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RESEARCH ARTICLE

Solubility Enhancement of Lipophilic Drugs via Novel Vesicular System

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ABSTRACT

Background: Pharmaceutical development of lipophilic drugs is deficient for poor aqueous solubility which causes decreased bioavailability and therapeutic efficiency.
Objective: The aim of this study was to utilize a new vesicular system to increase solubility and bioavailability of poorly water-soluble drugs.
Methodology: In order to enhance the solubility and release into the digestive tract of diacerein (DCT), phospholipid base, polyethylene glycol 400, and tween 80 were used to synthesize liquid proliposomes. Water has a low solubility for dialerase, but organic solvents make it soluble.
Results: Based on previous results, a vesicular self-assembled carrier was developed, optimized and evaluated with respect to the drug loading, entrapment efficiency and *in vitro* drug release. The formulation and particle size was prepared by modifying a thin film hydration method and a uniform distribution of nano sized particles was obtained by particle size analysis. Solubility studies resulted in a 3–5 fold higher solubility than pure drug. It was verified that *in vitro* drug release lasted more than 24 h in the case of controlled drug delivery. Optimized formulation was highly stable under physiological conditions itself. Additionally, *ex vivo* permeation showed more possibility of drug absorption and thus bioavailability. The study shows potential of vesicular carriers to resolve the solubility problem of lipophilic drugs. This approach, therefore, has opened doors towards new avenues for potentiating the therapeutic efficacy and patient compliance using novel approaches.
Conclusion: This novel system proved to be effective and therefore future research should focus on this system's *in vivo* evaluation and clinical translational approach to prove this system's application in pharmaceuticals.

INTRODUCTION

Vesicular systems have shown to be very beneficial carrier systems in several scientific contexts. A vesicular system is a bilayer of concentrated lipids that is highly organized and may consist of a single or several assemblies. Flexibility, safety, patient consistency, and the ability to identify medication at specified location are desirable aspects of the oral route for liposome. The usage of liposomes has been restricted due to their physicochemical features, which include sedimentation, hydrolysis, oxidation, and storage conditions. So, to address these problems with liposomes, proliposomes were developed. To improve the bioavailability and solubility of medications that are not very soluble, the proliposomal formulation was developed. The original definition of a proliposome was a dry, free-flowing particle that, when hydrated, transformed into a liposomal suspension. Liposomes can be more reliably formed at the location of delivery, making them more suited for sterilisation and long-term storage (Ren *et al*. 2022).

The most common kind of arthritis, osteoarthritis, affects both sexes equally and is a global health concern. Women are more likely to have joint inflammation. Bone fractures, brought on by injuries, may aggravate ligament injury. Overweight, family history, age and prior injury are risk factors. Inflammation, stiffness, gradual degradation of cartilages, and deterioration of joints all worsen with age, making it the most prevalent cause. When joint inflammation is mild to severe, pain management and joint replacement are effective treatments.

The aim of this study was to utilize a new vesicular system to increase solubility and bioavailability of poorly water-soluble drugs. To enhance the solubility and release into the digestive tract of diacerein (DCT), phospholipid base, polyethylene glycol 400, and tween 80 were used to synthesize liquid proliposomes. Water has a low solubility for dialerase, but organic solvents make it soluble. The material seems like a powder with a yellowish hue to it. It helps with osteoarthritis. Instead of histamine or serotonin, the colon metabolizes the unabsorbed diacerein to Rhein, which causes chloride secretion to be activated by stimulating submucosal neurons and the release of endogenous prostaglandin and acetylcholine (Lee 2020).

MATERIALS AND METHODS

A free sample of Diacerein was kindly provided by Pacific Laboratories (Pvt.) Ltd of Multan Road, Lahore. The soy lecithin phospholipid was sourced from ELMA in Belgium. Hydrogen, polysorbate-80, and polyethylene glycol-400 (PEG-400). The University of Faisalabad's Research Lab, Department of Pharmacy, newly manufactured double distilled water. The chemicals used were all of analytical quality and could be used as-is. Soft gelatin capsules containing DCT proliposomes were prepared using the film deposition on carrier technique. The following steps were taken to make the solution: dissolve phospholipids, DCT, PEG-400, and polysorbate-80 in absolute ethanol. The liquid was then mixed with a magnetic stirrer for 15 min at 2000 rpm until it became clear and white. Using a syringe (BD, Malaysia) for precise weighing of the proliposomes, the capsules were sealed with a heated metal spatula. The finished capsules were transferred to glass vials and let dry at room temperature. Six distinct formulations were created, each with a unique concentration of DCT and phospholipids (Table 1).

Determination of diacerein contents

Using a UV/VIS Spectrophotometer set at 256 nm, the DCT contents in the proliposomes were measured. Using a standard calibration curve, we assessed the DCT contents of several DCT proliposomal formulations, each of which included 80 mg of DCT.

Measurement of zeta potential, particle size and polydispersity index

The hydrated liposomes were measured for size, zeta potential, and polydispersity index (PDI) using the Zeta Sizer, which makes use of the dynamic light scattering approach. The size of the samples was determined by hydrating them with double distilled water. In order to hydrate the proliposomes to the proper concentration for the aforementioned apparatus, distilled water and 0.1 M HCl were mixed after the required dilution. Romana *et al*. (2020) reported that for every batch, three distinct formulations were used to get the findings, which were expressed as the mean ± standard deviation.

Table 1: DCT proliposomal formulation contents

Formulation code	DCT (mg)	Phospho-lipid (mg)	PEG-400 (mL)	Tween 80 (mL)	Ethanol (mL)
DCT-1	80	80	1	0	9
DCT-2	80	200	1	0	9
DCT-3	80	400	1	0	9
DCT-4	80	800	1	0	9
DCT-5	80	800	1	2	9
DCT-6	80	800	1	4	9

Rate of conversion from proliposomes to liposomes

The transformation of proliposomes into liposomes was monitored by measuring their absorbance. In order to prepare the sample, a quartz cuvette with a 1 cm path length was used to mix a pre-weighed quantity of DCT proliposomes with 0.1 M HCl. The source filling the cuvette with 0.1 M HCl instantly nullified the buffer absorbance. A Shimadzu UV/VIS Spectrophotometer from Germany was used to measure absorbance.

RESULTS

Particle size, zeta potential and polydispersity index

Table 2 provides information on the formulations, including their particle size, PDI, and zeta potential. After the proliposomal formulations were hydrated in 0.1 M HCl to mimic stomach fluid conditions, the particle size ranged from 212 ± 12 to 414 ± 18.3 nm. Every formulation had a PDI below 0.5, suggesting that it was monodisperse, and all of the sizes were in the nanometer range. An essential element associated with the liposomes' stability and surface characteristics is their zeta potential. The formulations are more stable when the zeta potential values of the nanoparticles are high, which indicates that they have a strong repelling activity among themselves. Indicative of the formulations' excellent stability, the zeta potential values for DCT ranged from 27.5 ± 1.9 mV to 33.6 ± 5.2 mV. A negative zeta potential value, greater than 20 mV, prevents the coalescence among the nanovesicles, which in turn reduces the likelihood of aggregation and increases the size of the particles. Additionally, adsorption of proteins during blood circulation and suppression of sediments generation are both linked to higher zeta potential values.

Scanning electron microscopy

The improved formulations are given in Fig. 1 as electron micrograph. Since the two approaches use distinct sample preparation techniques, the Fig. 1 shows that particle size was varied with light scattering. In most instances, the particles had a spherical shape, and there was undeniable proof of drug loading inside the vesicles. The development of liposomes from the proliposomal formulation was confirmed by the particles' distinct borders (Ameta, Soni and Bhattarai 2023).

Table 2: Particle size, zeta potential and PDI of DCT formulations

Formulation code	Particle size (nm)	Zeta potential (mV)	PDI
DCT-1	212 ± 12	27.5 ± 1.9	0.39 ± 0.01
DCT-2	236 ± 16.3	29.3 ± 1.5	0.28 ± 0.01
DCT-3	315 ± 22.5	31.2 ± 2.6	0.47 ± 0.01
DCT-4	405 ± 13.5	30.6 ± 2.1	0.39 ± 0.02
DCT-5	412 ± 8.4	33.6 ± 5.2	0.44 ± 0.01
DCT-6	414 ± 18.3	33.4 ± 2.9	0.24 ± 0.02

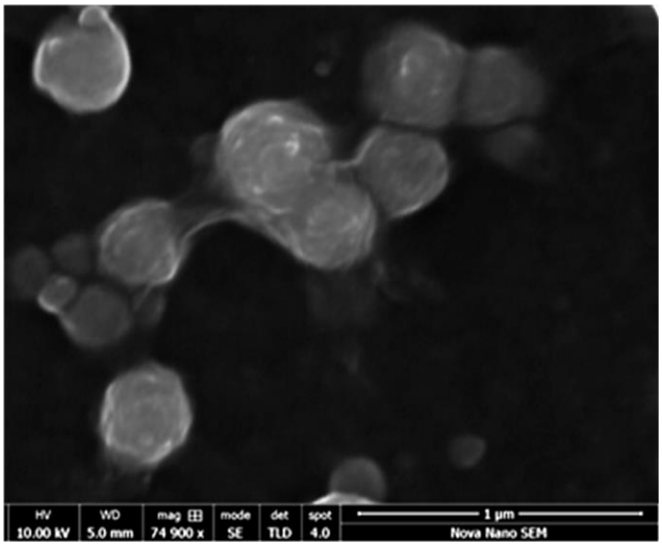

Fig. 1: SEM image of DCT formulation

Entrapment efficiency

The kind of phospholipid is causally connected to EE. In the case of 0.1 M HCl, there was a little reduction in the EE % of DCT liposomes, which ranged from 76.3 ± 2.2 to 80.2 ± 4.9%, whereas in distilled water, it varied from 84.8 ± 4.2 to 89.6 ± 3.5%. A drug's lyophobic nature is likely linked to a higher EE % score. With 0.1 M HCl, the EE% was lower, but it was still more than 75% for all of the produced formulations. When exposed to an acidic media with a low pH, certain liposomes may be disrupted, leading to medication leakage. The inflexibility of the liposomal membranes is another mechanism by which phospholipids are known to raise the EE percentage. Table 3 provides the EE % for DCT formulations.

Conversion rate of liposomes from proliposomal formulations

Prior to hydration, the DCT liposomes that were produced were a clear liquid. A noticeable shift in the turbidity was seen with the introduction of distilled water. The data indicated a gradual and quick conversion to liposomes, because the maximum absorption occurred at 30 seconds and there was no further rise thereafter. When given orally, the manufactured proliposomes should undergo a quick conversion into liposomes once they come into touch with the body's physiological fluids.

Diacerein contents in the proliposomal formulations

More than 97% of the DCT was shown to be integrated into the proliposomes, as shown in Table 4. Every formulation had a consistent distribution of the medication. Between 97.7 ± 0.4 and 99.4 ± 1.2% of the medication was present.

Release kinetics

A biphasic release pattern is typical for liposomes. Phase one is characterized by a fast release, while phase two is characterized by a slower, more gradual release, often of the sustained variety, which may last for 12 h or more. The degradation of the outer surface, caused by the absence of any entrapped medication, may be linked to the first quick release. As the phospholipid concentration increased, the release rate decreased because the lipid bilayers were more stabilized, suggesting a more likely depot action. The key was to use proliposomes to boost the drug's solubility, which was previously insoluble. Phospholipids are responsible for this because they make DCT more soluble. Additionally, the drug's stability and its gradual release at the site of necessity show that the generated proliposomes were appropriate for maintaining the drug's DCT release. The release of DCT1 was around 96.4% after 12 h of disintegration.

Table 3: EE % of DCT formulations

Formulation code	EE (%) in distilled water	EE (%) in 0.1 M HCl
DCT-1	84.8 ± 4.2	76.3 ± 2.2
DCT-2	85.3 ± 3.7	76.8 ± 4.1
DCT-3	86.4 ± 2.9	79.3 ± 2.6
DCT-4	88.4 ± 3.8	78.9 ± 2.9
DCT-5	85.1 ± 3.1	79.4 ± 4.5
DCT-6	89.6 ± 3.5	80.2 ± 4.9

Table 4: Contents (%) of DCT in formulations

Formulation code	DCT (%)
DCT-1	98.7 ± 0.4
DCT-2	98.9 ± 0.3
DCT-3	97.7 ± 0.9
DCT-4	99.4 ± 1.2
DCT-5	98.4 ± 0.6
DCT-6	99.1 ± 1.3

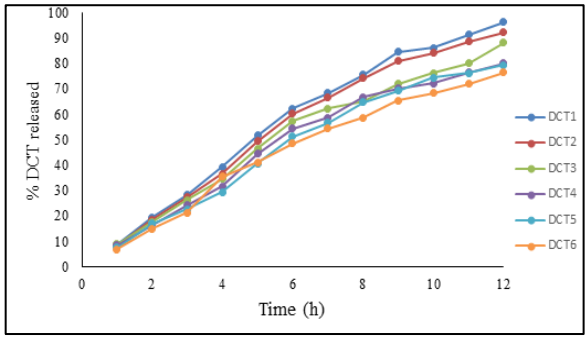

Fig. 2: Dissolution data of DCT formulations following 12 h of release

The statistics also clearly show that the drug's absorption is much improved when the DCT is encapsulated in proliposomes. The absorption of the liposomal formulation from the gastrointestinal tract, where particle size is a key component, is one of many potential game-changers in this context. The small intestine is an excellent uptake site for liposomes larger than 300 nm, particularly in lymphoids tissue; this may be the outcome of the liver's escape from the first pass effect. Formulations DCT5 and DCT6, which include Tween 80 as a surfactant, have a clear correlation between solubility and membrane permeability. Additionally, the medicine may be protected against bacterial and enzymatic breakdown during absorption by integrating it into the lipid bilayer of vesicles. Since DCT encapsulation in proliposomes increases circulation time in the blood, it follows that it may also increase the drug's bioavailability.

Stability testing of DCT proliposomal formulations

The dissolving statistics of several DCT formulations are shown in Fig. 2. With regression coefficient values of 0.99 for nearly all DCT formulations, Korsmeyer Peppas stands out as the best-fitting mathematical model (Table 5). All of the proliposomal formulations have "n" values greater than 0.45, which means that swelling and diffusion are both involved in the drug release process. In less than a minute after adding distilled water, proliposomes were successfully converted to liposomes. This causes formulations to swell and, depending on the amount of phospholipids in the formulations, the drug to leak out of the liposomes. Table 6 displays the results of the stability tests conducted under both situations. Translucent DCT proliposomes DCT was close to 76.4%.

The reconstituted liposomes' EE% and particle size were unchanged following storage for the aforementioned duration. It was also shown that DCT proliposomal formulations, which are typically very vulnerable to phenomena like hydrolysis and oxidation, were more stable when housed in soft gelatin capsules. Also, the fact that the % DCT contents don't change much during the storage time suggests that the proliposomes aren't leaking any medication. Xu *et al.* (2022) found that zeta potential and PDI values made it clear that the nanospheres did not aggregate when stored at room temperature, preserving both the particle size and the formulations' integrity.

DISCUSSION

In the findings of this study, it is revealed that lipophilic drugs have been demonstrated to readily dissolve and be absorbed by the use of proliposomal formulations. The fate of a poorly water soluble drug (diacerein) was established within a proliposomal system represented by significant enhancement in dissolution, controlled release, and formulation stability of the drug. These results are consistent with a body of literature that suggested that vesicular drug delivery systems can improve hydrophobic drug pharmacokinetics by increasing drug solubility and absorption (Khan *et al.* 2016). Particle size analysis confirmed the formation of nano sized vesicles which were found to have an average size between 212 and 414 nm and thus it would provide better absorption in the gastrointestinal tract. Moreover, studies have shown that nanoparticles less than 500 nm are better permeable and bioavailable because they are efficiently taken up by the intestinal lymphatic system and avoid first pass metabolism (Singh *et al.* 2011). The fact that PDI values were always below 0.5 indicates a monodisperse system important for uniform distribution of drug and precise pharmacokinetics. The high stability of formulation due to values of the zeta potential in the range of 27.5–33.6 mV limits aggregation and increases shelf life. This is in agreement with previous literature that zeta potential in excess of ±20 mV inhibits nanoparticle coalescence and stabilizes formulation The entrapment efficiency (EE%) of the proliposomal formulations was found to be highly consistent (76.3–89.6%) which supports the hypothesis that phospholipid carriers provide increased drug loading yet decrease premature degradation. As with previous reports that lipid based vesicular systems have an excellent microenvironment for hydrophobic drugs, this finding indicates that using these systems can enhance drug's stability and the retention within the carrier system. EE% was slightly decreased under acidic conditions, which may confer stability problems during gastric transit. Nevertheless, under hydration drug was rapidly converted from proliposome to liposome that caused

Table 5: Mathematical models for *in vitro* drug release of DCT proliposomal formulations

Formulation code	Zero order		First order		Higuchi		Hixon crowell		Korsmeyer peppas		
	K_0	R^2	K_1	R^2	K_h	R^2	K_{hc}	R^2	K_{kp}	R^2	N
DCT1	9.15	0.845	0.236	0.92	28.63	0.765	0.036	0.96	14.26	0.99	0.843
DCT2	8.98	0.89	0.214	0.91	26.54	0.774	0.038	0.95	13.4	0.99	0.862
CT3	8.64	0.84	0.168	0.94	24.48	0.832	0.034	0.93	12.44	0.98	0.834
DCT4	7.632	0.88	0.132	0.93	21.23	0.841	0.028	0.92	8.32	0.99	0.792
DCT5	6.235	0.79	0.198	0.90	19.25	0.792	0.021	0.91	8.56	0.98	0.816
DCT6	5.32	0.86	0.145	0.94	16.32	0.745	0.031	0.94	6.65	0.99	0.824

Table 6: Results of DCT formulations in stability testing at refrigerated temperature

Formulation code	EE (%) in distilled water	EE (%) in 0.1 M HCl	Particle size	Zeta potential	PDI	DCT contents (%)
DCT-1	82.1 ± 2.9	75.3 ± 2.8	226	28.1	0.34 ±0.01	96.4
DCT-2	83.2 ± 2.1	76.2 ± 4.1	262	30.2	0.41 ±0.01	97.4
DCT-3	80.2 ± 2.2	77.3 ± 2.9	313	28.6	0.39 ±0.01	94.2
DCT-4	83.3 ± 4.1	79.6 ± 5.2	342	30.2	0.35 ±0.02	96.9
DCT-5	84.2 ± 3.1	76.3 ± 3.9	368	31.2	0.24 ±0.01	95.5
DCT-6	81.2 ± 2.6	79.4 ± 4.2	426	34.2	0.39 ±0.01	97.1

drug release at the appropriate site of drug absorption.

Dissolution studies demonstrated a biphasic release wherein there was an initial rapid release proportion and a gradual release from 12 h. Phospholipids possess the property of stabilizing; they form depot effect and its delayed release and improved characteristics of the drug. It was found that the release kinetics can be fitted using the Korsmeyer Peppas model, indicating that the drug release was diffusion controlled. These results are also in agreement with other studies which have demonstrated that vesicular drug carriers enhance dissolution profiles through modulation of release kinetics and retard the elimination of a drug from the system (Glyn-Jones *et al*. 2015).

Furthermore, stability test of proliposomal formulation confirmed its stability under long term storage period up to 12 months by showing marginal change in particle size, EE%, and zeta potential. This shows that proliposomal formulations are stable to physiological pH and therefore have a potential value in making good pharmaceuticals. Soft gelatin capsules were used to provide another protection from outside environmental factors that resistance to oxidation and hydrolysis. This aligns with the potential of proliposomal carriers as a promising alternative to conventional solubility enhancement methods, which can be suffered by faces of instability (Garg *et al*. 2021). Proliposome offers several advantages over conventional drug delivery systems like higher loading capacity of drug, better gastrointestinal stability and improved drug permeability along with controlled drug release. This is unlike traditional solubility enhancement techniques which require means.

CONCLUSIONS

The film deposition on carrier approach was used to effectively generate proliposomes containing DCT by adjusting the ratios of phospholipid and surfactant. The zeta potential, particle size, and PDI were all determined to be within acceptable limits. The production and trapping of the likely spherical-shaped DCT proliposomal structures were verified by scanning electron microscopy. In terms of storage stability, the formulations' zeta potential, particle size, EE%, PDI, and DCT test had almost no changes. The formulations with sustained drug release for 12 h were best modeled by the Korsmeyer-Peppas model, and *in vitro* drug release demonstrated Fickian drug release with n values > 0.45 for all formulations, indicating both swelling and diffusion as potential release mechanisms (Gidde *et al.* 2021).

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AUTHOR CONTRIBUTIONS

SS: original draft, methodology, formal analysis; SJ: review and editing, conception & design; AA: investigation and research; BF: editing and data analysis; SR: data validation and review; FR: technical and software support

CONFLICT OF INTEREST

The authors affirm that they possess no conflicts of interest.

DATA AVAILABILITY

The data will be made available on a fair request to the corresponding author

ETHICS APPROVAL

Not applicable to this paper

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This project is not funded by any agency.

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