 4-second breaks at 30-second intervals after being vortex mixed for 5 minutes. For further research, niosomal suspension was refrigerated overnight at 4°C [14, 15]. The compositions of the Diacerin niosome formulations are shown in Table 1.

Table (1): Composition of different niosomal formulations.

Formula number	Surfactant: cholesterol	Span 40	Span 60	Tween 40	Tween 60	Cholesterol amount	Sonication time
F1	1:1	90				90	10
F2	1:1		90			90	10
F3				90		90	10
F4					90	90	10
F5	1:2		90			180	10
F6	1:3		90			270	10
F7	2:1		180			90	10
F8	3:1		270			90	10
F9	1:2		90			180	20
F10	1:2		90			180	30

Characterization of Diacerin Niosomes

Determination of vesicle size, PDI and Zeta potential

Using a 1:10 dilution ratio with distilled water, the sample must be diluted in order to measure the vesicle size and the particle size distribution index (PDI) by dynamic light scattering (DLS). For vesicle size and PDI, the measurements are shown as triplicates ±SD. The zeta potential of the formula selected above is measured using Malvern zetasizer (16).

Determination of Diacerin Entrapment Efficiency (EE%)

The free DCN concentration in the supernatant was used to estimate the niosomal vesicles' EE% using the ultrafiltration technique. After 1 mL of the dispersion is placed at the top of a centrifuge tube, the ultrafilter is centrifuged at 6000 rpm for 30 minutes. The DCN concentration of free unentrapped DCN should be determined using a spectrophotometer with a wavelength set at 258.8 nm after properly diluting the ultrafiltrate with phosphate buffer. Using Equation [1], the EE% was calculated. Results are presented in triplicate as the mean ± SD (17).

$$EE\% = \frac{Total\ amount\ of\ DCN\ added - Free\ DCN}{Total\ amount\ of\ DCN\ added} \times 100\% \quad \text{.....Equation (1).}$$

Statistical analysis

To guarantee reliability and reproducibility, the findings are provided as the mean ± standard deviation from three distinct experiments. A statistical analysis was performed with Prism GraphPad software, version 8. One-way Analysis of Variance (ANOVA) was utilized to ascertain statistical significance using the results that were acquired. The criterion for demonstrating a statistically significant difference was established at a p-value less than 0.05 ($p < 0.05$) to emphasize the experiment's findings.

Results and Discussion

Variables that affect niosomal formulations:

1. Effect of type of surfactant

Based on the information in Table (2), Tween40 (F3) had a larger vesicular size than Tween60 (F4), and the tween compositions were bigger than the span compositions, showing that the vesicle size rises as the surfactant's hydrophilicity increases. According to one theory, increasing the HLB of the surfactant used causes the vesicles to expand in size. Higher HLB values result in greater surface free energy, which accounts for this (18).

The data in table (2) revealed that the trapped medicine in the span preparation may have risen as a result of an increase in the hydrophobicity of the span over the tween. Both span 60 and span 40 are solids at normal temperature owing to their high Tm values of 530 0C and 420 0C, respectively. However, because span 60's longer chain than span 40 (C16) allows it to maintain lipophilic DCN and makes it more lipophilic, the EE% is higher (19,20).

The PDI of different surfactant formulations ranged from 0.16 to 0.35, indicating that the kind of surfactant has little impact on PDI.

Table (2): Mean Vesicle size (VS), Entrapment Efficiency and Polydispersity Index (PDI) of different DCN niosomal preparations, mean ± SD, (n=3)

	VS (nm)±SD	EE%±SD	PDI±SD
F1	265.27±0.48	54.38±0.22%	0.32±0.01
F2	210.82±0.43	68.75±0.55%	0.26±0.01

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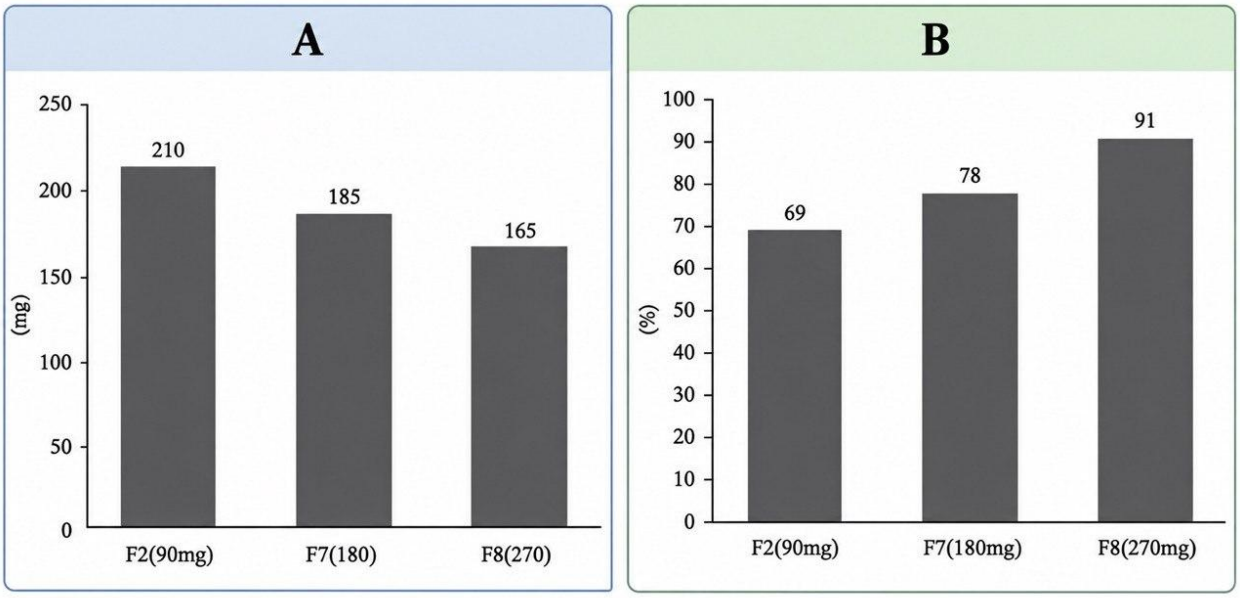
F3	786.45±1.13	42.87±0.67%	0.24±0.035
F4	645.61±0.69	35.77±0.81%	0.35±0.036
F5	245.31±0.97	55.74±0.67%	0.24±0.04
F6	311.3±1.00	46.79±0.35%	0.36±0.02
F7	187±0.56	78.32±0.37%	0.18±0.05
F8	164.92±0.41	91.52±1.0%	0.16±0.015
F9	144.57±1.19	56.37±0.45%	0.18±0.01
F10	138.53±0.60	44.69±0.62%	0.14±0.04

2. Effect of amount of surfactant

When the span 60 concentration was raised from 90 mg (F2) to 270 mg (F8), the entrapment efficiency significantly rose ($p<0.05$) from 68.75% to 91.52%. The observed increase in EE at higher concentrations of Span 60 may be attributed to the reduction in interfacial energy and the corresponding increase in the viscosity of the dispersion. These changes can contribute to restricting drug diffusion out of the vesicles. Furthermore, the long alkyl chain (C18) present in Span 60 enhances the stability of the lipid bilayer, thereby improving the entrapment efficiency by limiting drug leakage (21).

Figure 2A demonstrates a significant reduction ($p<0.05$) in vesicle size, from 210.82 nm to 164.92 nm, as the amount of Span 60 was raised from 90 mg (F2) to 270 mg (F8). This reduction may be related to the decrease in interfacial tension between the lipid and aqueous phases, which facilitates the formation of smaller vesicles (22). A comparable finding was also reported for the BS delivery system of dapsone (23).

Figure (2): (A) Influence of amount of surfactant on vesicle size, (B) Influence of amount of surfactant on entrapment efficiency.



3. Effect of amount of cholesterol

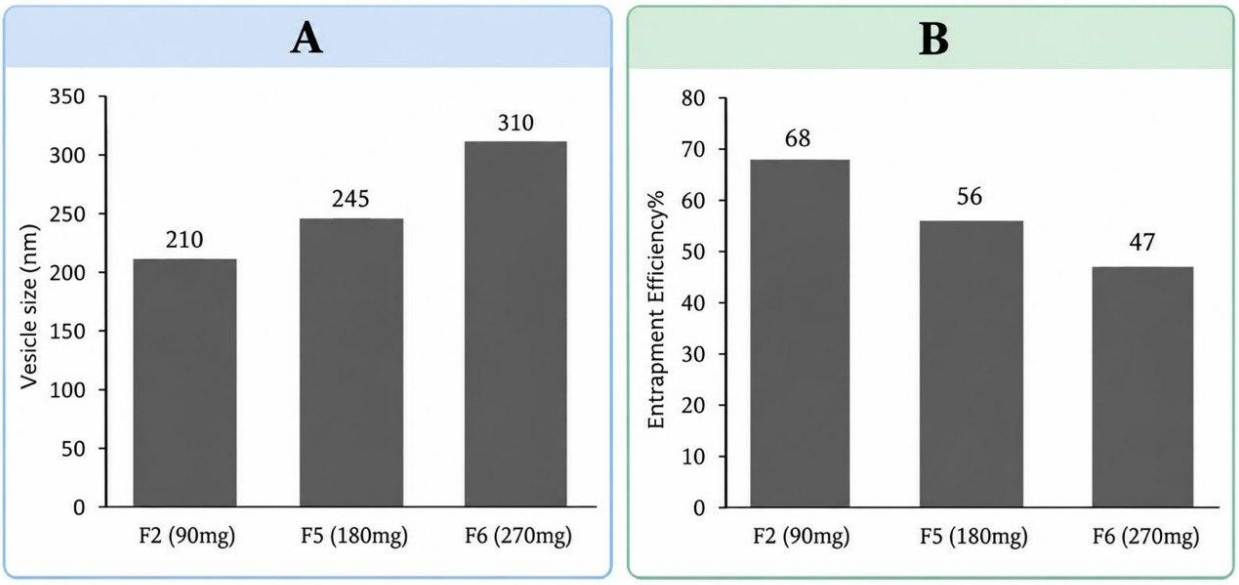
As shown in Figure (3A), increasing the cholesterol content resulted in a marked increase in particle size. The particle size increased from 210.82 nm in (F2) to 245.31 nm in (F5) and 311.3 nm in (F6), respectively. This increase can be explained by the effect of cholesterol on the arrangement and packing of the lipid components, which may reduce close packing of the vesicular membrane and consequently produce larger vesicles containing a greater aqueous volume within the niosomes structure (24).

Cholesterol also contributes to the stabilization of vesicular membranes by increasing their rigidity and reducing drug leakage (25). These effects may consequently influence the entrapment efficiency. However, according to the cholesterol concentrations presented in Table (2) for formulations (F2, F5, and F6), increasing the amount of cholesterol used in the preparation of DCN niosomes resulted in a decrease in the percentage of EE, as shown in Figure (3B). This finding may indicate that increasing cholesterol content alters the proportion of cholesterol incorporated into the niosomal bilayer, thereby reducing the amount of drug that can be effectively encapsulated within the vesicles (26).

Figure (3): (A) Effect of amount of cholesterol on vesicle size, (B) Effect of amount of cholesterol on entrapment efficiency.

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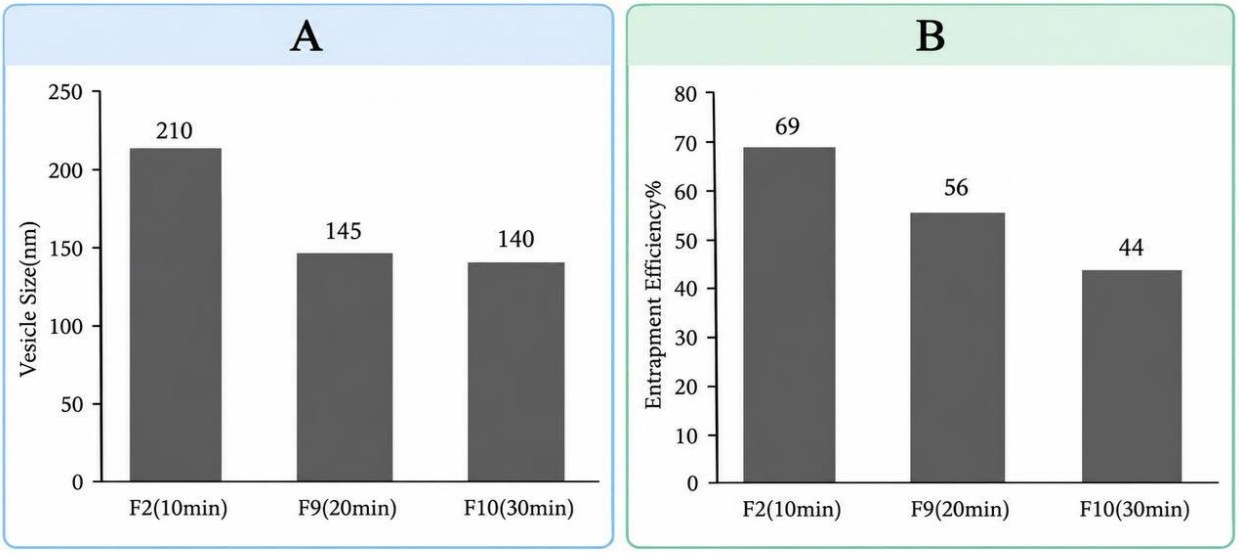
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4. Effect of sonication time

An increase in sonication time result in a gradual decrease in vesicles size. The longer the sonication period was in formulations (F9) and (F10), 20 and 30 minutes respectively, smaller vesicles were obtained compared to formulation (F2). This reduction was statistically significant ($p<0.05$) when compared to (F2) as present in the Figure (4A). This is similar to a previous study (27). Cavitation bubbles collapse during sonication which creates very high pressures, temperatures, and shock waves, all within a small local area. Thus the overall energy of the ultrasonic radiation leads to the rupture of larger vesicles into smaller discoid vesicles that subsequently re-arrange themselves into the thermodynamically more stable vesicles. As a result, the mean hydrodynamic diameter ($p<0.05$) was significantly reduced when using a bath sonicator as a size-reduction technique(27).
Entrapment efficiency was also found to be significantly different ($p<0.05$) with respect to the sonication time. The entrapment efficiency for formulation (F2) and (F9) was decreased from 68.75% to 56.37% by altering sonication time from 10 minutes to 20 minutes in these formulations. The entrapment efficiency in formulation F10 became less as the sonication time was further extended up to 30 minutes as shown in Figure (4B). The decrease might be attributed to the breakdown of the BS vesicles during extended sonication, allowing the drug to be released.

Figure (4): (A) Influence of Sonication time on VS, (B) Influence of Sonication time on Entrapment Efficiency.



Zeta Potential for the Selected Formula
Another important measurement for determining the stability of niosomes is zeta potential. A high value for the zeta potential's absolute value means that the surface of the niosomes has a high electrical charge that will likely make it repel any forces of aggregation. As seen from Fig5, the F8 niosomes are negatively charged (-33.94 mV), which is associated with the intrinsic charge of DCN due to the ionisation of it in the dispersion medium, which has a pKa of 2.98 at the pH of the dispersal medium (28). As a result, the dispersion that has been prepared is physically stable and has a low likelihood of aggregation andcrystal growth.

Figure (5): Zeta Potential for the selected DCN niosomal formula (F8).

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Conclusion

The present study aimed to propose that transdermal delivery could be achieved using a vesicular carrier to overcome the negative effects of oral delivery of Diacerin (DCN). The vesicle characteristics, such as size, trapping efficiency, and polydispersity index (PDI), were meticulously optimized. The perfect formulation, F8, had an acceptable EE%, a low PDI, and a vesicle size suitable for transdermal administration. A high zeta potential (ZP) indicated good physical stability and a lower risk of aggregation. This suggests that it could be possible to create a long-term niosomal delivery system for drug transdermal delivery to reduce the drawbacks of oral administration of Diacerin.

Recommendations

In addition to undergoing assessment for incorporation into an appropriate delivery vehicle, the identified formulation (F8) must be subjected to an ex-vivo permeation study as well as an in-vivo anti-inflammatory investigation.

Conflict of interest: None

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