

(RESEARCH ARTICLE)



FORMULATION AND EVALUATION OF CILNIDIPINE SPANLASTIC -A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The aim of the study was to design and optimize the Spanlastics as a novel carrier system for transdermal delivery of cilnidipine through modulation of the skin barrier property to improve bioavailability and therapeutic effectiveness. The Cilnidipine loaded Spanlastics were prepared by Ethanol Injection method using an Organic Solvent, Span-60 and tween-80 as non-ionic surfactant and edge activator. Prepared Spanlastics formulation and the compatibility of drug with excipients was checked by FTIR studies and results indicate no interaction. The evaluation studies were within acceptable limits. In vitro dissolution studies were done for spanlastics to find out the amount of drug release. The finding of this study concludes that the % drug release can be modulated by combining with Span-60, Tween-80, Ethanol in different weight ratio. These designed spanlastics was found to be satisfactory in terms of release of the drug after the diffusion time, thus the transdermal delivery system can be a good approach to release the drug.

Keywords: Cilnidipine; Span-60; Tween-80; spanlastics; Ethanol injection

1 INTRODUCTION

Spanlastics are a special class of vesicular carriers act as site specific drug delivery systems for targeting drugs to the transdermal area. Spanlastics can deliver both lipophilic and hydrophilic drugs to the transdermal system.^{1,2} The purpose of this study was to develop Cilnidipine spanlastics for treating hypertension transdermally. Hypertension is a chronic medical condition characterized by persistently elevated artery blood pressure.^{3,4} The risk of cardiovascular diseases is increased by hypertension. In hypertensive patients, long-term treatment and sometimes lifelong therapy are recommended. But most of the antihypertensive drugs due to extensive hepatic metabolism, requires frequent dosing.⁵ Cilnidipine (CIL) is a dihydropyridine calcium channel blocker and has exhibited excellent clinical efficacy for hypertension. The oral bioavailability of CIL is approximately 6–30% because of its poor aqueous solubility and first-pass metabolism.^{6,7} Therefore, the oral administration of CIL is not much effective in the treatment of hypertension. In addition, CIL has a low molecular weight (492.53 Da), a melting point less than 200 °C and low dose (5–10 mg once daily) making it suitable for transdermal delivery. Therefore, the present study was undertaken to formulate and evaluate Cilnidipine loaded Spanlastics with the aim to design and optimize a novel carrier system for transdermal delivery of cilnidipine through modulation of the skin barrier property to improve bioavailability and therapeutic effectiveness.

2 MATERIALS AND METHODS

2.1 Materials

Cilnidipine obtained from Mylan Laboratories, Tween 80, Span 60, Ethanol, Water.

2.2 Methods

Cilnidipine-loaded spanlastics were prepared using the ethanol injection method^{8,9} with minor modifications. The organic phase was prepared by dissolving a predetermined quantity of non-ionic surfactant (Span) along with the target drug in an optimized volume of absolute ethanol, followed by probe sonication for 5 minutes to ensure complete dissolution and homogeneity. Concurrently, the aqueous phase was prepared by dissolving a designated concentration of an edge activator (Tween-80) in distilled water. This aqueous phase was conditioned under continuous magnetic stirring at 800 to 1,600 rpm and maintained at a temperature of 70°C to 80°C for 1 hour to achieve thermal equilibrium. Subsequently, the organic lipid solution was slowly and continuously injected into the heated aqueous phase. Upon rapid diffusion of the ethanol into the aqueous environment, the lipid components spontaneously self-assembled to form highly flexible, drug-loaded spanlastic nanovesicles.

Table 1: Formulations of Cilnidipine spanlastics prepared with different Grades of span and edge activator.

Batches	drug in mg	Span-60 in mg	Span -40 in mg	Tween-80 in ml	Ethanol in ml	Water in ml
B-1	10	250	-	0.05	2	5
B-2	10	350	-	0.05	2	5
B-3	10	450	-	0.05	2	5
B-4	10	-	250	0.05	2	5
B-5	10	-	350	0.05	2	5
B-6	10	-	450	0.05	2	5

2.3 Evaluation

2.3.1 FTIR studies

The FTIR spectra for MEB, and optimized core and compression coated tablets were recorded using BRUKER-FTIR spectrophotometer in the wave number region from 4000 cm⁻¹ to 500 cm⁻¹. The KBr press was used to prepare potassium bromide pellets loaded with samples under the study. Samples and KBr were mixed in a ratio of 1:100 and pellets were prepared by finely grinding the mixture in a mortar. Finely grinded mixture was introduced into a stainless-steel die and pellets were prepared by pressing the die between polished steel anvils at a pressure of 10t/in².

2.3.2 Evaluation Tests

The developed spanlastics were studied for evaluation parameters viz., particle size, entrapment efficiency, drug content, in-vitro diffusion as per standard procedures and conditions.

2.3.3 Entrapment Efficiency

The separation of unencapsulated (free) drug from the Cilnidipine-loaded spanlastic vesicles was achieved via indirect centrifugation.^{10,11} Briefly, a 2 mL aliquot of the prepared spanlastic dispersion was transferred to centrifuge tubes and subjected to centrifugation at 15,000 rpm for 30 minutes. Following centrifugation, the supernatant containing the untrapped drug was carefully isolated and quantitatively diluted with phosphate buffer solution (pH 6.8). The concentration of free Cilnidipine in the supernatant was determined spectrophotometrically by measuring the absorbance at a maximum wavelength of 245.5 nm utilizing a UV-Visible spectrophotometer. The mass of encapsulated Cilnidipine was calculated by subtracting the concentration of unencapsulated drug found in the supernatant from the total initial amount of drug added to the formulation. The percentage encapsulation efficiency (EE%) was computed using Equation:

$$\% \text{ Encapsulation efficiency (EE)} = \frac{\text{Totaldrug} - \text{freedrug}}{\text{Totaldrug}} \times 100$$

2.3.4 Size and morphology^{12,13}

Spread a thin layer of formed spanlastics on a glass slide and observed the structure of vesicle under microscope, collected the images using digital camera. In each case vesicle size analysis was carried out using Malvern Zetasizer Nano ZS (Malvern Instruments, UK). The freshly prepared hydrated spanlastics were dispersed in double distilled water (DDW) and was used to characterize the vesicle size. Polydispersity Index (PDI) was also determined as a measure of homogeneity. Zeta potential of the spanlastic formulations was determined to estimate stability of the formulations.

2.3.5 In vitro diffusion study of spanlastic^{14,15}

In vitro release studies on CIL spanlastics were performed using Franz-diffusion cell. The dialysis cellophane membrane was mounted between the donor and receptor compartment. The receptor medium was phosphate saline buffer pH 6.8. A weighed amount of spanlastic preparation was placed on one side of the dialysis membrane. The receptor compartment was surrounded by a water jacket to maintain the temperature at 37 ± 1 °C. A Teflon-coated magnetic bead operated to a magnetic stirrer stirred the receptor fluid. Periodically remove the samples and replaced immediately with an equal volume of receptor media, further drug content was determined spectrophotometrically at 245.5 nm. Compute the In vitro drug release data by using PCP Disso V3.

2.3.6 Ex-vivo permeation study

An ex-vivo skin permeation study was conducted for the optimized formulation utilizing excised goat skin, following the general method described by Shinde et al.¹⁶ and schematically depicted in Figure 2.

The prepared goat ear skin was mounted securely between the donor and receptor compartments of a Franz diffusion cell, ensuring that the stratum corneum layer faced upwards toward the donor chamber. The effective diffusion surface area of the cell was 1.41 cm^2 . The receptor compartment was loaded with 20 mL of phosphate buffer solution (pH 6.8) and maintained at a physiological temperature of 37 ± 1 °C. An aliquot of the optimized spanlastic formulation (equivalent to 5 mg of the active drug) was spread uniformly over the exposed skin surface in the donor compartment. Hydrodynamic sink conditions were maintained by continuously stirring the receptor medium with magnetic beads. Samples were withdrawn from the receptor chamber at predetermined time intervals and immediately replenished with an equal volume of fresh, pre-warmed phosphate buffer media to maintain a constant volume. The collected aliquots were analyzed for cumulative drug content utilizing a UV-Visible spectrophotometer at a maximum wavelength of 245.5 nm. The total amount of drug permeated across the skin barrier over time, along with corresponding permeation parameters (such as transdermal flux and permeability coefficient), was subsequently calculated.¹⁷



Figure 1: Ex-vivo permeation studies

2.4 Stability studies^{18,19}

The short stability study was performed according to ICH guidelines. The optimized spanlastic preparation was filled in tightly closed glass vials and subjected to stability testing. The formulations were kept at refrigerated conditions (4 ± 1 °C) and at room temperature (25 ± 2 °C) and were analyzed for vesicle size, drug content and entrapment efficiency after 3 months.

3 RESULTS AND DISCUSSION

3.1 Appearance

The physical appearance was found that the formulae were homogenous and white with no precipitation. viscous gel, pH was measured by using digital pH meter and was found to be 5.5 to 6.2 (Table 2). The percent drug content was found to be in the range of 67.9 ± 0.0023 to 94 ± 0.0015 with low SD values indicate the drug distribution was uniform within the formulations.

3.2 FTIR studies

FTIR spectra of CIL and Optimized CIL loaded spanlastic gel were analyzed by Bruker FTIR spectrophotometer and the spectra were recorded in the region of 4000-1000 cm^{-1} . The spectra were shown in figure 3. FTIR spectra of CIL showed the characteristic peak at 3339.88 cm^{-1} (-Aliphatic $\text{NH}_2\text{-OH}$ stretching), 1655.64 cm^{-1} (C=O Stretching), 1588.13 cm^{-1} (Aliphatic N-H bending), 1026.81 cm^{-1} (C-O-C Symmetric stretching) and 1032.25 cm^{-1} (C-O-C Symmetric stretching). The characteristics peak of CIL corresponding to (Aliphatic $\text{NH}_2\text{-OH}$ stretching $\text{CH}_2=\text{CH}_2$, cyclohexyl) was observed at 3340.27 cm^{-1} and (C-O-C Symmetric stretching) at 1026.8 cm^{-1} in Optimized CIL loaded spanlastic gel. The other characteristics peak of clinidipine is also observed with slight shifting towards lower wavelength. The comparative FTIR spectra suggest no detectable changes, which confirmed the absence of any chemical interactions between them.

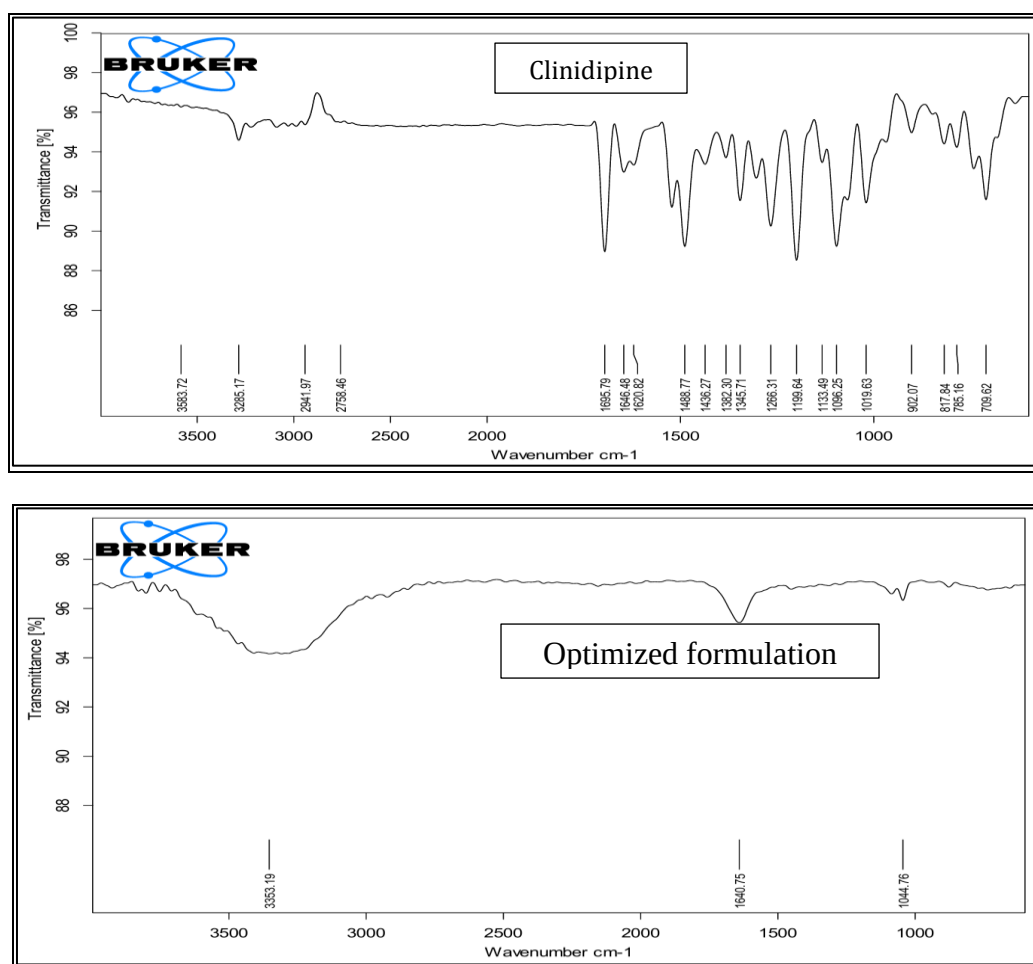


Figure 2: FTIR spectra of CIL and Spanlastic gel

3.3 Particle size analysis

Smaller vesicle size is advantageous to decrease the irritation and improve the penetration of the vesicles into the skin. The particle size of spanlastics prepared with span 60 were found to be lower as compared to the other grades like span 40 (table 2). As the concentration of Span surfactant increases in spanlastics, the vesicle size increases due to the insertion of more alkyl chains into the hydrophobic region of the vesicular bilayer. Higher amounts of the hydrophobic surfactant (such as Span 60) add more mass and volume to the hydrophobic core of the bilayer, expanding the overall dimensions of the vesicle.²⁰ The average particle diameter of CIL loaded spanlastics (figure 3) was found to be in the range of 4.513 μm to 6.7 μm , vesicles were discrete and separate with no aggregation or agglomeration. It was observed

that the vesicles were smaller with the presence of span 60 (B1, B2, B3) as compared to Span 40 (B4, B5, B6). Zeta potential (ZP) was found to be -34.1 mV with a negative charge (figure 5). For a pharmaceutical nanocarrier system (like your spanlastics, transfersomes, or proniosomal gels) to be considered stable, the desired zeta potential is generally $\geq +30$ or ≤ -30 mV. It was noted by Junyaprasert et al.²¹ that the negative surface charge of vesicles composed of nonionic surfactants is driven by the preferential adsorption of hydroxyl ions at the vesicle interface. Consequently, good physical stability of CIL within the formulated gel was achieved; the increased ZP enhanced inter-vesicular repulsion, which suppressed reaggregation and imparted electrical stability to the system^{22,23}. The average particle diameter of the CIL-loaded spanlastic gel was found to be in the range of 4.5–6.7 μm (Figure 3), characterized by discrete, non-aggregated, and non-agglomerated vesicles.

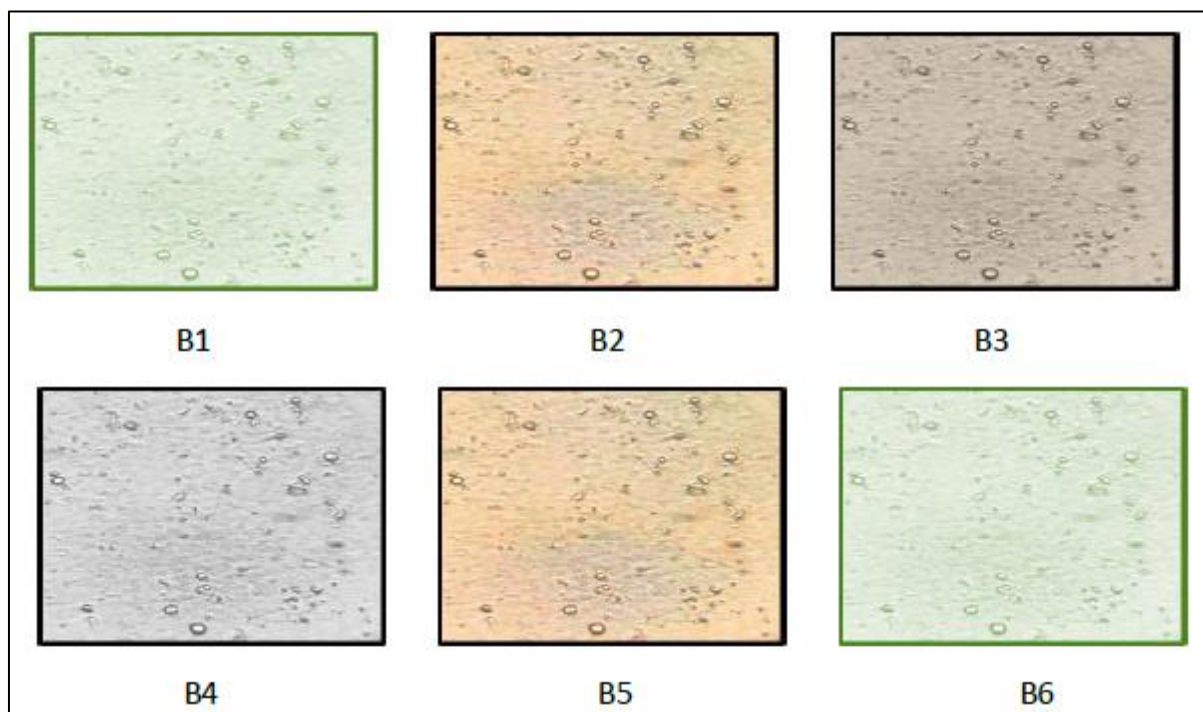


Figure 3: Microphotographs of CIL loaded spanlastic gel formulations

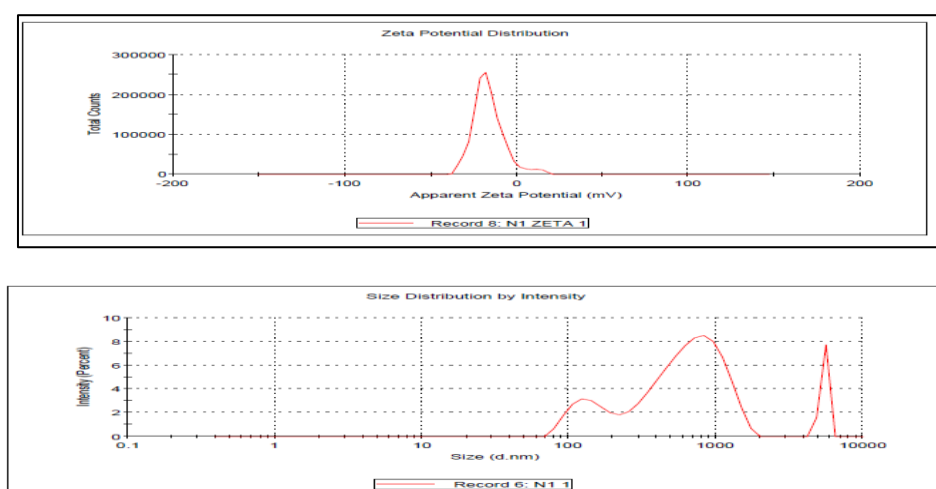


Figure 4: Average diameter and Zeta potential optimized formulation

3.4 Entrapment efficiency

The entrapment was expressed as the percentage of the total amount of CIL utilized in the preparation of spanlastic (table 2). The encapsulation efficiency depends on the type of surfactants, HLB value, their alkyl chain, and the phase transition temperature. The surfactants used in the preparations were span 60 and span 40. Span series has the same

head group with different alkyl chain and has HLB values 4.7 and 6.7 respectively and CPP ranges from 0.5 to 1. The lower the HLB of the surfactant, the higher will be the drug entrapment efficiency as in the case of spanlastics prepared using span series²⁴ The span 60 has lower HLB value and longer alkyl chain allows well closed uniformly packed bilayer structure within which CIL gets completely packed, these results are supported by Hao Y²⁵, Alsarra et al.²⁶ Span 60 has highest phase transition temperature (50°C) as compared to span 40 results increased % EE, because hydration temperature used to make spanlastics should usually be above the gel-to-liquid phase transition temperature of the system that results in spanlastics that are less leaky and have high entrapment efficiency. This could also be attributed to the structure, orientation, and packing behavior of the surfactants. Hence, spanlastics prepared from span 60 showed higher encapsulation efficiency of CIL compared to span 40. An increase in Span concentration leads to a decrease in encapsulation efficiency. Once the vesicular bilayer reaches saturation, the introduction of excess Span molecules causes overcrowding within the hydrophobic core. This structural overcrowding destabilizes the membrane integrity, ultimately promoting the leakage of the entrapped drug.²⁷

Table 2: The physical appearance, pH, % entrapment efficiency percentage (% EE) and, particle size, CIL loaded spanlastic gels

Batches	Physical appearance	pH(n=3)	% EE $\pm$ SD	Particle size (μ m)	PDI
B1	White and homogenous	5.8	94 $\pm$ 0.0015	4.5	0.547
B2	White and homogenous	5.5	92.3 $\pm$ 0.0005	4.7	0.612
B3	White and homogenous	6.2	88.0 $\pm$ 0.0011	5.4	0.307
B4	White and homogenous	5.9	86.7 $\pm$ 0.0017	6.4	0.584
B5	White and homogenous	6.0	83.5 $\pm$ 0.0015	6.5	0.389
B6	White and homogenous	5.6	67.9 $\pm$ 0.0023	6.7	0.412

3.5 In vitro diffusion of CIL from spanlastics

The drug release from spanlastic formulation was indicative of influence of nature and type of surfactant, and was shown in figure 5. The cumulative percent drug release was found to be 72.73 $\pm$ 0.09 and 78.21.93 $\pm$ 0.099 and 80.93 $\pm$ 0.12 for B1, B2 and B3 formulations; 80.77 $\pm$ 0.192407, 89.61 $\pm$ 0.995 and 97.65 for B4 and B5 and B6 formulations after 12hr. In all the formulations the faster drug release about 20 -30 % was observed after 2hr it is mainly due to release of drugs from the adhered spanlastics and improperly formed globules. The order of slow and controlled release from the formulations are B1 < B2 < B3 < B4 < B5 < B6. The In vitro drug release data for B1 to B6 formulations were fitted into various kinetic equations to find out the order and mechanism of drug release. The correlation coefficient showed that the release profile followed the first order, also from korsmeyer peppas model, the release exponent 'n' was found to be greater than 0.5 indicated the drug release followed anomalous behavior and release mechanism was indicative of diffusion controlled^{28,29}.

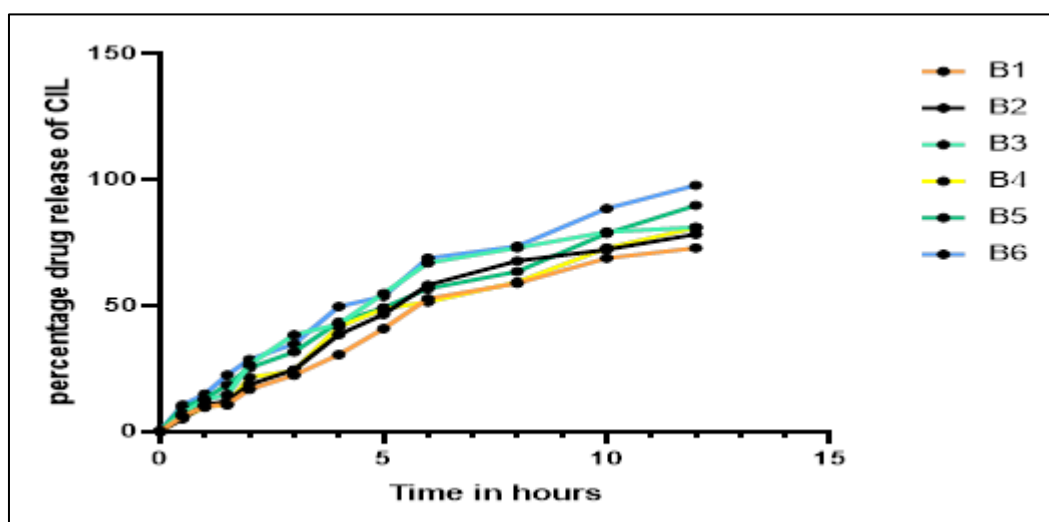


Figure 5: Comparative *In vitro* diffusion profiles of CLI loaded spanlastic gel

3.6 Ex vivo permeation studies

In vitro diffusion of Cilnidipine patches was studied in diffusion test apparatus containing 6.8 pH was used as diffusion medium, where prepared goat epidermis used as a semi-permeable membrane to measure release rates. The cumulative amount of drug release from spanlastic transdermal patch was found to be 82.34% whereas amount of drug permeated from plain transdermal patch was found to be 58.78% respectively. The improved permeation across goat skin is attributed to elastic and deformable nature of spanlastic which helped easy penetration of drug across membrane (figure 6).

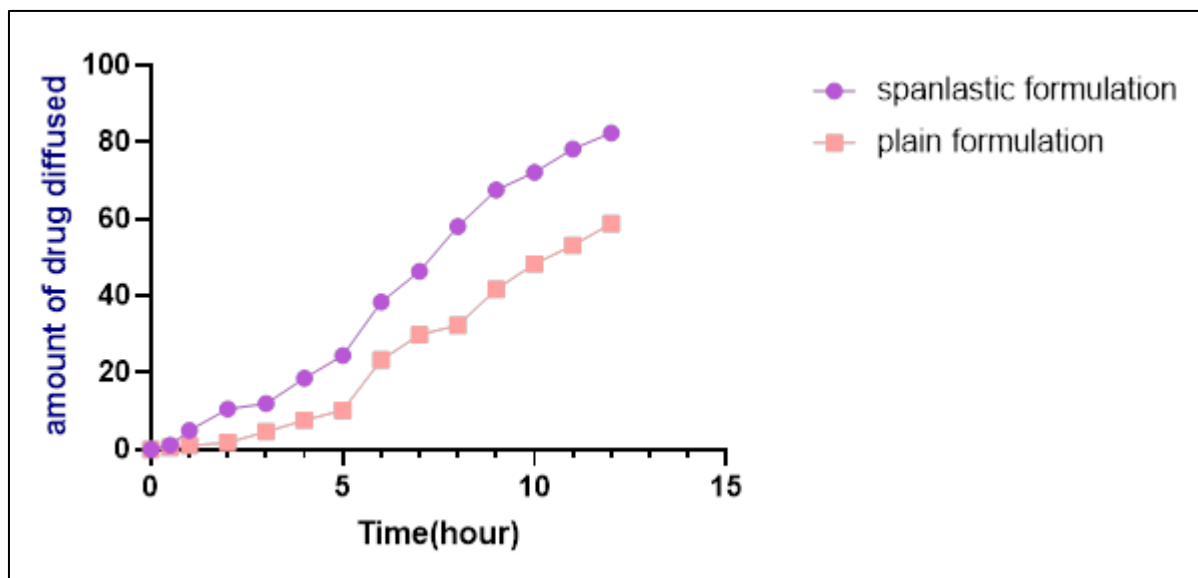


Figure 6: Cumulative amount drug permeated of optimized spanlastic and plain formulation gel formulation

3.7 Physical stability studies

In the present study, stability studies were performed on optimized formulation (B1). It was stored at $4^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 3 months and observed for the change in % EE, average PS of the vesicles. It was observed that there was no change in the physical appearance as there was neither change in the formulation consistency nor aggregation of vesicles. Furthermore, there was no significant change in EE%, PS of CIL spanlastic after the storage for 3 months. Our findings were in accordance with the study done by Sandeep et al. who explained the nonsignificant change in size and EE% in span 60 surfactant-based formulation due to its high phase transition temperature and low permeability³⁰. This result showed the high stability and suitability of spanlastics for the transdermal CIL delivery.

4 CONCLUSION

CIL-loaded spanlastics was prepared successfully by ethanol injection method. The prepared spanlastics exhibited desired entrapment efficiency and Particle size. It was found that B1 which chosen as a best formula according to entrapment efficiency, PS, and *In vitro* release study. It was found that B1 which contains high concentration of span 60 is the most appropriate surfactant for the preparation of spanlastic. *In vitro* release studies proved that the prepared spanlastic formulation contains CIL considered to be a successful topical transdermal drug delivery system and provide a sustained release of encapsulated drug. Furthermore, there was no significant change in EE% and PS of CIL spanlastics after storage for 3 months.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

There are no conflicts of interest.

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