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Preparation and Evaluation of Dapagliflozin Propanediol Monohydrate-Loaded Transferosomal Dispersion for Transdermal Delivery

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Abstract

The transdermal route of drug delivery has received significant attention in pharmaceutical research due to its ability to overcome many challenges associated with oral medication administration, including the ability to bypass first-pass metabolism, ensuring a more predictable and prolonged period of action, as well as minimizing the occurrence of adverse reactions. Transferosomes are a type of ultra-deformable lipid-based vesicles, that have the potential to offer several benefits compared to the traditional lipid-based vesicles such as liposome. The major goal of this research was to prepare (for the first time) dapagliflozin-loaded transferosomes to minimize the potential risk of hyperglycemia associated with oral administration for the treatment of diabetes. The transferosomes were prepared by the thin film hydration method with 5 mg of drug and different proportions of phospholipid and edge activators. The transferosomes were characterized for entrapment efficiency (EE), drug content, pH, vesicle size, PDI, zeta potential,viscosity, ***in vitro*** drug release, ***ex vivo permeation, FTIR*** and SEM. Tween 80-based transferosomes (F6) at a 95:5% w/w phospholipid:edge activator ratio yielded the highest EE (93±0.77%), drug content (99.7±1.68%), ***in vitro*** drug release within 24 hours (99±1.4%), vesicle size (105.8±1.61nm), PDI (0.436±0.01), viscosity (155±1.95 cP), and zeta potential (-35.15mV), which was selected as the optimum formula. The formula had good ***ex vivo*** permeation after 24 hours (289.8±5.2 µg/cm^2, 91% drug permeated), compatible drug-excipients according to FTIR, and nano-sized spherical shape vesicles according to SEM. Three months of stability testing according to the ICH guidelines revealed that the formula was stable at 4±2°C and 25±2°C. In conclusion, this research suggested that transferosomes can be prepared as a transdermal drug delivery system with suitable properties to be given once daily as a transdermal patch for the antidiabetic drug dapagliflozin.

Keywords: Dapagliflozin, Edge activaror, Entrapment efficiency, Span 60, Transferosome, Tween 80.

Introduction

Diabetes mellitus is one of the most researched illnesses and a critical global health issue. Any type two diabetes mellitus treatment aims to enhance glycemic control and lessen the risk of problems that go along with it[(1)]. There are significant drawbacks to current diabetic treatments, including patient noncompliance and intermittent hypoglycemia[(2)]. Additionally, oral administration has some major drawbacks, including first-pass metabolism, limited intestinal bioavailability, and the inability to manage drug distribution or adjust the place of absorption[(3)]. Researchers throughout the world are interested in the transdermal technique because it offers advantages over other approaches[(4)].The major principle in the development of transdermal systems is to reduce the skin's barrier function while avoiding negative side effects, particularly local discomfort[(5)].

Several methods, including electroporation, iontophoresis, magnetophoresis, sonophoresis, and microneedling, are being used to get over these restrictions, especially for large, hydrophilic medicines to be administered via the transdermal route. However, their mechanical influence on the structure of the skin has hindered their widespread use[(6)]. The vesicular drug delivery system is a flexible method that maintains and regulates the medication's release from the body, enhancing therapeutic efficacies[(7)]. Numerous vesicular drug delivery methods have been created, such as liposomes, cubosomes, ethosomes, niosomes, sphingosomes and transfersomes,.In comparison to conventional vesicles, the lipid bilayer of the vesicular drug delivery system can offer a better stability platform and can entrap both water-soluble and water-insoluble medicines[(8)].Lipid-based vesicles (transferosomes) are increasingly being exploited for the delivery of transdermal drugs[(9)]. They are bendable because of their highly deformable bilayer membrane[(10)].

Transferosomes may flex and travel through tiny constrictions (5–10 times smaller than their

diameter) without noticeable loss, which speeds up their quick penetration via the subcutaneous tissue intercellular lipid channel[11]. Additionally, these structures have the potential to include therapeutic compounds that exhibit a diverse range of solubilities, as they can accommodate both hydrophobic and hydrophilic components[12].Dapagliflozin is developed to treat type 2 diabetes mellitus (T2DM). It inhibits the reabsorption of glucose and encourages urine glucose excretion by acting selectively and reversibly on the sodium-glucose co-transporter 2 in the proximal tubules of the kidney[13]. Dapagliflozin's long half-life (12.5 hours) and the prolonged reduction of urine glucose reabsorption it causes over the course of 24 hours following administration at the recommended therapeutic dose (10 mg) make once-daily dosing possible[14]. It has been categorized as class III according to the Biopharmaceutical Classification System (BCS). This classification denotes a higher degree of solubility and a nearly impermeable nature[15]. It has a molecular weight of 408.87 g/mole [16]. Dapagliflozin is a powder that appears white to off-white in color and does not absorb moisture. It exhibits solubility in a variety of polar organic solvents. The water solubility at a temperature of 24 ºC is determined to be 1.6 mg/ml. At a temperature of 37 ºC, the pH within the physiological range does not have an impact on the water solubility of dapagliflozin propanediol.

The substance does not exhibit ionization within the pH range of 2 to 11. The compound has a partition coefficient of 2.45 in the n-octanol/water system at a pH of 7.4, and possesses a pKa value of 12.6[17].The work aims to prepare and evaluate transferosomes for dapagliflozin systemic delivery via the skin to lower the risk of hypoglycemia associated with the oral route and provide a dosage form suitable for unconscious patients, geriatric patients, and patients with vomiting and swallowing difficulties to improve patient compliance.

Materials and Methods

Materials

Dapagliflozin propanediol monohydrate (DAP) was purchased from (Golden-Shell Pharmaceutical Co., Ltd, China). Phospholipon®90G was purchased from (Shandong Bouliga Biotechnology Co., LTD, China). Span 60, Tween 80, chloroform, and methanol were purchased from (Thomas Baker (Chemicals) PVT., LTD, India).

Methods

Preparation of dapagliflozin (DAP)-loaded transferosomes

Thirteen formulations of dapagliflozin-loaded transferosomes were prepared using the thin film hydration method. Briefly, in an organic phase, phosphatidylcholine (phospholipon® 90 G) and different edge activators (EAs) (in several ratios) were dissolved in a 6 ml mixture of chloroform: methanol (2:1 v/v) in a round bottom flask by shaking. The organic phase was evaporated using a rotary evaporator (BUCHI Rotavapor R-205, Zurich, Switzerland) at 55 °C and 95 rpm for 30 minutes under reduced pressure to get a thin film. DAP was dissolved in 10 ml of pre-heated (55°C) PBS (pH 7.4) and added to the thin film with further rotation by rotary evaporation for 1 hour to produce the transferosomal dispersion. The dispersion was left for 2 hours at room temperature to complete hydration, then sonicated with a probe sonicator (HOVERLAB, india) to decrease the vesicles size at 50% power (75 W) for 5 minutes. The produced dispersion was filtered at 0.45 µm, followed by a 0.22 µm syringe filter[18].

One formulation (F14) was prepared using the vortexing-sonication method. In this method, phosphatidylcholine, an edge activator, and the active ingredient were combined in a phosphate-buffered saline solution with a pH of 7.4. The mixture was vortexed for five minutes in order to yield a milky solution. Subsequently, the solution was subjected to probe sonication for 5 minutes. The resulting dispersion was then filtered using a syringe filter[19]. Transferosomal dispersion was stored in a refrigerator at 4°C. The composition of the formulations is shown in Table 1.

Table 1. Composition of the prepared DAP-loaded transferosomes

Formula	Drug(mg)	PC:EA(w/w)	PC(mg)	Span 60(mg)	Tween 80 (mg)	Sonication time(min)	Method
F1	5	95:5	500	26.3		5	Thin film hydration method
F2	5	90:10	500	55.6	-	5	=
F3	5	85:15	500	88.24	-	5	=
F4	5	80:20	500	125	-	5	=
F5	5	75:25	500	166.66	-	5	=
F6	5	95:5	500	-	26.3	5	=
F7	5	90:10	500	-	55.6	5	=

Continued table 1.

F8	5	85:15	500	-	88.24	5	=
F9	5	80:20	500	-	125	5	=
F10	5	75:25	500	-	166.66	5	=
F11	5	95:5	500	-	26.3	3	=
F12	5	95:5	500	-	26.3	10	=
F13	5	95:5	250	-	13.16	5	=
F14	5	95:5	500	-	26.3	5	Vortexing sonication

PC= phospholipon®90G; EA= edge activator

Evaluation and characterization of the prepared transferosomal dispersions

Entrapment efficiency determination of transferosomal dispersions

All formulations(F1-F14) were evaluated for drug entrapment efficiency. One ml from each formula was diluted with 10 ml of phosphate-buffered saline (pH 7.4) and centrifuged using a cooling centrifuge (Hermle Z, Germany) for 1 hour at 15,000 rpm. The supernatant was withdrawn, and the entrapment efficiency was then estimated using a UV-visible spectrophotometer (UV mini-1240 Shimazu, Japan) at the λ max of the drug (223nm)[20]. The percentage of entrapment efficiency (EE%) was calculated using Eq.1.

$$EE\% = (Total\ drug - free\ drug\ in\ supernatant)/(Total\ drug) * 100\%$$ **-------Eq.1**

The formulas that gave high EE were subjected to further investigations.

Drug content determination of transferosomal dispersions

Methanol was used to dilute each of the formulas that exhibited high entrapment efficiency percentages. Subsequently, the absorbance was determined utilizing a UV-visible spectrophotometer at the wavelength corresponding to the maximum absorption (λ max) of the medication. The concentration was then determined by employing the equation derived from the methanol calibration curve[21].

pH determination of transferosomal dispersions

To determine if the pH of the formulas is proper for skin application, the pH of transferosomal dispersions with high EE% was checked using a pH meter (Selecta, Spain), by inserting the electrode tip inside the dispersion. The reading was taken after two minutes and recorded[22, 23].

Vesicle size, PDI & zeta potential determination

The vesicle size and polydispersity index (PDI) of transferosomal dispersions in the prepared formulas with high EE% were determined using the dynamic light scattering method measured by Brookhaven 90 Plus (Brookhaven Instruments Corp. particle sizing software Ver.5.34, USA) with scattering angle 15 and no dilution. Zeta potential was measured by Brookhaven Instruments-zeta potential analyzer after an appropriate dilution with distilled water at 25 ° C[24]. For both tests the measurement was repeated three times.

Viscosity of transferosomal dispersions

The viscosity of the formulations with high EE% was measured using a Brookfield viscometer (Brookfield LV, spindle no. S-63) at a rotational speed of 100 rpm and at room temperature. The viscosity measurement was taken promptly at the 30-second interval[25].

In-vitro drug release study of transferosomal dispersions

In-vitro release study was performed for the eight formulas with high EE% using a modified vertical Franz diffusion cell (Copley Scientific Limited, UK). The dialysis membrane with a molecular weight cutoff (MWCO) of 8000-14,000 Da was hydrated using phosphate-buffered saline (PBS) with a pH of 7.4 for an extended period of time prior to being positioned between the donor and receptor compartments. Two ml of the prepared formula was placed in the donor compartment while, the receptor medium consisted of 15 ml of PBS (pH 7.4). The receptor medium was continuously stirred at a rate of 100 rpm using a magnetic stirrer and the temperature was maintained at 37 °C. Aliquots of 1 ml of samples were withdrawn at definite time intervals from the sampling port and replaced with the buffer to maintain sink condition. By using a UV spectrophotometer at 223 nm, the samples were examined. The percentage of drug release during 24-hours was recorded[26].

Kinetics of drug release

The release data were applied to several kinetic models to determine the order and mechanism of drug release from the system. Kinetic modelling was done through Microsoft Excel, DD-solver by fitting the data to zero order, first order, Higuchi model, and Korsmeyer-Peppas model[27]. The adjusted correlation coefficient R^2 and the release exponent "n" in the Korsmeyer-Peppas model were obtained to understand the mechanism of release from the transfersomal formulas[26, 28].

Selection of the best transferosomal dispersion formula

The optimal formula was chosen depending on its highest entrapment efficiency, high drug content, acceptable pH and viscosity, excellent drug

release profile, optimum particle size, zeta potential and PDI.

Determination of ex-vivo transdermal permeated amount

This study was conducted with the approval of the animal ethical committee of College of Pharmacy/ Mustansiriyah University. An *ex-vivo* investigation was conducted to evaluate the penetration of DAP over de-haired rat skin. In this study the skin of the rat's abdomen was utilized as a diffusional membrane to examine dapagliflozin's penetration because it has a similar stratum corneum thickness and water permeability to human skin[29]. Three male Wister Albino rats, 2 to 3 months old and weighing between 200 and 250 g, were sacrificed by ether inhalation. The abdomen hair was then gently cut using an electrical clipper. A fresh rat's abdomen skin, measuring a few centimeters in each dimension and shaped like a square and thereafter immersed in phosphate-buffered saline (PBS) with a pH of 7.4 for an extended period of time. The skin that had been produced was affixed onto a Franz diffusion cell, with the side containing the stratum corneum facing the donor compartment from which the substance is released. A precise quantity of the formulated transferosomal dispersion, corresponding to 1 mg of DAP, was evenly delivered to the donor compartment. Additionally, 15 ml of PBS (pH 7.4) was introduced into the receptor compartment, ensuring direct contact between the dermal side of the skin tissue and the receptor medium. The surface area of the skin tissue that came into contact with the contents of both the donor and receptor compartments measured 3.14 cm^2. Receptor compartment samples (1 ml) were collected at predefined time intervals (2, 4, 6, 8, 12, and 24 hours) and subsequently substituted with buffer solution to uphold sink conditions[30].

The cumulative permeated amount of the medication (Q, µg/cm^2) was determined and graphed over time using a UV-visible spectrophotometer set at a wavelength of 223 nm[31]. The software package SAMPA version 1.04 was utilized for the calculation of permeation parameters in the study of skin and membrane permeation data. The primary objective of the SAMPA methodology was to eliminate ambiguity in the computation process, since it had the potential to introduce diversity in the data pertaining to skin penetration[32]. The permeation profile was obtained by plotting the cumulative amount of DAP (µg/cm^2) that penetrated through the rat skin on the Y-axis against the corresponding time (in hours) on the X-axis. The plot was utilized for the determination of permeation parameters, specifically the transdermal flux of DAP at steady state (Jss, µg/cm^2/h). Transdermal flux was calculated by determining the slope of the linear portion of the regression line. The lag time (T_{lag}) was determined by calculating the intercept of the regression line with the X-axis. The permeability coefficient (K_P, cm/h) is calculated by dividing the transdermal flux across the vertical Franz diffusion cell (Jss) by the initial concentration (C_0) of DAP in the donor compartment (Eq.2)[33].

$$Kp = Jss/C0 \text{ -------Eq.2}$$

Determination of fourier-transform infrared (FTIR) spectroscopy

The drug-excipient compatibility was assessed using FTIR 600 Biotech, UK. Comparisons were conducted among the fourier-transform infrared (FTIR) spectra of the pure medication, phospholipon® 90G, EA and the optimum transferosomal dispersion formulation. The samples were subjected to compression and encapsulated within a disc using potassium bromide (KBr) as the medium. Subsequently, the samples were analyzed using a scanning technique within the range of 4000-400 cm^{-1}[34].

Determination of surface morphology by scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to observe the vesicle morphology. One drop of transferosomal dispersion was uniformly spread on a glass slide and left to dry. After drying, the specimen was coated with platinum by a 208HR High Resolution Sputter Coater and then observed under an Inspect F scanning electron microscope (FEI Company, USA) at an accelerating voltage of 30 KV[35].

Stability study

The chosen formula was stored in firmly sealed vials and subjected to two distinct storage conditions: refrigerator temperature (4±2°C) and room temperature (25±2°C), in accordance with the guidelines set by the International Council for Harmonization (ICH). This storage was maintained for a duration of three months[36, 37]. The entrapment efficiency, vesicle size, pH and drug content were re-evaluated every month.

Statical analysis

All data were presented as mean ± standard deviation (SD). The results were analyzed statistically by one-way ANOVA, with significant results equaling ($p < 0.05$) and non-significant results equaling ($p > 0.05$).

Results and discussion

Fourteen formulas were prepared in order to study the effects of different variables on the transferosomal dispersions of DAP for optimization.

Entrapment efficiency of transferosomal dispersions

The entrapment efficiency for all the prepared transferosomal formulas (F1-F14) was determined and the results are shown in Table 2. The EE% of transferosomes was found to be in the range of 23±4.27% to 93±0.77%. The results revealed many variables affecting the EE%, including:

1. ***The effect of the method of preparation on the EE%***

Two alternative methods were employed in order to enhance the preparation conditions of transferosomes. The transferosomal formulation F14, which was synthesized utilizing the vortexing-sonication process, had an entrapment efficiency (EE%) of 54±2.31%. The EE% of F6, which was generated utilizing the thin film hydration technique with the same composition, exhibited an increase to 93±0.77% as compared to F14. The rotary evaporation technique may facilitate the formation of a thin film with a large surface area, which in turn might potentially enhance the complete hydration of vesicles[38]. This improved hydration may be a contributing factor to the observed significant difference ($p < 0.05$) in the EE%. Upon visual examination during the use of the vortexing method, it was seen that lipids tended to cluster and adhere to the inner walls of the vortexing vial, hence posing challenges to the process of vesicle hydration. The utilization of the vortexing approach resulted in the formation of uneven dispersion characterized by the presence of lumps, which posed challenges in achieving homogeneity and exhibited a high tendency for rapid sedimentation and aggregation[39]. Hence, the present study decided to use the thin film hydration method instead of the vortexing method.

Table 2. Drug entrapment efficiency values are mean±SD (n=3)

Formula	Entrapment efficiency %
F1	23±4.27
F2	43±2.13
F3	57±3.07
F4	77±0.96
F5	78±3.41
F6	93±0.77
F7	89±1.3
F8	87±2.9
F9	85±0.98
F10	81±2.41
F11	64±0.62
F12	71±1.13
F13	84±1.09
F14	54±2.31

2. The effect of different types of EAs on the EE%

The findings of the study indicated that the kind of EAs had a statistically significant effect ($P < 0.05$) on the trapping of DAP within the transferosomes that were created. The transferosomes that were created with Span 60 (F1-F5) had EE% values ranging from 23±4.27% to 78±3.41%. Conversely, the transferosomes made using Tween 80 (F6-F10) displayed EE% values ranging from 81±2.41% to 93±0.77% (Figure 1). The solubility of the hydrophilic medication DAP within the aqueous core is enhanced by the hydrophilicity of the non-ionic EA Tween 80 (HLB 15), resulting in a greater EE compared to Span 60 (HLB 4.7). Previous studies have indicated that an EA possessing a hydrophilic-lipophilic balance (HLB) value of 8.6 or higher exhibited increased entrapment efficiency for water-soluble drugs. Conversely, an EA with an HLB value ranging from 1.7 to 8.6 demonstrated reduced entrapment efficiency[40] .

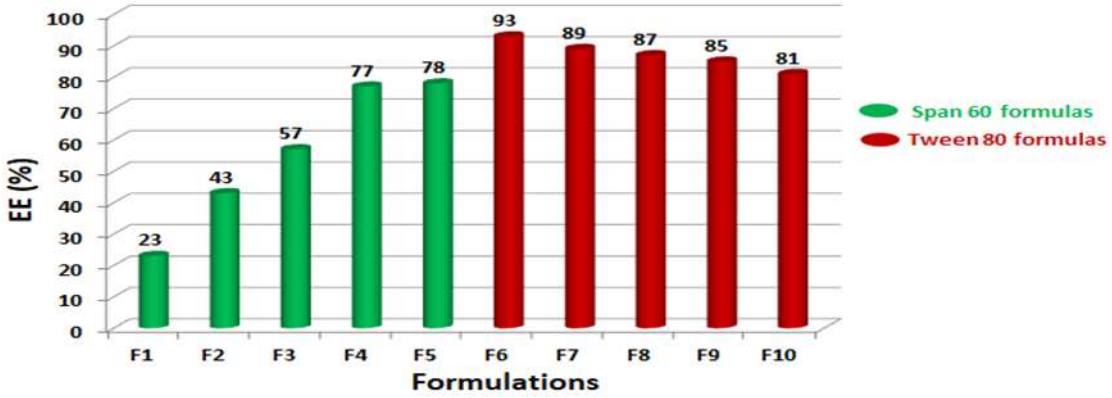

Figure 1. Effect of Span 60 (F1-F5) and Tween 80 (F6-F10) on EE%

3. The effect of different amounts of lipid on the EE%

The entrapment efficiency of formula (F13), which was made using 250mg of phospholipon® 90G with the same PC:EAs ratio as formula (F6) prepared with 500mg of phospholipon® 90G, exhibited a substantial drop ($p < 0.05$) from 93±0.77% for F6 to 84±1.09% for F13. This finding suggests that a drop in the overall quantity of lipids and edge activators resulted in a reduction in the number of vesicles, thereby leading to a fall in entrapment efficiency[41]. Similar results were observed with aceclofenac-loaded transferosomes[42].

4. Effect of sonication time on EE%

The formulae F11 and F12 were produced and subsequently subjected to probe sonication for durations of 3 and 10 minutes, respectively. The results of the study indicated that the entrapment efficiency for F11 was determined to be 64±0.62%, while for F12, it was discovered to be 71±1.13%. When comparing F6 (sonicated for 5 minutes, with an entrapment efficiency of 93±0.77%) to F11 (sonicated for 3 minutes), it was observed that increasing the sonication duration from 3 minutes to 5 minutes (F6) led to a statistically significant improvement ($p<0.05$) in the entrapment efficiency. This improvement can be attributed to the increased mixing time, which resulted in a higher number of vesicles being formed and consequently increased the amount of medication entrapped within the lipid vesicles[43].

While, the entrapment efficiency significantly decreased ($p < 0.05$) with extended sonication for up to 10 minutes (F12). This can be attributed to the observation that longer sonication durations lead to the formation of smaller vesicles[44]. Similar results were reported with the transferosomes of silymarin[45].From these results concerning EE%, the formulas (F4-F10 and F13) that gave the higher EE% were subjected to further investigations.

Drug content of transferosomal dispersions

Table 3 shows the drug content of the transferosomal dispersion formulations (F4-F10 and F13). All of the formulas had high drug contents (95±2.64-101±2%), demonstrating the suitability of the preparation process and the consistency of the created formulas' content[46].

pH of transferosomal dispersions

The pH of the eight transferosomal dispersions (F4-F10 and F13) was determined through the use of a pH meter. The pH values observed in Table 3 varied from 6.11 to 6.9, which aligns with the required pH range for topical pharmaceuticals in order to prevent skin irritation[47].

Vesicle size, PDI and zeta potential of transferosomal dispersions

The findings from the analysis of vesicle size, polydispersity index (PDI), and zeta potential, as presented in Table 3, demonstrate that all transferosomal dispersions (F4-F10 and F13) exhibited diameters falling within the nanometer scale (ranging from 85±2.68 nm to 223.3±3.1 nm). The mean vesicle size of formulas prepared with Span 60 (F4 and F5) was found to be larger compared to those prepared with Tween 80 (F9 and F10), while maintaining the same PC/EAs ratio. This observation can be attributed to the use of EAs with high hydrophilic-lipophilic balance (HLB) values, such as Tween 80, which led to the formation of smaller vesicles. This is likely due to the higher reduction in surface tension caused by EAs with high HLB values as opposed to those with low HLB values, such as Span 60[48] . Similar results were observed with the hydrophilic drug ivabradine HCl transferosomes[40].

Regarding EA amount, the vesicle size increased with increasing EA amount, as seen with formula F5 (containing 166.66 mg Span 60) that have larger size (210±3.05 nm) than F4 (containing 125mg Span 60) with 128.7±2.09 nm vesicle size, as well as with Tween 80 based formulas F6,F7 and F8 (containing increasing amount of Tween 80) with vesicle size 105.8±1.61nm, 143.4±3.18 nm and 184.9±5.21 nm respectively (Figure 2). This in agreement with prior findings that suggested the inclusion of EA molecules inside the lipid bilayer might augment its diameter, increasing transferosomal size[49]. However, upon further increase in EA amount (F9 and F10) there was a significant reduction in vesicle size, as the presence of a higher level of EA may lead to the formation of micelles with small vesicle size[50]. In general, the presence of EA in sufficient amount is important for small and homogenous sizes [51].

The polydispersity index ranged from 0.005±0.06 to 0.541±0.16, indicating a homogeneous size distribution and the presence of more uniformly sized vesicles with enhanced stability[(52]. There was no significant ($p > 0.05$) change in PDI of Span 60 formulas as the ratio of span increased from 20% to 25%, while Tween 80 formulas had the lowest PDI at 10% of EA (F7) and significantly ($p < 0.05$) higher values at 5% and 15%. Further increasing the Tween 80 to 20% and 25% significantly ($p < 0.05$) decrease the polydispersity index of the formulas. Our results in agreement with the results of eprosartan mesylate transferosome[53] .

Zeta potential is an important parameter for determining the stability of the transferosome. It has been established that a nanoparticle may behave as a stable dispersion molecule and can inhibit aggregation if its zeta potential value is greater than (+/-) 30 mV. Because of electrostatic repulsion and the greater distance between the layers[54]. The obtained zeta potential values for the transferosomal formulations (F4-F10 and F13) are presented in Table 4. These values indicate that the transferosomal dispersions possess suitable zeta potential, suggesting satisfactory physical stability. The presence of the lipid (phospholipon® 90 G) was the main factor contributing to the overall negative charge seen on the resulting transferosomes in all formulations[55] (Figure 3). Our results are in agreement with the results of the felodipine transferosome[56].

Table 3. Vesicle size, poly dispersity index and zeta potential observation results, values are mean±SD (n=3)

Formula	Drug content %	pH	Vesicle size (nm)	Poly dispersity index	Zeta potential (mV)
F4	99±4.36	6.7±0.1	128.7±2.09	0.300±0.09	-49.3±0.6
F5	96.1±1.15	6.8±0.33	210±3.05	0.297±0.03	-61.17±2.4
F6	99.7±1.68	6.7±0.14	105.8±1.61	0.436±0.01	-35.15±1.2
F7	99.3±3.09	6.5±0.54	143.4±3.18	0.005±0.06	-37.6±1.8
F8	100.3±1.53	6.3±0.11	184.9±5.21	0.541±0.16	-41.11±2.05
F9	96.6±2.51	6.5±0.09	85.6±2.24	0.298±0.02	-45.03±1.3
F10	95±2.64	6.11±0.51	85±2.68	0.238±0.06	-55.47±2.1
F13	98.4 ± 1.23	6.9±0.08	136.2±2.11	0.212±0.07	-14.13±0.01

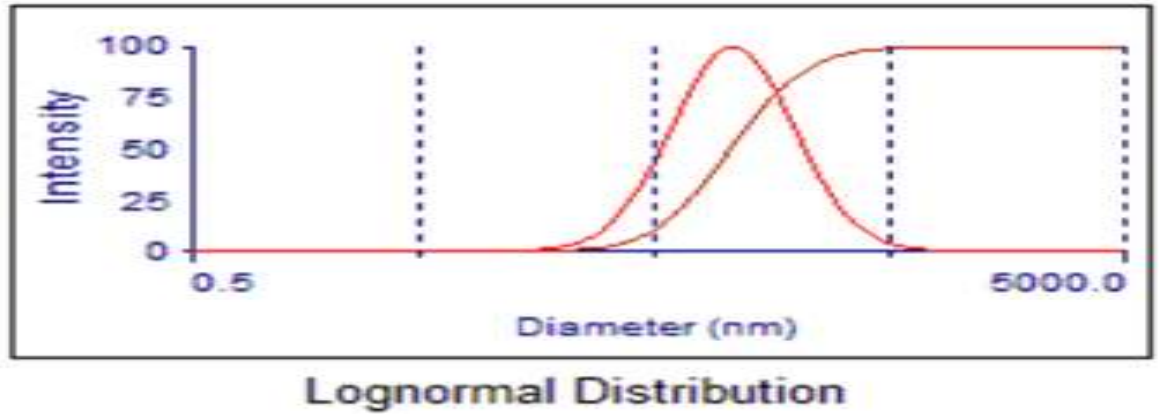

Figure 2.particle size distribution for formula F6

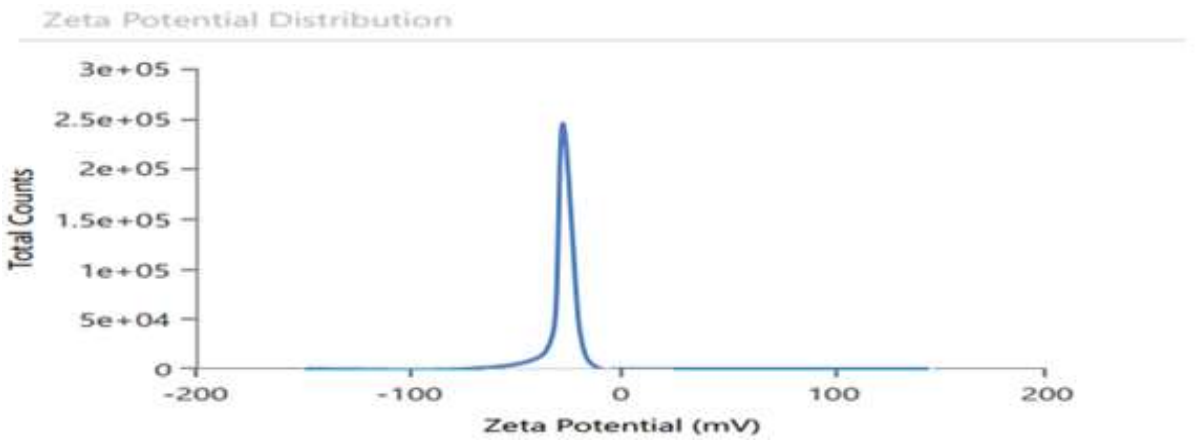

Figure 3. Zeta potential for formula F6

Viscosity of transferosomal dispersions

The objective of this study was to determine the viscosities of transferosomal dispersions (F4–F10 and F13) in order to assess their suitability for topical application and stability. Viscosity adjustment is important to control the sedimentation rate, because the sedimentation rate had an inverse proportion with the viscosity according to Stokes' law[57]. The measured viscosities are presented in Table 5. The findings from the analysis of all eight dispersion formulae indicate that there were no statistically significant differences ($p > 0.05$) seen between the viscosity of Span 60-based formulations (F4 and F5) and Tween 80-based formulas (F6-F10). In relation to the amount of EA, it was observed that the viscosity exhibited a rising pattern with increasing amount of Span 60 (F4–F5) and Tween 80 (F6–F10 and F13). The absence of charge on the hydrophilic head of these non-ionic EAs resulted in an elevation in flow resistance during the batch emulsification procedure[51].

Table 4. The viscosity of transferosomal dispersions, values are mean±SD (n=3)

Formula	Viscosity (cP)
F4	205±4.09
F5	346.3±3.26
F6	155±1.95
F7	222.33±2.8
F8	406±5.3
F9	540±3.26
F10	698±4.54
F13	87±7.87

In-vitro drug release of transferosomal dispersion

Dapagliflozin-loaded transferosomal dispersions (F4–F10 and F13) were chosen to perform the *in-vitro* release study, as they have the highest EE. Figure 4 displays the cumulative release percent of DAP at various time intervals up to 24 hours. In all eight transferosomal dispersions, a biphasic release pattern was observed. The first release phase occurred during the first 4 hours, followed by a persistent release phase that extended up to 24 hours. The early release phase may be attributed to the presence of free medicine adsorbed on the surface of the lipid vesicles, whereas the gradual diffusion of the entrapped medication occurs from within the lipid vesicles[40]. Regarding the type of edge activator, Tween 80-based transferosomal dispersions (F6-F10 and F13) demonstrated a higher cumulative amount of drug release after 24 hours than Span 60-based transferosomal dispersions (F4 and F5). This tendency could be brought on by the lipid bilayer's varying stiffness and permeability, where Tween 80 has a lipophilic tail with a longer carbon chain length (C18) in comparison to Span 60, which makes it easier for it to be integrated into lipid bilayers with more permeable vesicle membranes[52].

Concerning the amount of edge activators, the results of the Span 60-based formulas revealed that formula F5 gave a higher level of drug release after 24 hours (80.2±1.69%) than formula F4 (72.9±1.82%), as it contains a higher amount of Span 60, which causes the ordered lipid membrane to weaken and become more permeable, resulting in greater drug release[58]. The release of Tween 80-based formulas (F6, F7 and F8) showed no significant differences upon increasing Tween 80 amount to give 99±1.4%, 99.8±1.12% and 100±1.8% after 24 hours, respectively, but significantly decreased with formulas F9 (85±1.81%) and F10 (83.1±2.5%) that contained a high amount of Tween 80, due to the loss of vesicular structure and formation of rigid mixed micelles upon high Tween 80 amount (loss of elasticity)[59]. These findings are in agreement with the results of oestradiol transferosome[50]. Regarding the amount of lipid, formula F13, which contained 250 mg of phospholipon® 90G in comparison to formula F6, which contained 500 mg with the same PC/EA ratio (95:5), showed a non-significant difference ($P>0.05$) in drug release after 24 hours (99.9± 1.82%).

Kinetics of drug release

The DD-Solver program was used to fit the in vitro drug release data to various kinetic models, such as Zero-order, First-order, Higuchi, and Korsmeyer-Peppas (Table 5). The model that has the highest R^2 (closest to 1) would be the best one. The Higuchi model was found to be well-fitting for all developed formulas, as demonstrated by the R^2 adjusted values higher than those of other models. This suggests that the Higuchi model is a good fit for explaining DAP release from the transfersomes. Additionally, the value of "n" for each formulas in the analysis of the Korsmeyer-Peppas model was smaller than 0.5, validating the Fickian release mechanism of DAP from the transfersomes[60].

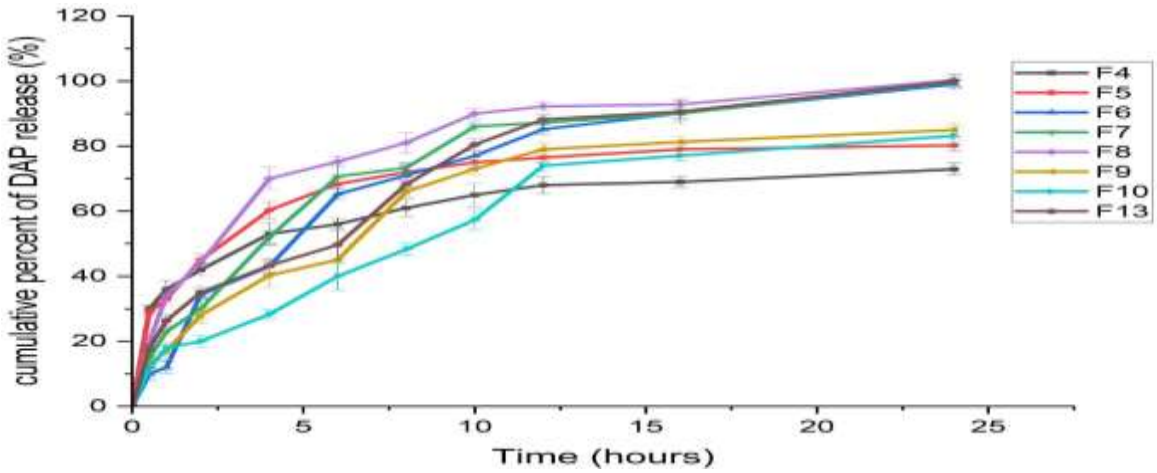

Figure 4. Cumulative percent of DAP release from transferosomal dispersions (F4-F10 and F13)

Table 5. Kinetic modeling of drug release profile

formula	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	N
F4	-0.5515	0.4369	0.9843	0.9776	0.228
F5	-0.3547	0.7368	0.9476	0.9216	0.255
F6	0.6162	0.9813	0.9879	0.9389	0.472
F7	0.4803	0.9888	0.9942	0.9349	0.420
F8	0.1148	0.9717	0.9834	0.9224	0.328
F9	0.5716	0.9671	0.9797	0.9289	0.455
F10	0.7546	0.9676	0.9733	0.9505	0.443
F13	0.5745	0.9561	0.9961	0.9557	0.445

Selection of the best transferosomal dispersion formula

The formula F6 was determined to be the most optimal formula because it has the highest EE% (93±0.77%), optimum drug content (99.7±5.68%), high *in-vitro* drug release within 24 hours (99±1.4%), suitable vesicle size (105.8±5.61nm), PDI (0.436±0.01), acceptable viscosity (155±1.95) and zeta potential (-35.15 ±1.2mV).

Ex-vivo transdermal permeation of dapagliflozin

Ex-vivo transdermal permeation study of DAP-loaded transferosomal dispersion (F6) was carried out using rats skin. As shown in Figure 5, the cumulative amount of DAP permeated from transferosomal dispersion (F6) was 289.8±5.2µg/cm^2 after 24 hours, representing about 91±1.6% of the initial amount, which was significantly ($p < 0.05$) higher than the cumulative amount of DAP permeated from DAP solution that found to be 106.36±5.6 µ/cm^2 after 24 hours, representing about 33.4±2.3% of the initial amount. Table 6, shows the permeation parameters obtained through the use of SAMPA software version 1.04 such as the transdermal flux at steady state (J_{ss}) and permeability coefficient (K_P) for DAP from F6 which were significantly higher ($P < 0.05$) than those for DAP solution. In addition, the lag time was significantly ($p < 0.05$) shorter for drug from F6 (0.047 hours) than from DAP solution (0.32 hours). The cumulative amount of drug permeated and the permeation parameters study indicate the capability of the prepared transferosomal dispersion to permeate due to its elastic, deformable structure. Similar results were observed with transdermal eprosartan mesylate-loaded transferosomes [18].

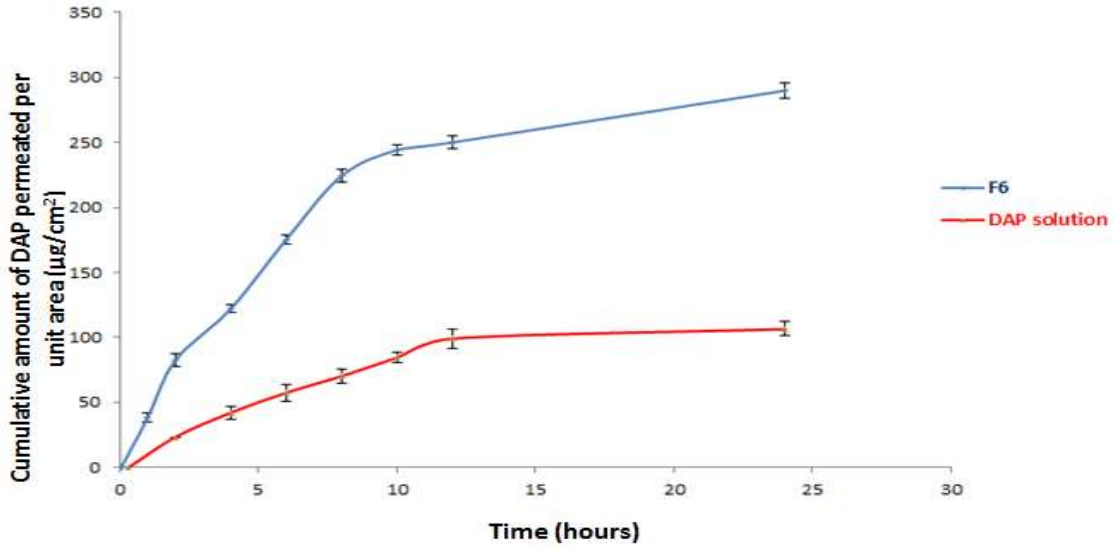

Figure 5. Permeation profiles of DAP from it's solution and F6

Table 6. Ex vivo permeability parameters of DAP from DAP solution and F6 values ± SD (n=3)

Formula	J_{ss} (µg/cm^2/h)	T_{lag}(h)	K_P (cm/h)	% of DAP permeated /24 h
F6	38.05±0.63	0.047±0.01	0.0761±0.001	91±1.6
DAP solution	11.18±0.4	0.32±0.02	0.0224±0.002	33.4±1.2

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra are commonly employed to identify potential incompatibilities between drugs and excipients. Figure 6 depicts the FTIR spectra of pure DAP, phospholipon® 90 G, Tween 80, and the selected DAP-loaded transferosomes (F6). The fourier transform infrared (FTIR) spectra of DAP displayed distinct absorption peaks at 3350.14 cm^{-1}, corresponding to the stretching of the hydroxyl (OH) bond; 2860.11 cm^{-1}, indicating the stretching of the carbon-hydrogen (C–H) bond; 1611.08 cm^{-1}, representing the stretching of the aromatic carbon-carbon (C=C) bond; and 1243.30 cm^{-1}, signifying the stretching of the ester (C–O) bond. The FTIR spectra of the formula (F6) exhibited the expected FTIR bands associated with the medication, but with a notable reduction in intensity. It is suggested that there was no observed undesirable interaction between the drug and the excipients included in the formulations. The obtained result provides strong evidence supporting the compatibility of the elements included in the formulation[61].

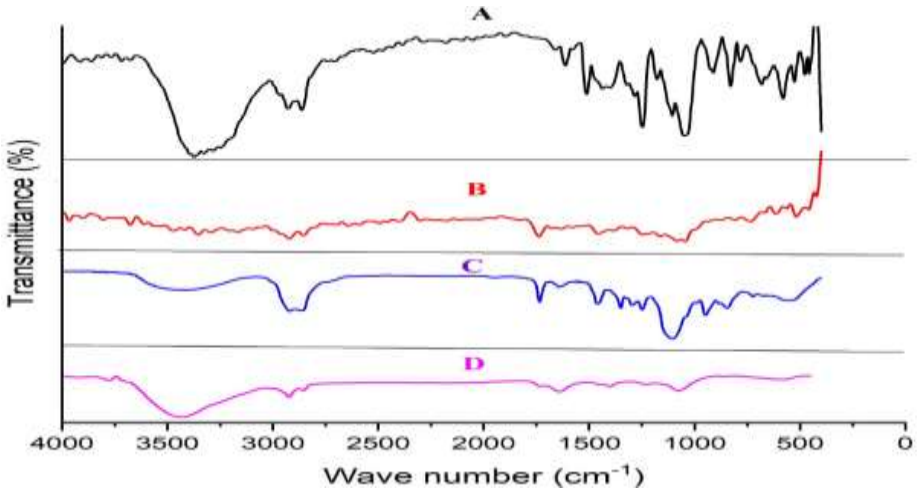

Figure 6. FTIR spectra of (A) pure DAP, (B) phospholipon® 90 G, (C) Tween 80 and (D) the selected DAP-loaded transferosome (F6).

Surface morphology by scanning electron microscopy (SEM)

The surface morphology and size of the transferosomal dispersion (F6) were further verified by SEM as shown in Figure 7. The shape was found to be spherical and nano-sized indicating the suitability of the method and components used[62].

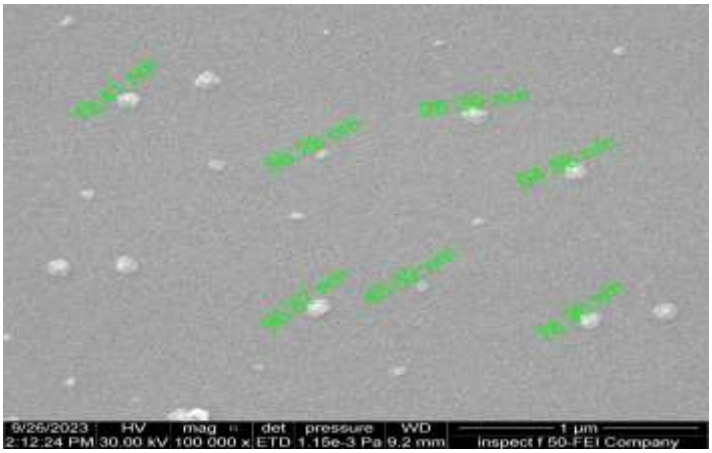

Figure 7. SEM of the selected DAP-loaded transferosomal dispersion (F6)

Stability study of DAP-loaded transferosomal dispersion

The entrapment efficiency of the DAP-loaded transferosomal dispersion and their size were assessed at refrigerator temperature (4±2° C) and room temperature (25±2° C) during a period of 1, 2, and 3 months, as seen in Table 7. The findings indicated a statistically non-significant reduction in entrapment and a statistically non-significant rise in transferosomes diameter over the course of three months, with a $p > 0.05$. The observed phenomenon of transferosomal vesicles increasing in size over time has been attributed to the propensity of these vesicles to undergo coalescence, which is driven by the weak van der Waals and cohesive forces acting within the vesicles[63].

Table 7. Stability study for the selected transferosomal dispersion formula (F6) under different temperature (4±2 C° and 25±2 C°), values are mean±SD (n=3)

Parameter	Initial	4±2° C			25±2° C		
		Month 1	Month 2	Month 3	Month 1	Month 2	Month 3
EE%	93±0.77	93±2.33	92.5±1.2	92.2±1	92.3±1.1	91.8±0.8	91.1±0.6
Vesicle size	105.8±1.61	107±1.3	110.4± 0.9	112.7± 0.8	109.2± 1.6	112.5± 0.4	114.92±1
pH	6.7±0.14	6.7±0.19	6.7±0.3	6.6±0.2	6.5±0.6	6.3±0.41	6.1±0.17
Drug content	99.7±1.68	99.1±1.4	98.3±2.1	97.9±0.9	98.4±2.6	98.2±3.1	97.1±1.2

Over a period of three months, a decline in pH levels was observed mostly in samples stored at room temperature. Nevertheless, the decline in pH remained within the optimal pH range of 4.5-7 for semi-solid preparations[64]. The results were in agreement with the results of the capsaicin transferosome stability study[65]. The results of the drug content study showed that there was a minimal reduction in the drug content percent, specially, at refrigerator temperatures.

The results of the stability study indicate that the transferosomal dispersion formula (F6) was stable and no significant changes were observed.

Conclusion

DAP-loaded transferosomal vesicles were successfully prepared, characterized, and evaluated. The thin film hydration method was considered a suitable method of preparation. Tween80 was found to be an appropriate edge activator to incorporate the hydrophilic drug DAP into the transferosome. This work succeeded in preparing a transferosomal dispersion with a phospholipid:EA ratio of 95:5 %w/w with optimum drug release and drug permeation profile to be dispersed as a transdermal patch (10cm^2) applied once daily that could be a very promising alternative for oral treatment with lower hypoglycemic risk.

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Conflicts of Interest

The authors declare there are no conflicts of interest.

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Ethics Statements

The study protocol was approved by the Ethics Committees of the College of Pharmacy/Mustansiriyah University (approval No. 18, Research No. 18).

Author Contribution

The authors confirm the contribution to the paper as follows: study conception and design: Mohsin and Nidhal; formulation, analysis and interpretation of results and draft manuscript preparation: Mohsin; supervision and review: Nidhal. Both authors reviewed the results and approved the final version of the manuscript.

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تحضير وتقييم داباجليفلوزين بروبانديول مونوهيدرات المحمل بالترانسفيروسوم المشتت للتوصيل عبر الجلد

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الخلاصة

حظي طريق توصيل الدواء عبر الجلد باهتمام كبير في الأبحاث الصيدلانية نظرًا لقدرته على التغلب على العديد من التحديات المرتبطة بإعطاء الدواء عن طريق الفم, وتشمل القدرة على تجاوز عملية الايض للمرور الأول، مما يضمن فترة عمل أطول وأكثر قابلية للتنبؤ بها، فضلاً عن تقليل حدوث الاعراض الجانبية. تعتبر الترانسفيروسومات نوعًا من الحويصلات الدهنية شديدة التشوه، والتي لديها القدرة على تقديم العديد من الفوائد مقارنة بالحويصلات الدهنية التقليدية مثل اللايبوسوم. كان الهدف الأساسي من هذه الدراسة هو إعداد (للمرة الاولى) ترانسفيروسومات محملة بالداباجليفلوزين بغرض تقليل المخاطر المحتملة لفرط سكر الدم المرتبط بالإعطاء عن طريق الفم لعلاج مرض السكري. تم تحضير الجسيمات الناقلة بطريقة ترطيب الأغشية الرقيقة باستخدام ٥ ملغ من الدواء ونسب مختلفة من الفوسفوليبيد و منشطات الحواف. تم فحص الناقلات من حيث كفاءة الانحباس، ومحتوى الدواء، ودرجة الحموضة، وحجم الجسيمات، ومؤشر التشتت المتعدد، وإمكانات زيتا، واللزوجة، وتحرير الدواء، ونفاذ الدواء عبر الجلد، والأشعة تحت الحمراء و المجهر الإلكتروني الماسح. ترانسفيروسوم (F6) قائم على توين ٨٠ عند نسبة ٩٥:٥٪ وزن/وزن من الفوسفوليبيد:منشط الحواف, أعطت أعلى نسبة احتباس (93±0.77%)، ومحتوى الدواء (٩٩,٧±١,٦٨٪)، وتحرير دواء خلال ٢٤ ساعة (99±1.4٪)، حجم الجسيمات (١٠٥,٨±1.61نانومتر)، ومؤشر التشتت المتعدد (0.436±0.01)، اللزوجة (155±1.95 سنتي بويز)، وإمكانات زيتا (-٣٥,١٥ مللي فولت)، لذلك تم اختيارها كصيغة مثالية. كان للصيغة نفاذية جيدة عبر الجلد بعد ٢٤ ساعة (٢٨٩,٨±5.2 ميكروغرام / سم٢، ما يعادل ٩١٪)، ومكونات دوائية متوافقة وفقًا للأشعة تحت الحمراء ، وحويصلات كروية بحجم النانو وفقًا للمجهر الإلكتروني الماسح. كشفت ثلاثة أشهر من اختبارات الثبات وفقًا لإرشادات ICH أن التركيبة كانت مستقرة عند ٤ ± ٢ درجة مئوية و٢٥ ± ٢ درجة مئوية. في الختام، اقترح هذا البحث أنه يمكن تحضير الترانسفيروسوم كنظام توصيل للدواء عبر الجلد مع خصائص مناسبة ليتم إعطاؤها مرة واحدة يوميًا كلصقة عبر الجلد للعقار المضاد لمرض السكر داباجليفلوزين.

الكلمات المفتاحية: داباجليفلوزين, منشط الحواف, كفاءة الانحباس, سبان ٦٠, ترانسفيروسوم, توين ٨٠