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Comparison study between tween 20 and tween 80 as an edge activator for preparation of transdermal ondansteron HCL transfersomal nano particles

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ABSTRACT

In ordinary clinical practice, poor patient compliance with oral and parenteral drug administration modalities is a prevalent problem. As a result, pharmaceutical research has developed a strong interest in the transdermal route of drug delivery. They are noninvasive, self-administered administration techniques that can improve patient compliance. However, the barrier function of the skin's top layer presents the biggest challenge for transdermal delivery systems. Ionized chemicals and compounds with molecular weights greater than 500 Da cannot pass through skin. As a result, this method can only be used to deliver a few medicines. A possible solution to this issue is to include the medications in transfersomes. Transfersomes are vesicles composed of phospholipids and edge activators, used to transport drug from outer skin layer into the systematic circulation through a semipermeable membrane. Tween 20, 80 (Polysorbates) are edge activators employed in medicines for a variety of reasons, including modifying the absorption of active ingredients. Ondansetron is an antiemetic medication that has been given parenterally and orally. Formulating this medication as transdermal transfersomes may provoke a great advantage in medical adherence.

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INTRODUCTION

Transdermal Drug Delivery Systems

Transdermal Drug Delivery Systems (TDDS) is a painless method of systemically delivering pharmaceuticals that involves applying a drug formulation to intact and healthy skin. The medication first passes through the stratum corneum without collecting in the dermal layer and then into the deeper epidermis and dermis. Once the medicine reaches the dermal layer, it is ready for systemic absorption. It can be utilized as a noninvasive substitute for parenteral procedures, eliminating the fear of injection. Because of the enormous surface area of skin and ease of access, a range of transdermal absorption and placement options are available,[1] As seen in figure 1.

Advantages of TDDSs

Transdermal delivery systems have gained much interest due to their advantages compared to conventional oral and parenteral delivery systems. These advantages could be summarized as[3]:

- Patient compliance is often high (no needle anxiety, no chance of complications from inadvertent needle jabs, no need to ingest tablets, and fewer side effects).
- Long-term drug delivery (advantageous in long-term drug therapy and for patients who forget to take their medications regularly).
- Avoidance of metabolism and interactions in the gut and liver (beneficial for medicines with a robust first-pass impact, nausea, interactions with food and other pharmaceuticals, or inactivation in the GI tract)
- TDDS has had a considerable impact on administering various therapeutic drugs, particularly in pain management, hormone therapy, and the treatment of cardiovascular and central nervous system illnesses.

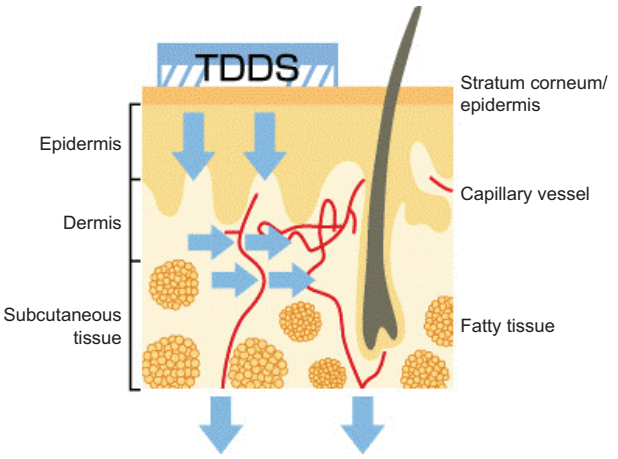

FIG 1. Transdermal Drug Delivery Systems.[2]

Limitation of TDDSs

Some limitations are associated with TDDS, including[4];

- The intrinsic skin barrier prevents it from reaching its full potential. The epidermis, which protects the skin, and the dermis, which contains blood vessels and creates skin cells, are two layers of skin that include features that interfere with the transdermal distribution.
- Difficult to prepare and stabilize procedure
- Plasma level affected by the site of application
- For high-dosage medicines, TDDS is not indicated and is not suitable for potent doses.

Drugs with a low molecular weight (less than one kDa), a preference for both lipophilic and hydrophilic phases, a short half-life, and minor skin irritation are better for transdermal administration and therapeutic effectiveness. Species variations, skin age and site, skin temperature, condition of the skin, application area, exposure time, skin moisture content, and pretreatment and physical features of the penetrant are all factors that impact medication penetration of the skin.[1]

Transferosomes

Transferosomes are vesicular carrier systems that feature at least one inner aqueous compartment

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encompassed by a lipid bilayer and an edge activator. This aqueous core is enclosed by a lipid bilayer, resulting in ultra-deformable vesicles that may self-optimize and regulate themselves.[5] As a result, transferosomes are elastic. They may bend and squeeze themselves as whole vesicles without discernible loss via tight pores or skin constrictions substantially less than the vesicle size,[6] As seen in Figure 2;

Advantages of Transfersomes

Transfersomes have a peculiar structure that allows hydrophilic, lipophilic, amphiphilic, and charged hydrophilic medicines to be entrapped. The transfersomal carrier system allows low- and large-molecular weight medicines to permeate the skin. These systems provide a number of benefits;[2,8–9]

- Transfersomes can distribute drugs in a regulated and targeted manner.
- The capacity of transfersomes to release the medicine in a sustained way for a more extended period is a desirable characteristic.
- Transfersomes can deform and infiltrate the deeper layer of the skin via the stratum corneum's slight constriction because of their flexible and elastic nature.
- Its size might shrink by 5–10 times upon penetration compared to its original size.
- Transfersomes have high entrapment efficiency and can preserve the medication entrapped from metabolic breakdown. By avoiding first-pass metabolism, which is a significant limitation in oral medication delivery, the drug's bioavailability is improved.
- These vesicles are biocompatible and easy to eradicate from a biological system since the main chemicals utilized in creating transfersomes are naturally accessible.

Limitations of Transfersomes

In spite of the many advantages of transfersomes, there are few limitations to its use.[2]

- They are prone to oxidative deterioration, which makes them chemically unstable.

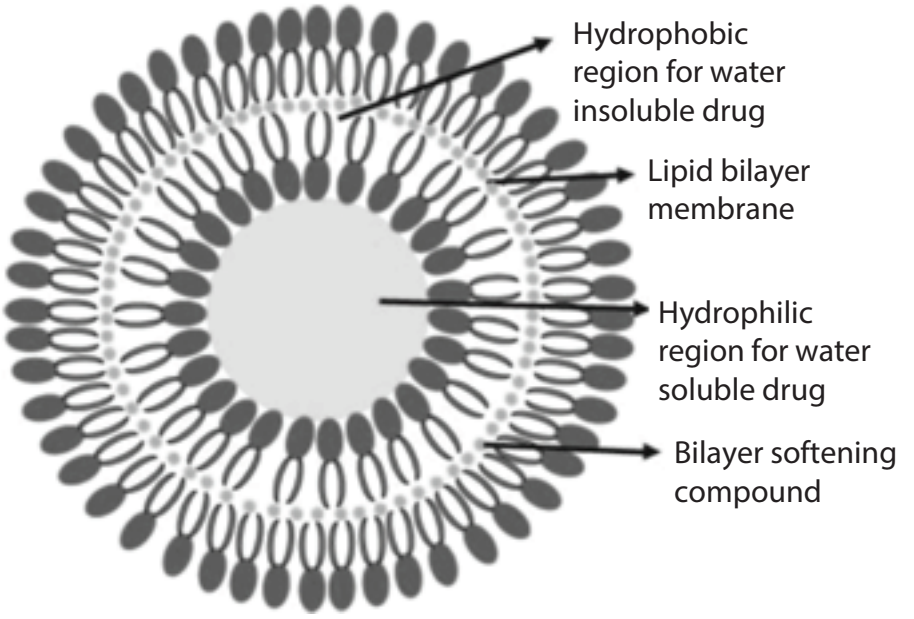

FIG 2. Structure of transfersome.[7]

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- Because it is challenging to maintain the purity of natural phospholipids, transfersomes are not widely used as drug delivery systems.
- The price of these formulations is high.

Mechanism of Action

Vesicles are colloidal particles consisting of an aqueous compartment surrounded by a concentric bilayer of amphiphilic molecules. They're great for vesicular drug delivery because hydrophilic pharmaceuticals are contained in the inner aqueous chamber, while hydrophobic drugs are confined to the lipid bilayer.

Transfersomes are extremely deformable (ultra-flexible) and self-optimizing new drug carrier vesicles, with membrane flexibility, hydrophilicity, and the capacity to retain the vesicle's integrity being the most critical factors in their passage over the skin.[11,12]

Composition of Transfersomes

The transfersome is made up of these two major aggregates:[5,13,5]

- Amphipathic ingredients, such as phosphatidylcholine, self-assemble to form lipid bilayers in aqueous solvents and then close into straightforward lipid vesicles.
- Surfactants, such as sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65, and Span 80), and dipotassium glycyrrhizinate, which are biocompatible bilayer-softening substances that increase the vesicles' bilayer flexibility and improve the permeability, are the most frequently used edge activators in transfersome preparations.
- The solvent is either water or a saline phosphate buffer, while the hydrating medium contains roughly 3–10% alcohol (ethanol or methanol) (pH 7.4)

Ondansetron Hydrochloride

Ondansetron (OND) is a potent and specific 5-HT3 receptor antagonist. Its ability to counteract retching and vomiting caused by chemotherapy and radiation in animals and humans was the first indication of its antiemetic properties.

Ondansetron was created in the 1980s by GlaxoSmithKline and has been recognized as safe and effective by the US FDA since January 1991.[15]

Ondansetron Hydrochloride's Physicochemical Features

Some of ondansetron Hcl properties are shown in Table 1.[16,17]

Dosage Forms of Ondansetron

Ondansetron doses of 4–8 mg can be administered intravenously or orally every 8 hours. When taken as a pill, ondansetron disintegrates in the stomach. Injection: 2 mg/mL (2, 20 mL).[14]

MATERIALS AND METHODS

Materials

Ondansetron Hydrochloride was a gift from the Pioneer Company; Sodium deoxycholate and Phosphatidylcholine (99% purity) were from Lipoid-Germany; Ethanol, (China) Methanol, (China) Polyoxyethylene sorbitan monooleate (Tween 80), Polyoxyethylene sorbitan monolaurate (Tween 20), (CDH, India), Sodium dihydrogen phosphate, Sodium chloride, and Poloxamer 407 polymer (China).

Methods

Preparation of Transfersomes

See Figure 4.

Vesicles Optimization

Effect of Tween 20

The influence of the concentration of tween 20 transfersome features was examined by using

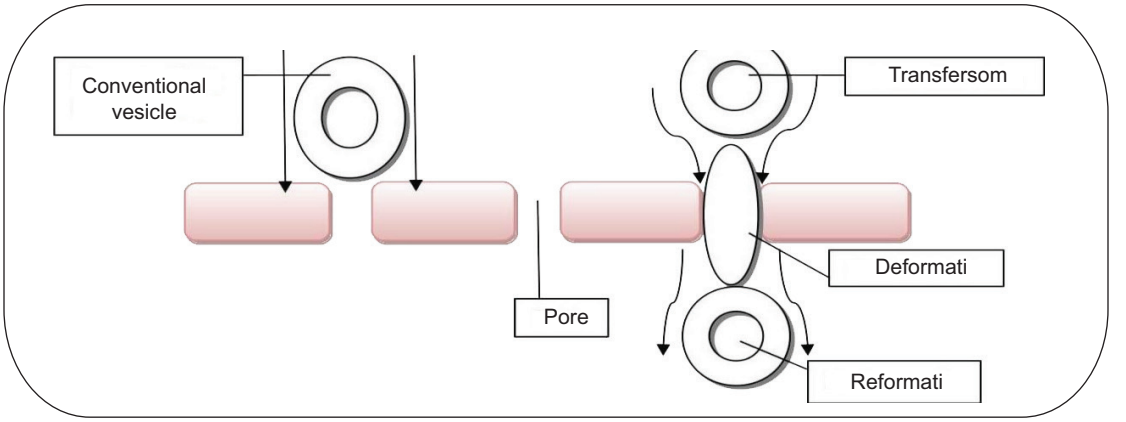

FIG 3 Mechanism of transfersome penetration through the skin[10]

TABLE 1. Physiochemical properties of ondansetron hydrochloride.

Gross appearance	Powder
Color	Off-white to white powder
Physical description	Solid
Structural formula	C18H19N3OHCl2H2O
Molecular weight	329.824
Melting point	178.5–179.5ºC
Solubility	Sparingly soluble in water Very soluble in acid solutions
Brand name	Zofran®, Zuplenz®
Log p	2.07
Pka	7.4

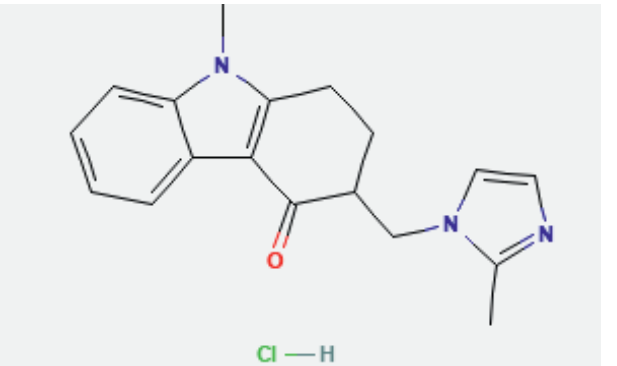

FIG 3. Chemical structure of ondansetron Hcl.[16]

a fixed amount (300 mg) of phosphatidylcholine, SDC (sodium deoxycholate) (85), and ondansteron Hcl (20 mg), and an increasing amount of tween 20 (0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 mg) w/w as stated in Table 2, formula from (F1 to F6)

Effect of Tween 80

Employing a fixed amount of phosphatidylcholine (300 mg), SDC (85), and Ondansteron Hcl (20 mg), and an increasing amount of tween 80 (0.1, 0.2, 0.3, 0.4, 0.5, and 0,6 mg) w/w), As stated in Table 2, formula from (F7 to F12).

Characterization of Transfersomal Vesicles

See figure 5.

Preparation of Skin

Rabbit skin in phosphate buffer (Ph 7.4) solution was utilized for in vitro drug testing. Fresh rabbit skin was taken from the animal·s house and utilized for the penetration test. The rabbits were then killed by breathing in chloroform. The abdomen skin was dehaired, and the skin was moisturized with normal saline solution. The adipose tissue layer of the skin was massaged away with a piece of cotton immersed by diethyl ether. Skin was maintained in a regular saline solution at 0–4°C. Human

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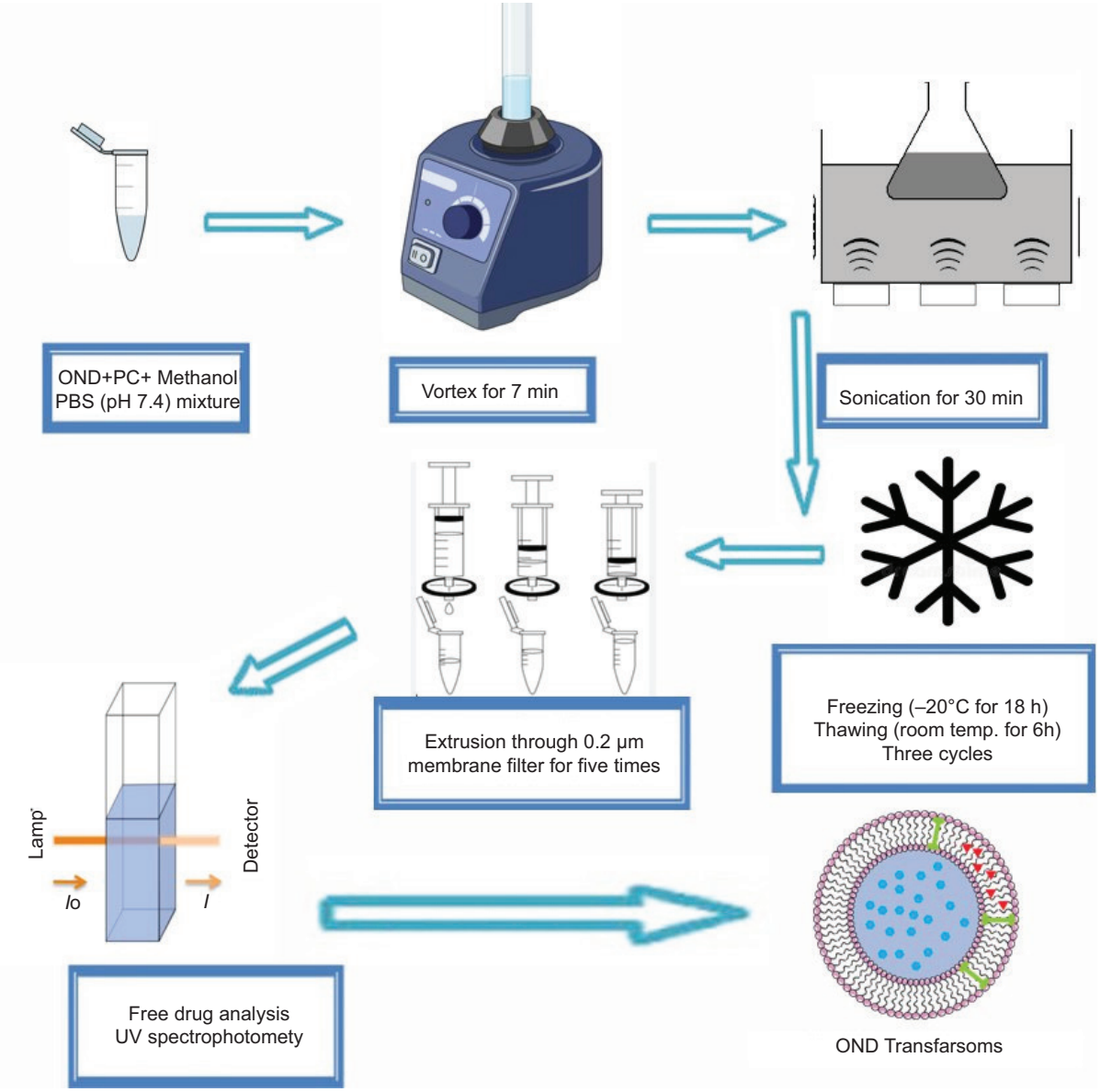

FIG 4. Preparation of Transfersomes by the Vortexing Sonication Method.

skin was not employed in this investigation due to limited resources and a substantial logistical effort. Despite the acknowledged distinctions between the properties of human and rabbit skin, pertinent results could be obtained utilizing rabbit skin rather than human skin. We used male rabbits that were "obtained from the animal home" and weighed between 3.2 and 4.2 kg.[18,19]

Preparation of Nano-Transfersomal Gel

The best nano-transfersomal dispersion formula (F 4) was used to make gel formulations containing 1% Ondansetron HCl using gelling agents (gel bases) in a ratio (1:1) dispersed transfersomal gel. This was accomplished by utilizing Combine the gelling agent and the selected mixture using a spatula and a magnetic stirrer until a uniform, smooth gel was obtained.

TABLE 2. Formula Prepared By Tweens 20 and Tweens 80 as Edge Activator.

No	Phosphatidylcholine (mg)	Ond (mg)	Tween20 (mg) w/w	Tween80 (mg) w/w	SDC
1	300	20	0.1		85
2	300	20	0.2		85
3	300	20	0.3		85
4	300	20	0.4		85
5	300	20	0.5		85
6	300	20	0.6		85
7	300	20		0.1	85
8	300	20		0.2	85
9	300	20		0.3	85
10	300	20		0.4	85
11	300	20		0.5	85
12	300	20		0.6	85

Statistical Analysis

The findings of all experiments were evaluated using one-way ANOVA, Microsoft Excel 2019 with significant results equaling ($p< 0.05$) and nonsignificant results equaling ($p<0.05$). The results of all experiments were taken as mean samples with standard deviation.

RESULT AND DISCUSSION

Nano-Transfersomal Dispersions' Preparation and Characterization

The Vortexing Sonication method was used to generate all formulations (F1–F12) of the nano-transfersomal dispersion of Ondansetron Hcl using phospholipids such as phosphatidylcholine and soya and egg lecithin along with various types and ratios of edge activators.

Physical Appearance

The formulas (F1–F12) presented as a homogeneous milky dispersion as seen in Table 3 represent all formula proprieties

Entrapment Efficiency

The entrapment efficiency *EE%* of the Ondansteron Hcl nanotransfersomal dispersion formulae. The great majority of the formulae showed acceptable entrapment efficiency, proving the viability and dependability of the vortexing technique employed in their creation. Furthermore, the outcomes supported existing findings that suggested that this technique might be utilized to create a variety of lipid-based vesicles. On the effects of several factors on the success of trapping, more research was conducted.

Effect of Tween 20 as EA on Entrapment Efficiency

In formulations (F1–6), As seen in Table 2, the entrapment efficiency of Ondansetron Hydrochloride inside the formulated lipid carrier was generally increased gradually with increasing of Polysorbate 20 (tween-20) contents (Figure 8). After incorporation of tween-20 at concentrations of 0.3, 0.4, 0.5, and 0.6 mg along with sodium deoxycholate (at 85 mg), the entrapment efficiency of Ondansetron Hydrochloride was increased significantly ($p < 0.05$) to 70.0, 80.0, 82.0, and 83.0%, respectively, when compared to that seen with sodium deoxycholate alone (65.0%) (Figure 8). No significant changes ($p > 0.05$) were obtained after the treatment of lipid carrier with Tween-20, at 0.1 and 0.2 mg, respectively, when compared with the untreated sample, in the presence of sodium deoxycholate.

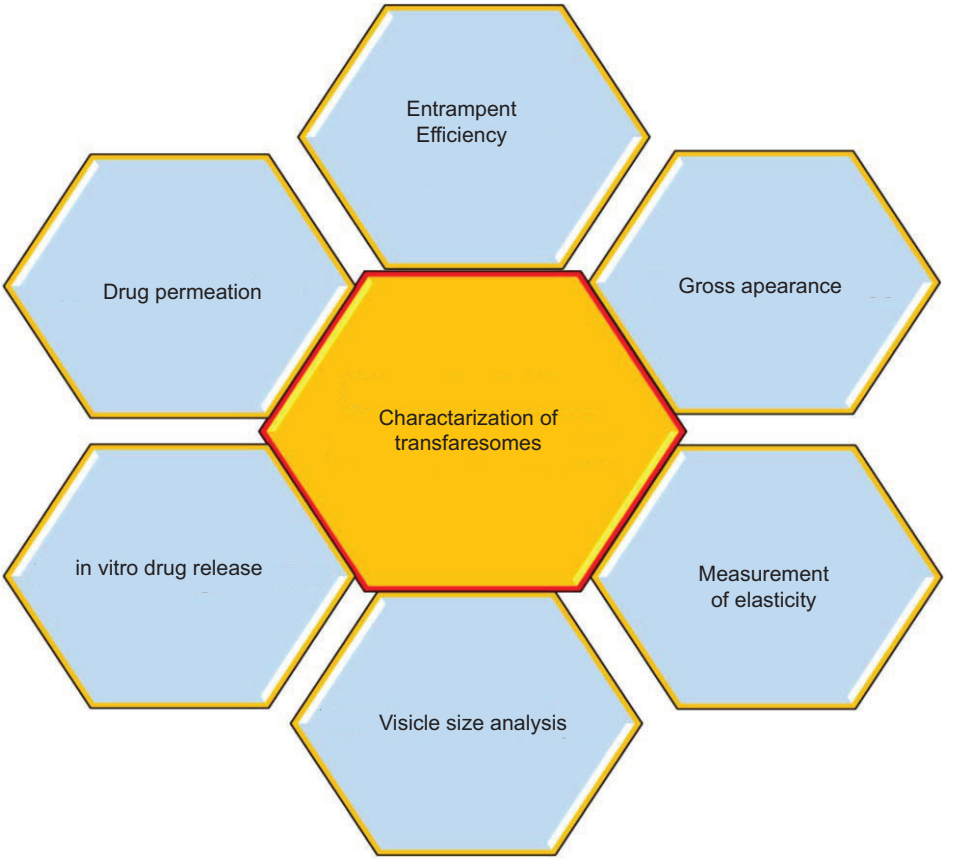

FIG 5. Characterization of Transfersomal Vesicles.

Effect of Tween 80 as EA on Entrapment Efficiency

The effect of transfersome with Polysorbate 20 (Tween-80) on entrapment efficiency were also investigated at different doses. In formula-F19-F 24 (As seen in table 2-3), levels of the entrapment efficiency of Ondansetron hydrochloride inside formulated transfersome were significantly (p<0.05) lower than seen with sodium deoxycholate alone (65.0%) by 30%, 54%, 58%, 60% and 62% after incorporation of tween-80 at concentrations of 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg and 0.5 mg , respectively (Figure 9).

However, the incorporation of tween-80, at 0.6 mg, in the presence of the sodium deoxycholate (at 85 mg), into the lipid matrix significantly ($p < 0.05$) caused elevation in entrapment efficiency of drug up to 83.0% when compared to that seen with sodium deoxycholate alone (65.0%) (Figure 9).

The proportion of Tween-20 and Tween-80 ranged from 0.1 till 0.6% (Figures 2 and 7). On the whole, drug entrapment efficiency is improved when higher concentrations of Tween-20 and Tween-80 are employed (usually up to 0.6%). On the other hand, ratios of 0.1, 0.2, 0.3 0.4, and 0.5%, in the case of Tween-80, led to lower drug encapsulation (from 65.0 to 30–50%). For this reason, the lipid bilayer of the Ondansetron Hydrochloride–loaded transfersome became disrupted and more leaky releasing the encapsulated Ondansetron Hydrochloride. A mixed matrix can co-exist with the formulated lipid carrier when the Tween-20 and Tween-80 exceeds 15% of the total composition, leading to partial

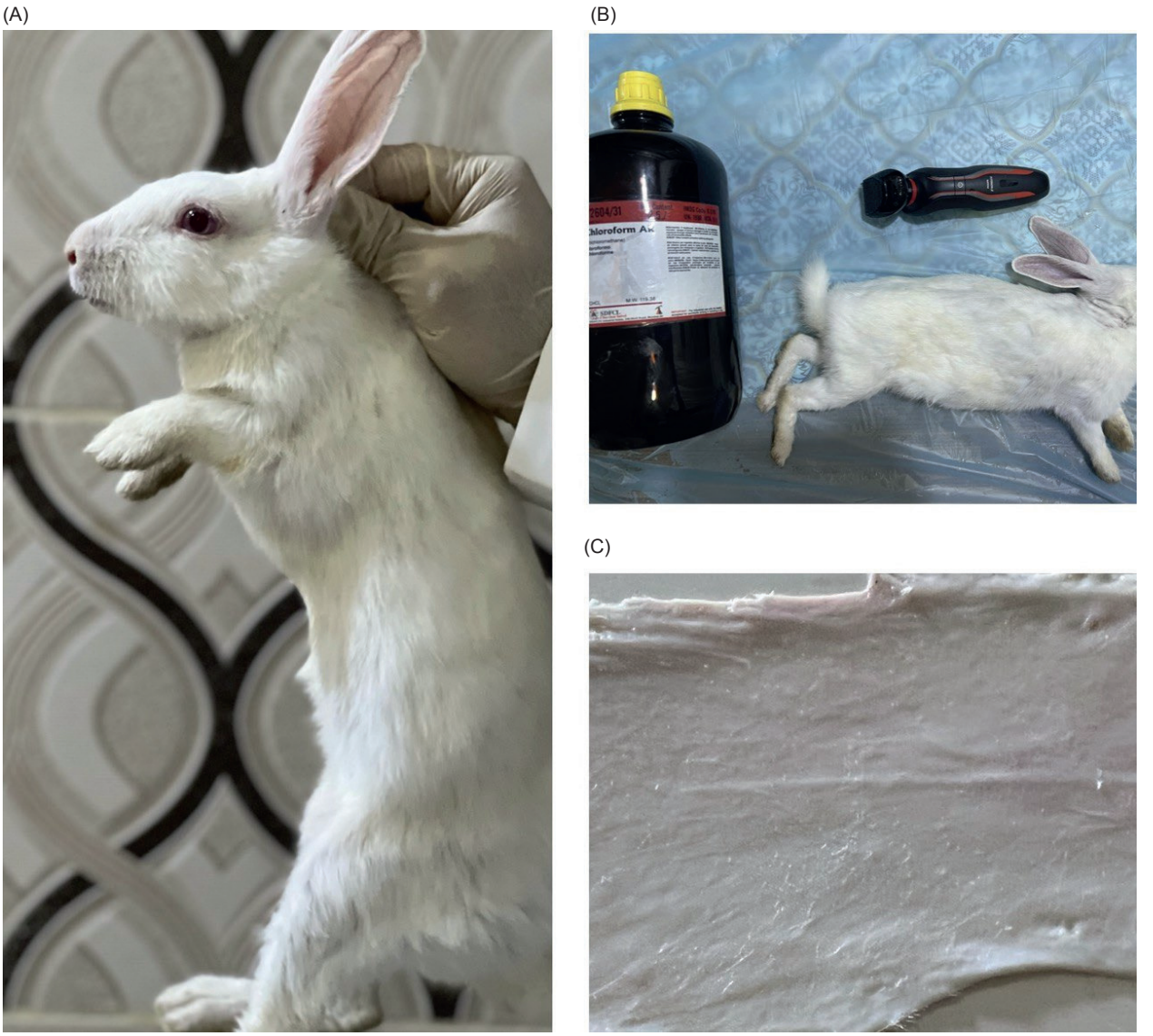

FIG 6. Process of obtaining rabbit skin. (A) Albino male rabbit, (B) Shaving rabbit skin using clipper, and (C) Rabbit skin after defatting and processing.

drug entrapment contained by small size micelles and hence, lower compound encapsulated within the transferosomes.[20,21] Highest encapsulation efficiency with higher elastic time were observed when sodium deoxycholate was used as edge activator at 100 mg (1.7-fold higher entrapment efficiency than using sodium deoxycholate at 40 mg). Overall, Ondansetron Hydrochloride–loaded transfersome including sodium deoxycholate have resulted in better permeation.

Vesicle Size Analysis

Light microscopy was used to determine the size and shape of the chosen nanotransfersomal formulae (F4), as shown in figure 10. Even after mechanical stress, the vesicular structure

TABLE 3. Physical appearance of Ondansteron hcl Transfersomes Prepared from Various Phospholipid Types with the Addition of EA.

No.	Formula code	Color	Odor	Apparent viscosity	Physical appearance	Response extrusion
1	F 1	Milky emulsion	Pungent odor	Medium viscosity	Showed a significant amount of residues under light microscopy that do not form vesicles	Difficult to extrusion
	F 2					
	F 3					
2	F 4	Milky emulsion	Pungent odor	Medium viscosity	Showed a significant amount of residues under light microscopy that do not form vesicles	They need extra pressure
	F 5					
	F 6					
3	F 7	Milky emulsion	Pungent odor	Medium viscosity	Showed a significant amount of residues under light microscopy that do not form vesicles	They need medium pressure
	F 8					
4	F 9	Milky emulsion	Pungent odor	Medium viscosity	Showed a significant amount of residues under light microscopy that do not form vesicles	They need low pressure
	F 10					
5	F 11	Milky emulsion	Pungent odor	Medium viscosity	Showed a significant amount of residues under light microscopy that do not form vesicles	They need low pressure
	F 12					

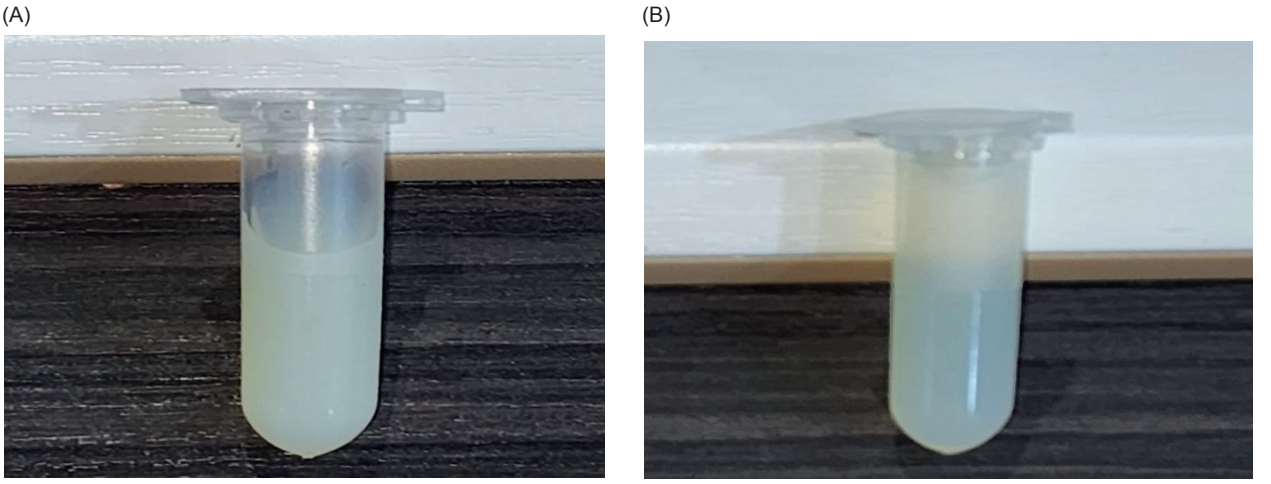

FIG 7. Physical appearance of Nano-transfersomal dispersion formulae. (A) phosphatidylcholine plus SDC 85 mg plus tween 20 0.4 mg (B) phosphatidylcholine plus SDC 85 mg plus tween 80 0.4 mg.

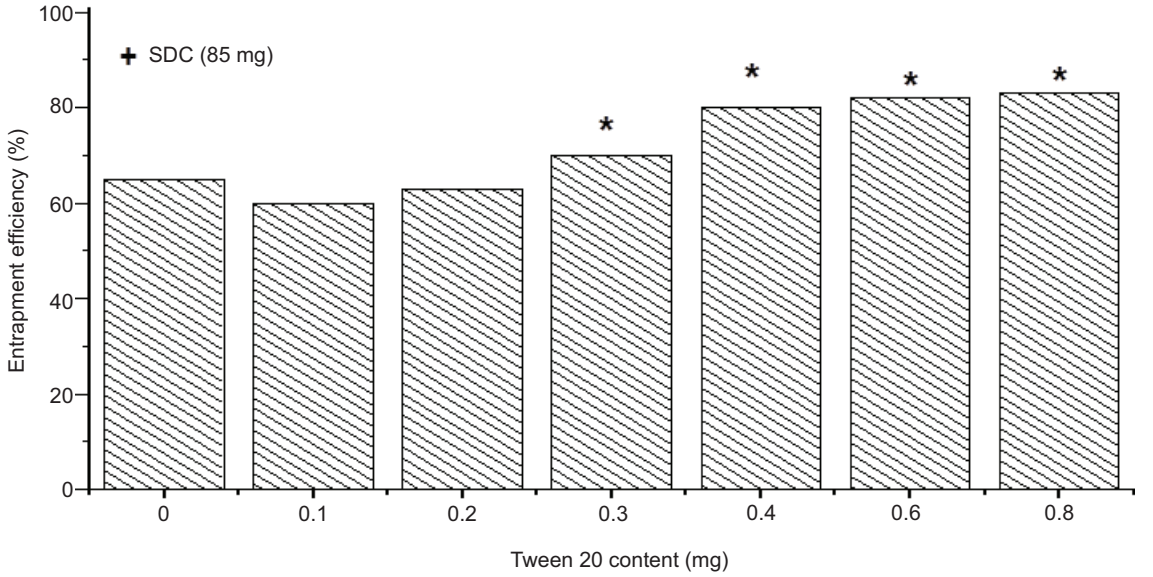

FIG 8. Effect of Polysorbate 20 (Tween-20), at different concentrations, on entrapment efficiency of Ondansetron Hydrochloride inside the formulated lipid carrier. Values are means ± standard deviations (n = 3). *P < 0.05 compared to control.

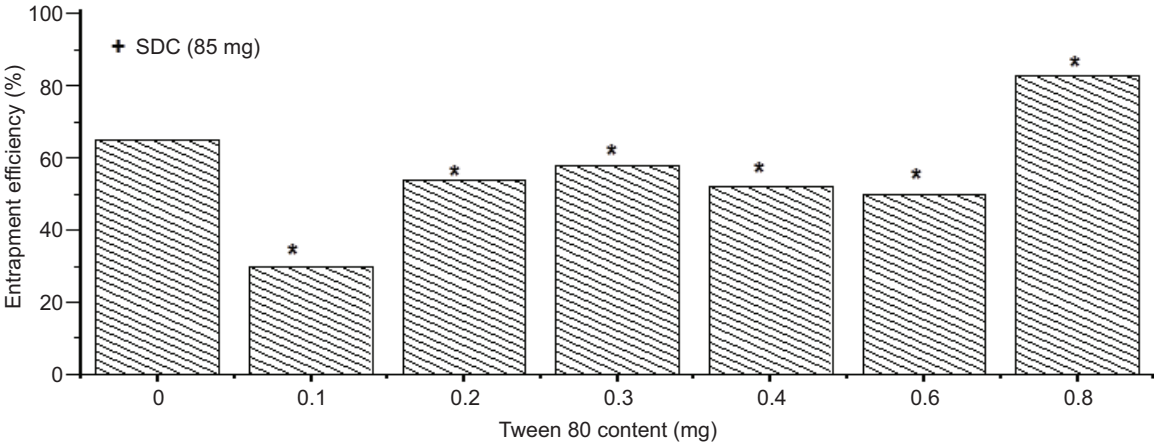

FIG 9. Effect of Polysorbate 80 (Tween-80), at different concentrations, on entrapment efficiency of Ondansetron Hydrochloride inside the formulated lipid carrier. Values are means ± standard deviations (n = 3). *P < 0.05 compared to control.

of the well-identified sealed spherical structure was not disrupted (sonication). It was discovered that phosphatidylcholin-containing formulations displayed more consistently spherical-shaped vesicles.

In Vivo Drug Release

The cumulative release profile of Ondansetron Hydrochloride from Ondansetron Hydrochloride–loaded transfersome in phosphate buffer solution PBS (pH 7.4) is shown in Figure 11. The Ondansetron

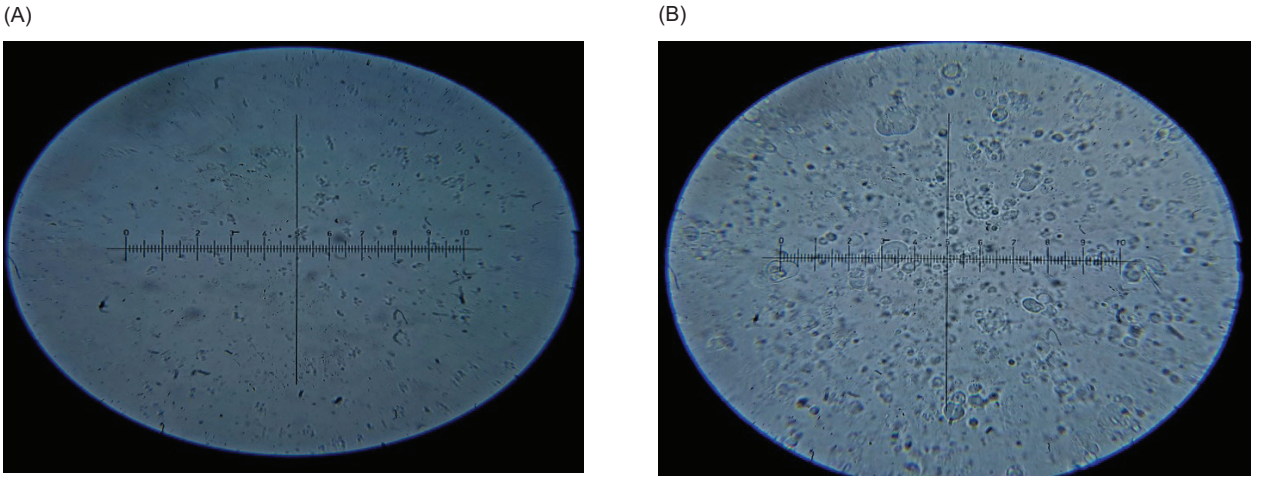

FIG 10. Light microscope examination of prepared formulae (A & B). Slide (A) contains SDC 85 mg in addition to 0.4 mg of tween 20, as seen in the microscopic examination. This formula had the best shape of vesicles with good properties. Slide (B) contains SDC 85 mg and tween 80 0.4 mg, as seen in the microscopic examination 400×. This formula had poor extrusion and high elasticity and raptured vesicles.

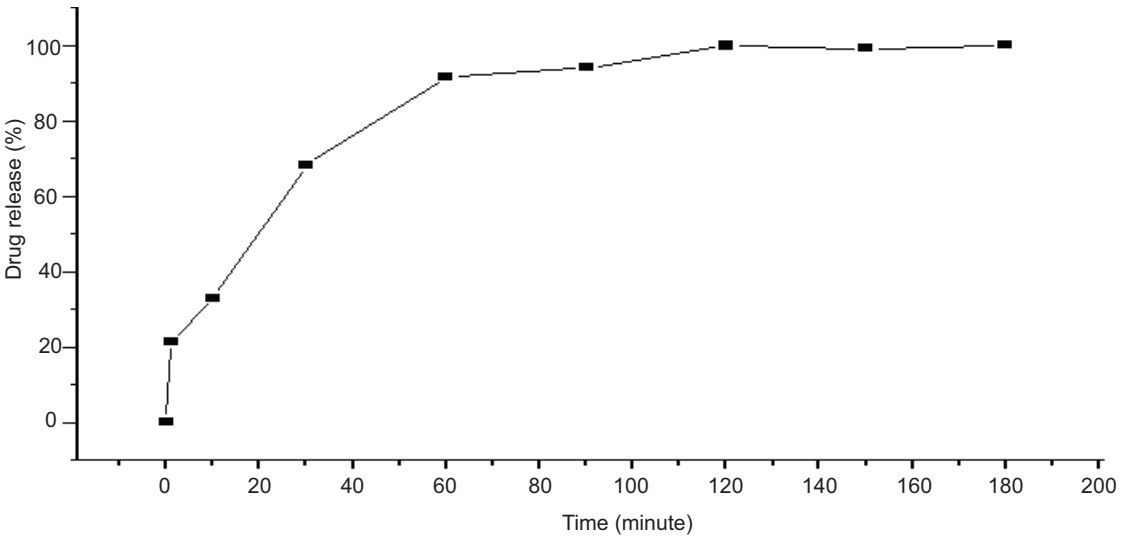

FIG 11. Release profiles of Ondansetron Hydrochloride from Ondansetron Hydrochloride–loaded transfersome in phosphate buffer solution PBS (pH 7.4). Values are means ± standard deviations (n = 3). *P < 0.05 compared to control.

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Hydrochloride–loaded transfersome showed sustained-release effects in phosphate buffer solution PBS (pH 7.4), with the total drug content released after approximately 180 minutes.

In phosphate buffer solution PBS (pH 7.4), the release rate within the first 10 minutes reached 32.95%. This first aliquot contained a large number of Ondansetron Hydrochloride, which induces the "burst effect." However, the Ondansetron Hydrochloride incorporated into transfersome gradually released the drug over time, in phosphate buffer solution PBS (pH 7.4) (Figure 11).

Drug Release Kinetics

To analyze the profile of drug release from prepared complex, software KinetDS 3.0 (Mendyk et al., 2012) matched with Matlab v. 7.3.0 (MathWorks. Inc.) was used. The results of drug release were fitted to different kinetic models as explained in chapter two.

The readings were fitted to nine models describing drug dissolution (See chapter two). In media, at pH of 7.4, the release profile of Ondansetron Hydrochloride did not follow the zero-order, first-order, second-order, Higuchi, KorsmeyerPeppas, Hixson-Crowell, Michaelis–Menten, and Hill. The kinetic model that best described the dissolution curves for our formulation was the Weibull model (Figure 12). This investigation allows for the characterization of mechanisms of drug release from the diffusion exponent. The Akaike information criterion, Bayesian information criterion, Schwarz criterion, Empirical R^2, and root-mean-squared error values were the best for describing the release kinetics of

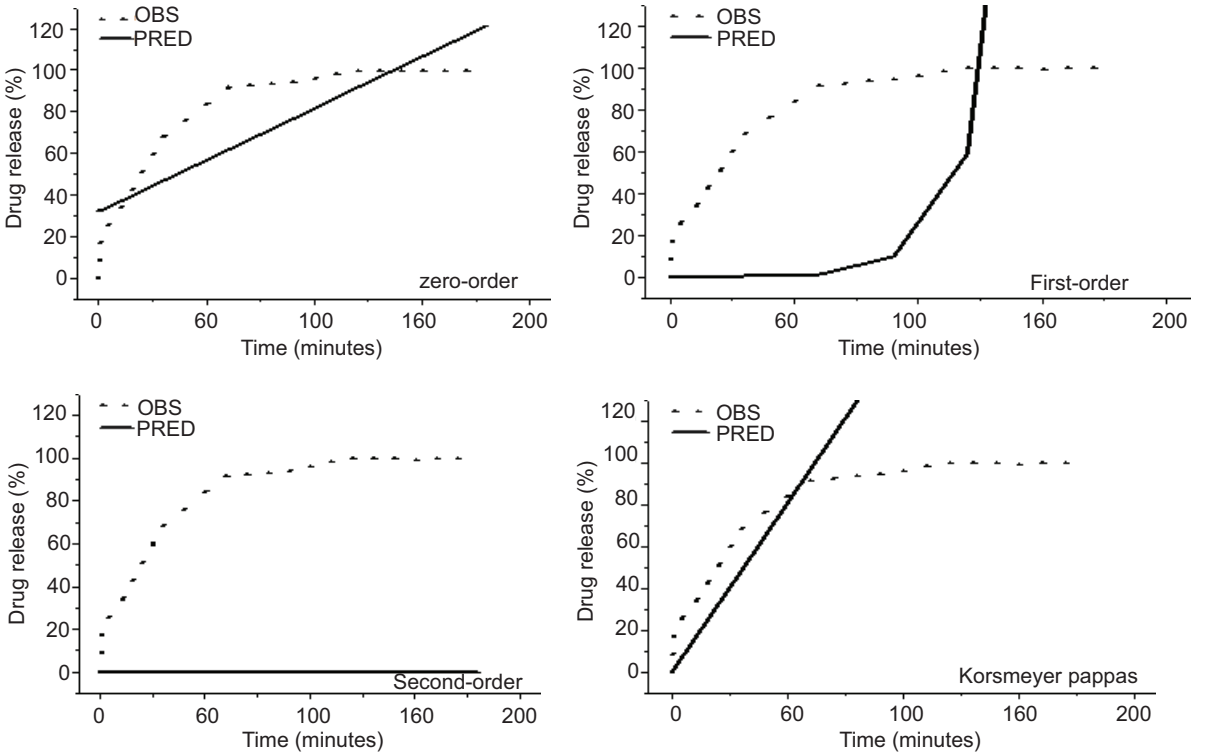

FIG 12. Kinetic models of Ondansetron Hydrochloride release from Ondansetron Hydrochloride–loaded transfersome in phosphate buffer solution PBS (pH 7.4). OBS = observed value, PRED = predicted value. Values are means ± standard deviations (n = 3). *P < 0.05 compared to control.

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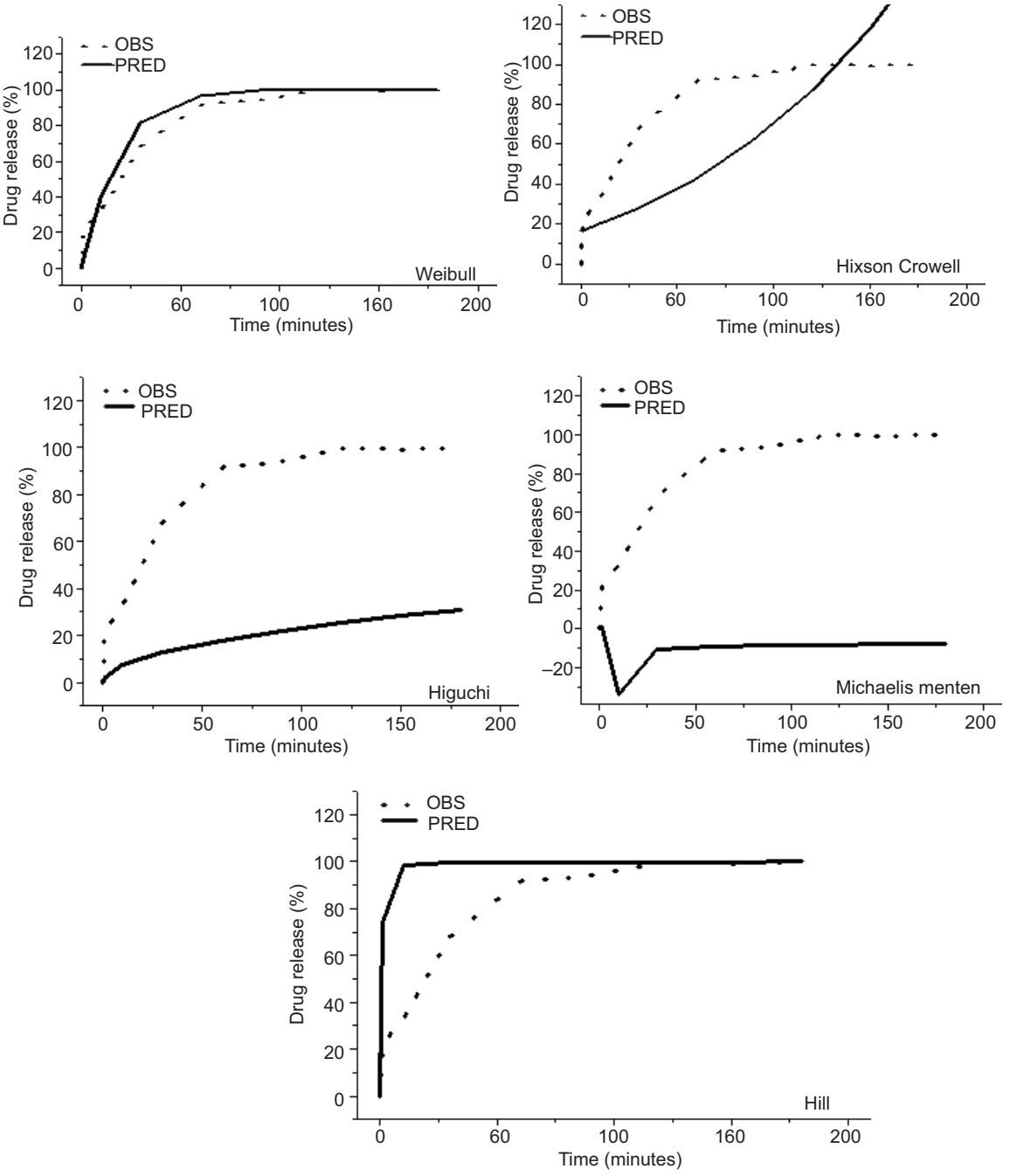

FIG 12. Continued

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Ondansetron Hydrochloride from our formulated transfersome (Table 4). The highest coefficient of determination R^2 and Empirical R^2, lowest Akaike information criterion, Bayesian information criterion, Schwarz criterion, and root-mean-squared error were 0.993304, 0.731548, 61.4628, 61.8572, 8.11542, respectively (Table 4). These findings produced the best model, which referred to the Weibull model.

Skin Permeation Test of Selected Formula

In this research, a permeation study was conducted to determine how transferosomes could improve the transdermal delivery of Ondansterone Hcl. The maximum Ondansteron Hcl penetration from the optimal formula (F4) through the skin of the rabbit was 84.21% after 240 minutes (4 hours), as shown in Figure 13. The reason behind medication's high skin penetration may be due to its greater connection with the lipid bilayer of transfersomal vesicles, which showed ultra-flexibility and ultra-deformability. This interaction may enhance the drug's activity. The graph shows that Ondansteron Hcl penetration through the skin increased significantly ($P < 0.05$) after application of the transfersomal gel mixture (F4), with a cumulative permeated amount of 1 mg/3 cm^2 over a period of 6 hours.

According to the results of permeation investigation, Ondansteron Hcl can be delivered using transfersomal gel formula in 1 mg/3 cm^2 with sustained release over a period of 6 hours. This method, when applied to patients, may increase the bioavailability of medications, patient compliance, and adherence to therapy while preventing the GIT side effects associated with oral delivery.

CONCLUSION

In this study, it was concluded that addition of tween 20 as edge activator with SDC to the formula had a greater effect on entrapment efficiency, elasticity time, physical appearance, drug release, and drug permeation than the addition of tween 80 alone or with SDC, which showed decreased permeability and unstable integrity of the vesicle membrane with greater number of raptured vesicles and decreased entrapment of the drug inside the transfersomes.

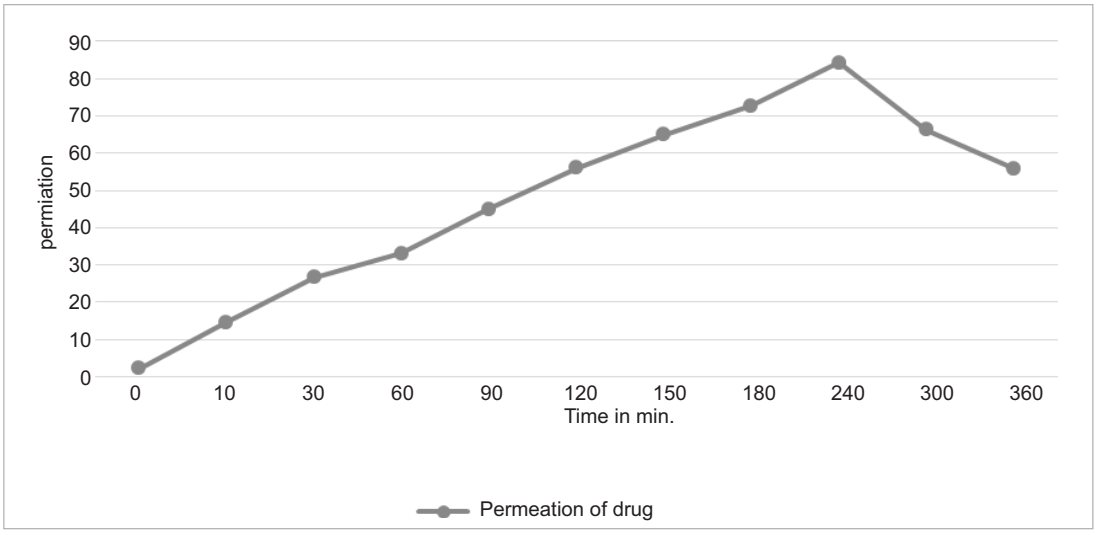

FIG 13. Permeation of Ondansetron Hydrochloride from Ondansetron Hydrochloride–loaded transfersome in phosphate buffer solution PBS (pH 7.4).

TABLE 4. Data-fitting for ondansetron hydrochloride release from ondansetron hydrochloride–loaded transfersome in phosphate buffer solution PBS (pH 7.4).

Model	Slope	Intercept	R^2	R^2emp	RMSE	AIC	BIC	*k*
Zero-order	0.494350	32.2721	0.724307	0.724307	19.3822	77.1334	77.5278	–
First-order	0.0593957	–3.04968	0.193792	–3.06230	668.1918	140.9	141.3	–
Second-order	–19594776.35673	2506694627.20095	0.157003	–204399429064057 0.00000	76.9174	101.9442	102.3387	–
Korsmeyer-Peppas	0.99760	0.48637	0.98472	–0.03840	18.8744	22967.2	22978.1	1.62641
Weibull	1.05730	–3.07072	0.993304	0.731548	8.11542	61.4628	61.8572	21.5573
Hixson-Crowell	0.0157050	2.55223	0.473765	–2.94283	31.8350	86.0652	86.4597	0.0157050
Higuchi	0.500000	0.832658	0.00000	–1.461324	57.9127	96.8359	97.2303	2.299423
Michaelis-Menten	1.00000	–0.129804	1.00000	–0.0430638	85.9418	103.9411	104.3355	–7.70395
Hill	1.311510	1.054930	0.659122	–1.789107	30.0759	85.0421	85.4365	0.348217
MTD	26.6865	–	–	–	–	–	–	–
DE	85.1741	–	–	–	–	–	–	–
No. of timepoints	9	–	–	–	–	–	–	–

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