ORIGINAL RESEARCH

Proniosomal Telmisartan Tablets: Formulation, in vitro Evaluation and in vivo Comparative Pharmacokinetic Study in Rabbits

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Objective: The purpose of this study was to prepare proniosomal vesicles of Telmisartan (TEL) to be compressed into tablets which will be further evaluated in vitro and in vivo.

Materials and Methods: An experimental design was adopted using surfactants of different HLB values (span 40-brij 35), different cholesterol ratios (20–50%) and different phospholipid types (egg yolk-soyabean). Different responses were measured followed by tablet manufacturing. The highest EE was shown in F3 (85%) while the lowest value was obtained in F7 (8.4%). Finally, zeta potential results were in the range of −0.67 to −27.6 mv. Compressibility percent revealed that F5 showed an excellent flowability characteristic with a value of 9.74±1.61 while F3 and F6 showed good flowability characteristics. By the end of the release, F6 showed approximately 90% drug release.

Results: F6 was selected for the in vivo study; C_{max} was increased by 1.5-fold while $AUC_{0-\infty}$ also increased significantly by 3-fold when compared with commercial tablet and finally, t_{max} was increased by 3-fold indicating sustained release pattern. The relative bioavailability was also increased by 3.2-fold.

Conclusion: The results of this study suggested that the formulation of compressed tablets containing more stable proniosomal powder extended the release of TEL and increased its bioavailability as well.

Keywords: telmisartan, TEL, proniosomal-derived niosomes, entrapment efficiency, EE, sustained-release tablet, bioavailability, multifactorial design

Introduction

According to Biopharmaceutical Classification System (BCS), class II drugs have no problems with the permeation through membranes. The actual problem for this group of medications is concerned with its low aqueous solubility, thus their introduction into circulatory system is dissolution rate limited. Different systems have been endorsed for upgrading the dissolution profile of these practically insoluble medications by complexation, derivatization of the medication, solid state manipulation, incorporation of surfactants, expanding the surface area exposed for dissolution by preparing nano measured vesicles, microencapsulation, solid dispersions and spray drying.[1–3] Noticeable effort had been done to encapsulate these drugs in novel vesicular drug delivery systems (VDDS) covering various routes of administration. These systems aim to achieve controlled and targeted drug delivery. It is supposed that VDDS can prolong the residence time of the drug in general circulation.

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Consequently, a variety of vesicular drug delivery systems such as liposomes, niosomes, ethosomes, transferosomes, and sphingosomes were formulated and characterized. The utilization of phospholipid vesicles (liposomes) as a drug carrier system has few limitations because of physical instability and corruption of the phospholipids used in the preparation. This pharmaceutical issue requires extraordinary taking care of storage conditions, which make it difficult to produce and scale up liposomal formulae with the exception of very profitable and valuable medications utilized as a part of tumor-targeting strategies because of the cost issue.[4,5] Thus, vesicles of nonionic surfactant "niosomes" have come into existence to offer therapeutic performance and enhanced medication bioavailability through various techniques such as: increasing the drug circulation time, protecting the drug molecules from degradation inside the biological system and restricting effects to the target tissue. Niosomal innovation is approved to upgrade the dissolution of drug molecules and enhance their penetrability by their amphiphilic properties.[6]

Unlike liposomal vesicles, niosomal dispersions can withstand the GIT acidic and enzymatic environment.[7] Unfortunately, niosomal dispersions also encounter some physical instability concerns such as, vesicle agglomerations, fusion, vesicle growth, and medication leakage to the outside. A solid adjustment for the previous stated niosomal problems has already expressed as a provesicular system called proniosome which is defined as anhydrous free flowable product of water-dissolvable transporter coated with surfactant intended for prior reconstitution with water to acquire niosomal vesicles. The dry product characteristics make it more advantageous in stability during sterilization, transfer, measuring and storage make it a very promising delivery system.[8] Moreover, compression of the proniosomal powder into a more convenient and common dosage forms "tablets" is promising from mechanical and pharmaceutical point of view.

Telmisartan is an antihypertensive drug classified as a non-peptide angiotensin-II receptor (type AT1) blocker. It lessens the vasoconstrictor and aldosterone-emitting impacts of angiotensin-II by particularly obstructing its signaling to the AT1 receptor in adrenal gland and smooth muscles vasculature. TEL demonstrates an inadequately water-dissolution behaviour which constrains its penetration through lipid bilayer layers in humans and other living creatures. It is delegated a class II drug having a low aqueous solubility. For this reason, TEL was carefully chosen for our study which focused on formulating, portraying, and assessing TEL proniosomes fabricated by the slurry technique in both powdered and tablet formulations. The pharmacokinetic parameters of the prepared systems were calculated after oral administration to rabbits as model animals.

Materials and Methods
Materials
Telmisartan was received as a free sample from International Drug agency for pharmaceutical Industry (IDI) (Egypt). Maltodextrin, span 40 and cholesterol were purchased from S.D. Fine Chemicals (Mumbai, India). Brij 35 and egg yolk phospholipids were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Soya bean phospholipids were a free sample from Lipoid (Germany). Chloroform and all other chemicals were obtained from El-Nasr Pharmaceutical Chemical Co. (Cairo, Egypt). Avicel was a free sample compassionately provided by the Egyptian International Pharmaceutical Industries Co., EIPICO (Egypt). All materials utilized as a part of the examination were of systematic review and utilized without further filtration.

Methods
Experimental Design
A multivariate approach differs a few factors at the same time. Multivariate methodologies are subdivided into successive and concurrent ones.[9] In the present study, the impact of three independent factors on the nature of the prepared formulae was researched utilizing a full factorial plan (Design Expert7). Three components were decided for investigation, the surfactant HLB, cholesterol proportion and the phospholipids type. The quantity of tests in full factorial outline is given by a $(3^1 *2^2)$ mixed factorial design.[10]

Twelve formulae were prepared using experimental design; the first factor (type of SAA) was investigated with two levels. Two types of surfactant were selected for this study span 40 with a low HLB value of 6.7 and brij 35 with a high HLB value of 16.9. The second factor (cholesterol ratio) was also investigated with two levels. Cholesterol was added with two ratios 20% and 50%. Finally, the third factor (phospholipid type and ratio) was chosen regarding the phospholipids with three levels. Formulae prepared with or without phospholipids with two different types either soybean phospholipids or egg yolk phospholipids. Phospholipids were added to the formulae replacing a part of the surfactant depending on its amphiphilic activity with

the ratio of (1:1). All the twelve formulae prepared by the full factorial design were given in (Table 1).

Preparation of Telmisartan (TEL) Proniosomes

The slurry technique is used to prepare proniosome powder utilizing maltodextrin as a water-soluble carrier after carefully assessing its flowability attributes. The lipid framing blend (250 μmol) and TEL (40 mg) were dispersed in a chloroform/methanol system (2:1 v/v). The resultant blend was brought into a 100-mL round-base flask containing the maltodextrin carrier (maltodextrin/surfactant, 2:1). Extra chloroform/methanol blend was added to form slurry. A rotational evaporator at decreased pressure was utilized to aid the solvent to evaporate at 70 rpm and temperature of 60°C ± 2°C leaving a totally dry product in a free-flowing state.[11] The resultant proniosomal powder was additionally stored under reduced pressure at room temperature overnight. The subsequent dried proniosome powders were put away in firmly sealed containers in a cooler (4°C) and were utilized for the preparation of proniosome-derived niosomes.

Preparation of Niosomes from Proniosomes

Proniosomes were changed over to niosomes by hydrating the dried powder with 10 mL of phosphate-buffered solution (PBS) with a pH of 6.8 at 80°C ± 1°C by vortexing the blend for 2 mins. Particle size analysis, zeta potential assurance and entrapment efficiency studies were performed on the resultant niosomal dispersion.[11]

Determination of TEL Entrapment Efficiency in Proniosome-Derived Niosomes

Entrapment efficiency of TEL in proniosome-derived niosomes was done by applying freeze thawing/centrifugation technique. The solidified samples (1 mL each held at −20°C) of hydrated niosomes prepared as prescribed above were allowed to defrost outside cooler. The resultant dispersions were centrifuged at a speed of 14,000 rpm for 30 min at 4°C. Niosomal deposits were isolated and reconstituted again in PBS (pH 6.8), at that point centrifuged once again to ensure the removal of unentrapped from the voids separating proniosomes.[12]

The aforementioned washing system was duplicated twice to remove any traces of the un-entrapped TEL in the niosomal dispersion. The supernatants were gathered after each run and arranged for the UV test of the free medication concentrations. TEL content was estimated spectrophotometrically using utilizing Hitachi U-2900, UV spectrophotometer (Japan) at λ_{max}296 nm utilizing chloroform as a blank. Each outcome was recorded as the mean of three readings (±SD). The entrapment efficiency was characterized as the ratio of the captured drug amount inside the vesicle to the total drug amount and figured by the accompanying equation:[13]

$$EE\% = \left(\begin{array}{c} \text{total amount of drug} - \\ \text{amount of free drug} \end{array} \right) / \text{total amount of drug} \\ \times 100$$

Particle Size and Particle Size Distribution

The mean vesicle estimate distribution was performed utilizing a laser diffraction strategy using Mastersizer X Ver. 2.15 (Malvern instruments Ltd. Malvern, UK). The estimations were performed at 25°C, utilizing a 45-mm center focal point and a bar length 2.4 mm. Each investigation was resolved in triplicate.[6,13]

Table 1 Compsition of Proniosomes Formulae According to the Full Factorial Design

Formula Number	Factor 1 A: Type of Surfactants	Factor 2 B: Cholesterol Ratio	Factor 3 C: Phospholipids Presence and Type
F1	Brij 35 (High HLB) (125 μmol)	High Ratio (125 μmol)	Absent
F2	Brij 35 (High HLB) (62.5 μmol)	High Ratio (125 μmol)	Egg yolk Phospholipid (62.5 μmol)
F3	Brij 35 (High HLB) (62.5 μmol)	High Ratio (125 μmol)	Soya PL Phospholipid (62.5 μmol)
F4	Brij 35 (High HLB) (200 μmol)	Low Ratio (50 μmol)	Absent
F5	Brij 35 (High HLB) (100 μmol)	Low Ratio (50 μmol)	Egg yolk Phospholipid (100 μmol)
F6	Brij 35 (High HLB) (100 μmol)	Low Ratio (50 μmol)	Soya PL Phospholipid (100 μmol)
F7	Span 40 (Low HLB) (125 μmol)	High Ratio (125 μmol)	Absent
F8	Span 40 (Low HLB) (62.5 μmol)	High Ratio (125 μmol)	Egg yolk Phospholipid (62.5 μmol)
F9	Span 40 (Low HLB) (62.5 μmol)	High Ratio (125 μmol)	Soya PL Phospholipid (62.5 μmol)
F10	Span 40 (Low HLB) (200 μmol)	Low Ratio (50 μmol)	Absent
F11	Span 40 (Low HLB) (100 μmol)	Low Ratio (50 μmol)	Egg yolk Phospholipid (100 μmol)
F12	Span 40 (Low HLB) (100 μmol)	Low Ratio (50 μmol)	Soya PL Phospholipid (100 μmol)

Zeta (ζ)-Potential Measurements

The zeta potential of the diluted proniosomes dispersions was estimated utilizing a zeta meter framework. The proniosomes were diluted with a proportion of 1:2500 (v/v) with refined water and blended with magnetic stirrer. Zeta-potential was resolved utilizing the Zetasizer (Malvern instrument, UK).[13,14]

Transmission Electron Microscope

The shape and size of hydrated niosomes arranged from proniosomes were resolved utilizing transmission electron microscopy (JeolJem Dos electron microscopy, Japan). The prepared sample was recolored using a specific stain (2% potassium phosphotungstate).[15]

Scanning Electron Microscopy (SEM)

Vesicle shape analysis was carried out by SEM using JEOL JSM-T330A scanning microscope. Cleaned brass specimen studs were used for taking the samples. Wet solvent paint was added on these studs and while the paint was wet, the proniosome powder was put on each stud and allowed to dry. Then photomicrographs were selected.[16]

Micromeritic Study

The proniosomal powder blend was assessed through measuring the following parameters: Angle of repose, Hausner ratio and Carr's index.[17]

Angle of Repose

It was figured utilizing the fixed funnel technique. The powder blend was poured through a funnel which was raised vertically at a fixed height equivalent to 1 cm in all experiments. Radius of the powder heap (r) was estimated. Angle of repose (Θ) was figured by the accompanying formula:

$$Tan\,\theta = {}^1\!/_r$$

where Θ =Angle of repose, 1 = height of the funnel (cm), r = radius of powder heap.

Bulk and Tapped Densities

Apparent bulk density (D_b) was estimated by pouring a predetermined weight (M) equivalent to 5 g of the powder blend into a graduated estimating cylinder. Bulk volume (V_b) was determined. Bulk density was calculated using the following equation:

$$Db = {}^M\!/_{Vb}$$

where M = Weight of powder (5 g), V_b = Bulk volume of powder.

The estimating cylinder containing the known weight of the powder mix (M) was tapped for a specific number of times (10 times) for all formulae. The minimum tapped volume (V_t) got in the cylinder was measured. Apparent tapped density (D_t) was computed by the accompanying equation:

$$Dt = {}^M\!/_{Vt}$$

where M = Weight of powder (5 g), V_t = volume in the wake of tapping for 10 times (tapped volume of powder).

Hausner Ratio

Hausner ratio is an indirect estimate of flowability of a powder. It is the proportion between tapped density and bulk density.

$$Hausner\,ratio = {}^{Dt}\!/_{Db}$$

Carr's Index (Compressibility %)

Apparently, it is a basic simple method for estimation of powder flowability. This percent is concerned with the cohesiveness, relative flow rate, and particle size of the powder. It can be ascertained from the equation: $Compressibility\,\% = \frac{(Dt - Db)}{Dt} \times 100$

Preparation of Compressed Tablets

Proniosomal tablets were prepared from proniosomal powders of TEL as per the accompanying formula which figured to prepare 20 tablets each containing 40 mg of TEL with average weight of every tablet was 330 mg (TEL proniosomes 4.6 g and Avicel 2 g). Compression was performed on a single punch tablet machine (Korsch Frogerais, type AO, Berlin, Germany) outfitted with flat-faced10-mm punches.[11]

In vitro Evaluation of Tablet
Weight Variation

Twenty tablets were randomly selected from each prepared proniosomal formula then the average weight was checked. At that point, every tablet was weighed, and the weight of every tablet was contrasted with the average weight.[11] The mean ± SD was calculated.

Thickness and Diameter

Thickness and diameter of tablets were measured using digital Mitutoyo caliper (Japan) and expressed in mm. The

test was performed using ten tablets from each batch and the mean ± SD was ascertained.

Hardness

Hardness of the tablets was estimated by Campbell tablet hardness tester (India) and expressed in kg/cm^2. This test was done utilizing ten tablets from each batch and the mean ± SD was ascertained.

Friability

Friability check for the tested tablets was assessed utilizing Roche Friabilator. Pre-weighed sample composed of 10 tablets was placed in the friabilator and the tablets were rotated at a speed of 25 rpm for 4 min (100 rounds). Tablets were then carefully dedusted using a brush and reweighed again.[11] The % friability (F) was calculated according to the following formula:

$$F = \frac{(W\ initial - W\ final)}{(W\ initial)} \times 100$$

F represents the percentage weight loss; $W_{initial}$ and W_{final} are the initial and final weights, respectively.

Drug Content

Three tablets were randomly chosen from every batch and independently ground in a procelain mortar utilizing a suitable pestle.[18] Each one was then dissolved in phosphate buffer (pH 6.8) and passed through a Whatman filter paper. The supernatant was diluted with the buffer solution and TEL content was determined spectrophotometrically at λ max (296 nm) utilizing Hitachi U-2900, UV spectrophotometer (Japan).

Disintegration Time

Tablets were immersed in the disintegration apparatus using 10 mL of phosphate buffer solution of pH 1.2 at 37°C as the immersion liquid simulating the gastric environment. The time required for disintegration of the tablets was noted. The disintegration test was done on ten tablets and the mean ± SD was calculated.[19]

In vitro Release of TEL from Proniosome Tablet

TEL dissolution from the tablets was conducted through the USP XXIII tablet dissolution test apparatus I (rotating basket) (Erweka DT 600 six axle dissolution analyzer) at a revolution speed of 50 rpm. The dissolution medium comprised of 900 mL of phosphate buffer pH 6.8 kept up at 37 ± 0.5°C which was maintained till the end of the 24 h of the experiment. One tablet was kept in every

basket and submerged in the dissolution medium. Test samples of 2 mL were withdrawn at predetermined time intervals of 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h and the volume was repaid to the initial volume by replacing with fresh dissolution medium after each sampling.[20] The gathered samples were filtered and analysed spectrophotometrically at 296 nm. The trial was done in triplicate and the data of in vitro dissolution were presented as mean ± SD.

Ethics Approval

All the experimental procedures used in the present study were conducted according to the protocol for utilization of experimental animals set by the ethics committee of the Faculty of Pharmacy, Cairo University, Egypt with serial number: PI(1318).

Male rabbits (weighing 1.5–2 kg) were utilized for the bioavailability study. Candidates were housed in the institutionalized conditions at the animal place of the Faculty of Pharmacy, Sinai University, Egypt. All animals were acclimatized and kept under steady temperature (25°C±2°C).

In vivo Study

Rabbits were divided into three groups of six rabbits in each group in a parallel design. Group 1 and group 2 got a proportionate dosage of 40 mg TEL.[21] Group 1 got TEL commercial tablets while the second group got TEL proniosomal tablet F6 (the best formula that showed the best dissolution behaviour). Group 3 was a blank group with no treatment.[22]

Blood samples (around 1 mL) were pulled back from the sinus orbital into heparinized tubes at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after every administration. The blood tests were centrifuged promptly at 3000 rpm for 10 min to acquire the plasma tests and were put away at −20°C for HPLC measure.

Each plasma test sample (0.2 mL) was extracted with 1 mL acetonitrile, trailed by centrifugation at 3000 rpm for 10 minutes. Supernatant (100 μL) was then diluted with 500 μL acetonitrile- water-acetic acid (15/85/0.1). At last, an aliquot (20 μL) was infused onto chromatographic system.[23]

The HPLC investigation was completed on HPLC (Hitachi LaChrome Elite, Tokyo, Japan) instrument. A blend of methanol and acetonitrile (70:30%v/v) was chosen as mobile phase. Division and quantitation were made on a 250 x 4.6 mm (i.d.), 5μm ODS segment (Inertsil, Tokyo, Japan). The mobile phase was infused to the framework utilizing paired pumping mode at a stream rate of 0.7 mL/min. For all samples, infusion volume and run time were settled as 20 μL and 10 min, respectively.[22]

Pharmacokinetic analysis of plasma Telmisartan concentration was performed using pharmacokinetic add-in package for Microsoft excel 2016 applying non-compartmental analysis. The determined pharmacokinetic parameters were maximum concentration in plasma (C_{max}), the time for maximum concentration in plasma (T_{max}), the area under plasma concentration versus time curve from zero to 72 hrs (AUC_{0-6}), area under the plasma concentration versus time curve from zero to infinity ($AUC_{0-\infty}$), mean residence time (MRT) and relative bioavailability (RB). Data are presented as mean ± standard deviation (SD) and were analysed using one-way ANOVA with extended LSD post hoc tests (subsequent multiple comparisons using Tukey's test), except for T_{max} data which were analysed by non-parametric Kruskal–Wallis test. All statistical tests were performed using IBM SPSS Statistics version 23, 64-bit edition, NY, USA. A P value of less than 0.05 was considered statistically significant.

Results and Discussion
Preparation of Proniosomes
Dried proniosomal formulations of TEL were successfully prepared using span 40 and brij 35 with cholesterol of two different ratios, with both types of phospholipids or without their presence. Further characterization showed the optimum formula compositions which yield the desired release characteristics of the prepared proniosomes. All prepared proniosomal formulae were directly converted into niosomal vesicles without any technical defects upon hydration utilizing hot water (55–60°C).

Determination of TEL Entrapment Efficiency in Proniosome-Derived Niosomes
The detailed results of this test are shown in (Table 2).The TEL entrapment efficiency showed a wide range of values as a result of different formulae compositions. The highest EE was shown in F3 (85%) while the lowest value was shown in F7 (8.4%). The formulae prepared with Brij 35 showed a significant increase in the EE than those which were prepared with Span 40. The formulae prepared utilizing soybean phospholipids demonstrated significantly more EE than those which were prepared without its incorporation. More focusing study is required to make an acceptable slice theory about the use of phospholipids.[24]

Table 2 The Entrapment Efficiency, Particle Size Measurement and Zeta Potential Values of the Prepared Proniosomal Formulae

Formula Number	Response 1 EE %	Response 2 Particle Size	Response 3 Zeta Potential
F1	12.5 ± 1.5	1117±23	−1.39±0.5
F2	62.5±2.3	1132±13	−1.07±0.4
F3	85±2.1	751±7	−0.67±0.2
F4	19.75±1.2	1389±21	−2.2±0.2
F5	51±1.3	326±4	−1.29±0.1
F6	62.25±2.3	277±0.5	−27.6±1.2
F7	8.4±0.2	2543±21	−24.1±2.1
F8	10±0.12	5203±23	−7.96±1.2
F9	34.9±1.1	352±4	−16.7±2.1
F10	12.4±1.2	403±10	−16.3±1.4
F11	44.25±2.1	293±4	−14.5±1.8
F12	44.5±1.7	1766±6	−0.9±0.3

Three different formulae (F3, F5 and F6) were chosen taking in consideration the highest EE% ensuring high drug content, the lowest PS ensuring good dissolution and permeability characters and a zeta potential with a large negative charge ensuring the stability of the systems. According to design expert 7, a desirability factor was considered as 0.8 (Figure 1).[25]

Particle Size and Particle Size Distribution
Vesicle size analysis of the proniosome-derived niosomes shows a distinct variation in the result obtained. The highest value of particle size was shown in F8 (5203) ± SD (nm) and the lowest value was obtained in F6 (277) (nm) with polydispersity value 0.35 as shown in Figure 2. The lowest particle size distribution was found in F6 which was prepared with brij 35.20% of cholesterol and soybean phospholipids. The detailed results of this test are shown in (Table 2).

An overall increase in particle size of proniosomes formulae prepared by span 40 in F7 to F12 was noticed. Formulae prepared with pure surfactant content without addition of phospholipids were shown to have a particle size >1000 nm except in formula F10 which showed a relatively large particle size distribution in comparison with the low value obtained in formulae prepared by addition of the phospholipids.

Zeta (ζ)-Potential Measurements
The results were in the range of −0.67 to −27.6. The detailed results of this test are shown in (Table 2).

The high value of zeta potential will participate in better stability of the system as shown in F6. The presence of fatty acids in the structure of the excipients used to give the surface
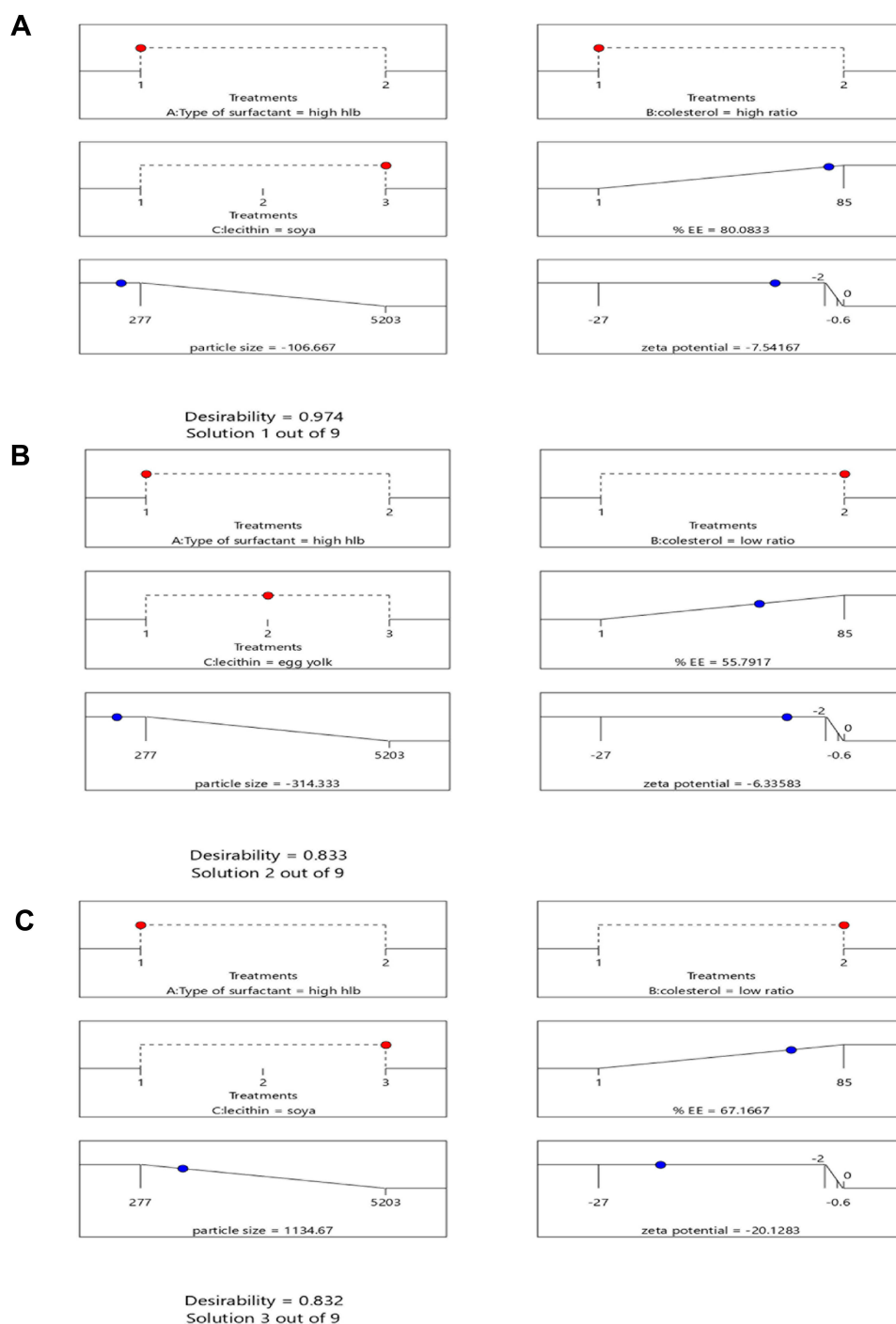
A

Desirability = 0.974
Solution 1 out of 9

B

Desirability = 0.833
Solution 2 out of 9

C

Desirability = 0.832
Solution 3 out of 9

Figure 1 F$_3$, F$_5$ and F$_6$ desirability factors according to design expert 7.

charge of the droplet negative values. Nanoparticles with zeta measurements more than −15 mv regularly bring a certain degree of stability.[26]

The literature reported stable colloidal systems composed of non-ionic components with relatively low values of zeta potential which considered nearly neutral charge and not affected by body membrane charge during absorption. The results were in perfect agreement with the previous researchers who prepared stable colloidal system with a low negative zeta potential system.[27,28]

The absolute values of zeta potential were lower than the literature which may be attributed to the presence of non-ionic surfactant which sterically stabilizes the system by forming a coat around their surface.
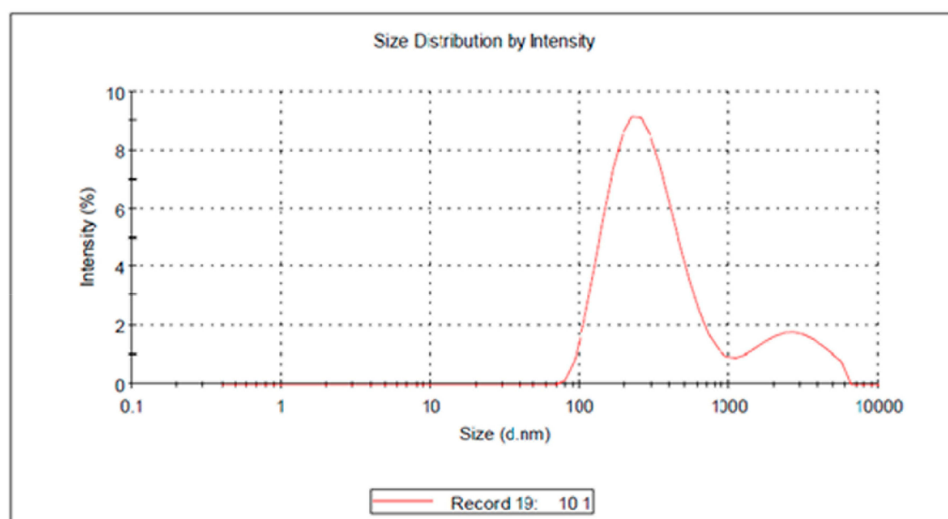
Figure 2 Particle size measurement of formula 6.

Transmission Electron Microscope

The TEM demonstrated homogenous well-divided spheres with a brilliant background and the average droplet measure was confirmed 100 nm or less for all the studied samples which affirm those consequence got formerly from Malvern Zetasizer as shown in (Figure 3).

Scanning Electron Microscopy

Concerning illustration indicated in (Figure 4), scanning electron microscopy for uncoated maltodextrin. Furthermore, dry proniosome powder revealed that there is a slight distinction in the manifestation for their surfaces. The surface of proniosome powder seems to be smoother demonstrating a slim and uniform covering of lipid layers of surfactant and phospholipids over that maltodextrin powder which has surface irregularities and sharp edges. Furthermore, those examined electron micrograph of the dried proniosome-derived niosome dispersions infers that the niosomes produced after hydration of proniosomes were discrete furthermore uniform.

Those outcomes of the electron microscope for its both sorts uncovered that proniomes-derived niosomes were discrete furthermore uniform in the nano range confirming those results got in the particle measure determination segment. The smoothness of the proniosome surface may be due to the incorporation of surfactant and phospholipids inside the fine openings located onto the top of the carrier.

Also, it must be taken into consideration the dissolution of surface particles of maltodextrin in the (methanol/chloroform) mixture sprayed onto the carrier surface which will recrystallize onto the newly formed proniosomal surface upon solvent evaporation.

Micromeritic Study

All the prepared formulae showed reasonable Micromeritic characteristics which are suitable for subsequent compression into tablet. Maltodextrin was chosen as a carrier with a ratio to the surfactant used 2:1 which proved its ability to
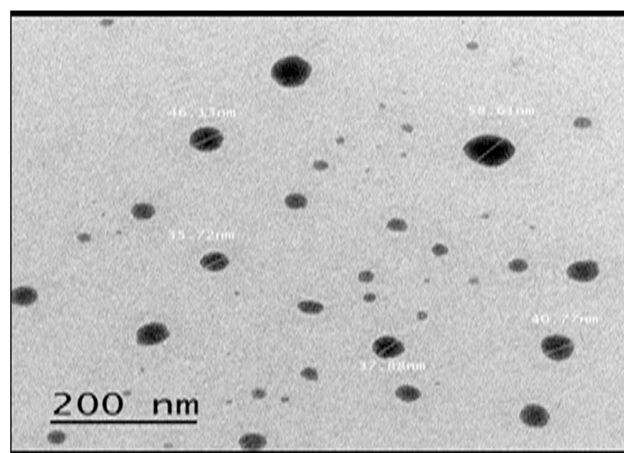

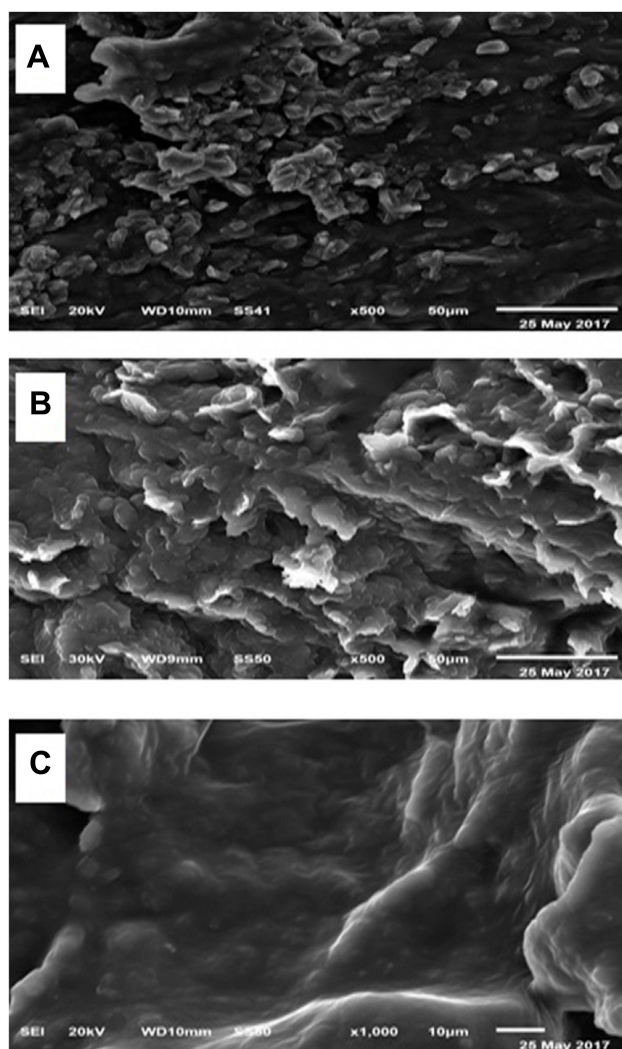**Figure 3** Transmission electron microscope micrograph of F3.

Figure 4 Scanning electron micrograph of (**A**) maltodextrin powder (uncoated), (**B**) proniosomes (F3), and (**C**) niosomes derived from proniosomes.

convert liquid proniosome into a dry proniosomes formulation which on hydration yields niosomes thus eliminating the physical and chemical stability problems.

Angle of Repose
The values obtained for the angle of repose of the TEL formulae ranged from 28.28±0.18° to 24.19±0.44°, as illustrated in (Table 3).

The Bulk and Tapped Densities
The values obtained for the bulk densities of the prepared TEL powder blend ranged from 0.53±0.008 to 0.48±0.034 g/cm3, while the values obtained for the tapped densities of the prepared TEL powder blend ranged from 0.625±0.01 to 0.58±0.017 as illustrated in (Table 3).

Hausner Ratio
The values obtained for the Hausner ratio of the prepared TEL powder blend ranged from 1.11±0.02 to 1.19±0.05, as illustrated in (Table 3).

Carr's Index (Compressibility %)
Compressibility percent is indirectly related to the relative flow rate, a compressible material will be less flowable. F5 showed an excellent flowability characteristics with a value of 9.74±1.61 while F3 and F6 showed a good flowability characteristics with a value of 16.22±1.12 and 15.7±3.79, respectively.[29]

Tablet Evaluation
The obtained weight variation was found to be acceptable in a range stated in the USP (±5%) (USP 30, 2007). The thickness of all TEL formulae was between 3.143±0.07 to 3.164±0.05 mm showing a fairly uniform tableting procedure as illustrated in Table 4. The diameter of all formulae was between 9.867±0.06 to 9.95±0.02 as shown illustrated in Table 4. Thickness of ten tablets for each formula was measured and all the results were found in accordance with USP stated limit. The hardness of all formulae was measured in kg/cm^2. Hardness of all formulae was in the range of 4.805±0.19 to 6.547±0.14 kg/cm^2 as illustrated in Table 4. Minimum permitted hardness range for satisfactory tablets is 4 kg.[30]

Friability test results for TEL formulae were within the specified limits ie friability % for all formulae were less than 1%.[31] The loss in total weight of the tablets due to friability was in the range of 0.19±0.03 to 0.45±0.05% as illustrated in Table 4. The disintegration time was found to be approximately in the range of (25–28 mins) for TEL proniosome-loaded tablets.

In vitro Release of TEL from Proniosome Tablet
The release of TEL from Proniosome F3 dosage form was evaluated in buffers of pH 1.2, 4.5, and 6.8. The data showed that release of TEL was faster in phosphate buffer of pH 6.8 than other two media. As shown in (Figure 5), after 1 hr of release, the commercial product showed a 66% drug release while the release of all proniosomes formulae didn`t exceed 28% during the first hour. The release of all proniosomes formulae showed a sustained release of TEL during the 24 hrs of experiment. At the end

Table 3 Angle of Repose, Bulk, Tapped Densities, Hausner Ratio and Carr's Index of Best TEL Proniosomal Powder Formulae

| Formula Code	Angle of Repose	Bulk Density	Tapped Density	Hausner Ratio	Carr's Index
F3	28.28±0.18	0.51±0.013	0.625±0.01	1.19±0.02	16.22±1.12
F5	26±0.55	0.53±0.008	0.58±0.017	1.11±0.02	9.74±1.61
F6	24.19±0.44	0.48±0.034	0.58±0.018	1.19±0.05	15.7±3.79

Table 4 Quality Control Evaluation of TEL Plain and Proniosome-Loaded Tablet (Mean ± SD)

Formulae	Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Disintegration (mins)
F3	329.85±1.65	3.148±0.06	9.95±0.02	4.805±0.19	0.19±0.03	99.66±0.06	26.45±0.56
F5	330.05±2.16	3.143±0.07	9.867±0.06	5.554±0.48	0.45±0.05	98.47±0.45	28.65±0.02
F6	329.63±1.46	3.164±0.05	9.945±0.03	6.547±0.14	0.33±0.07	99.67±0.15	25.66±0.21

of the release, F6 showed approximately 90% drug release while the commercial product release showed 81% only.

The pH-dependent solubility of drug can be responsible for higher release in pH 6.8 even after gradual increase in the pH for the same formula simulating the gastric environment. The pH-dependent solubility of telmisartan is attributed to its three pKa values 3.5,4.1, and 6.0 corresponding to its carboxylic (acidic) and two benzimidazole (basic) functional groups, respectively.[32] A one-way examination of fluctuation (ANOVA) accompanied eventually by the least significant difference (LSD) as a post hoc test might have been applied; utilizing SPSS system form 17 product. The contrasts were acknowledged noteworthy if P<0. 05. The measurable investigation might have been carried at Q $_{1hr}$. Furthermore Q $_{24hr}$,
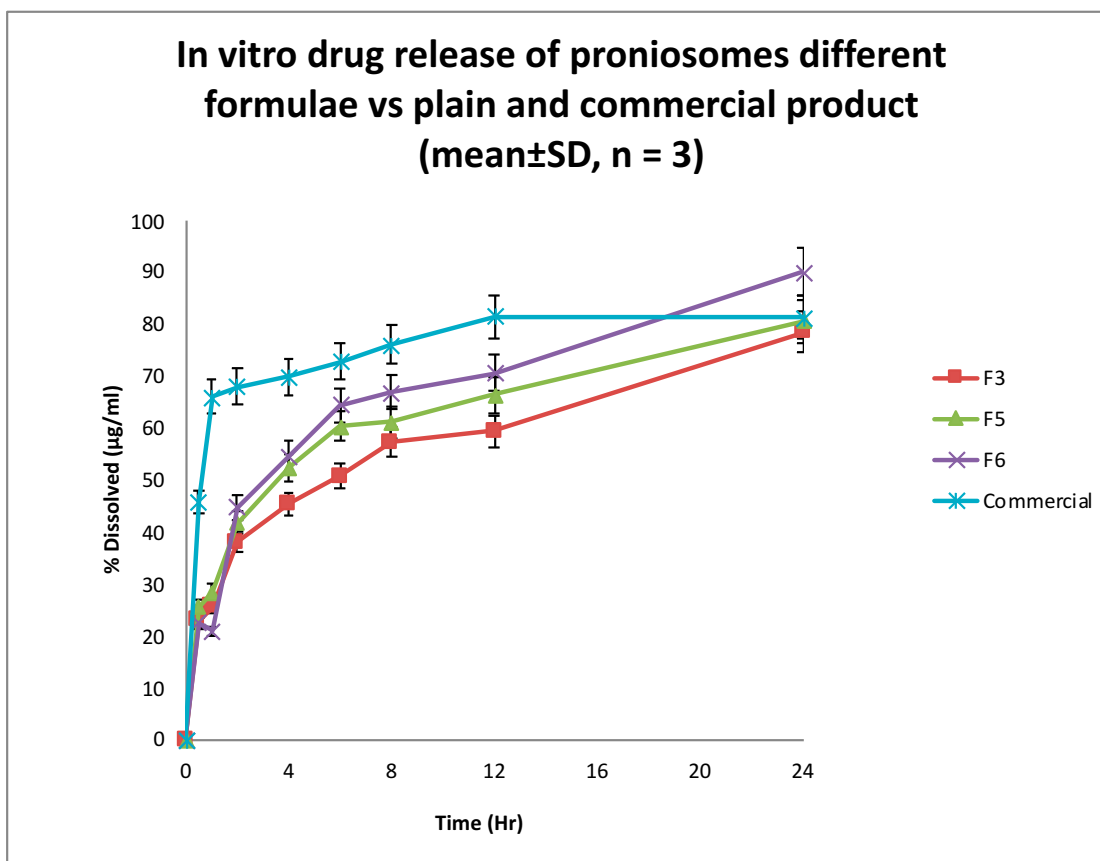
Figure 5 Dissolution profile of Telmisartan from different preparations.

the medication release from each proniosomes formulae demonstrated a significant difference demonstrating the effectiveness of the system done in expanding % dissolved of the medication enhancing its bioavailability because of the diminished vesicle measure of the formulae.

In vivo Study

A one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) as a post hoc test was applied; using SPSS program version 17 software. The differences were considered significant if $P<0.05$. The column effluent was detected spectrophotometrically at 298 nm.

Retention time for TEL was 4.5 min as shown in (Figure 6) which also revealed that there were no peaks due to formula compounds that might interfere with the assay. Calibration curves were constructed for TEL in the range of 100–4000 ng/mL, being linear (r2>0.99). Plasma concentration C_{max} and $AUC0\rightarrow\infty$ are significantly increased for proniosomal formula than those for the commercial tablet. T_{max} is increased for proniosome formula and it was 12 h for F6 and 4 h for commercial tablet indicating a sustained release pattern as shown in (Figure 7). Relative bioavailability is increased 3.2-fold. The mean pharmacokinetics parameters of TEL from different formulae represented by C_{max} (ng/mL),
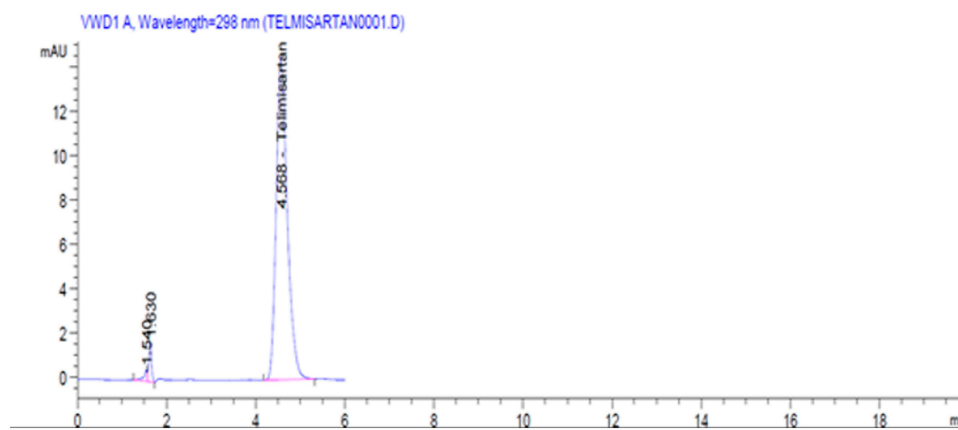

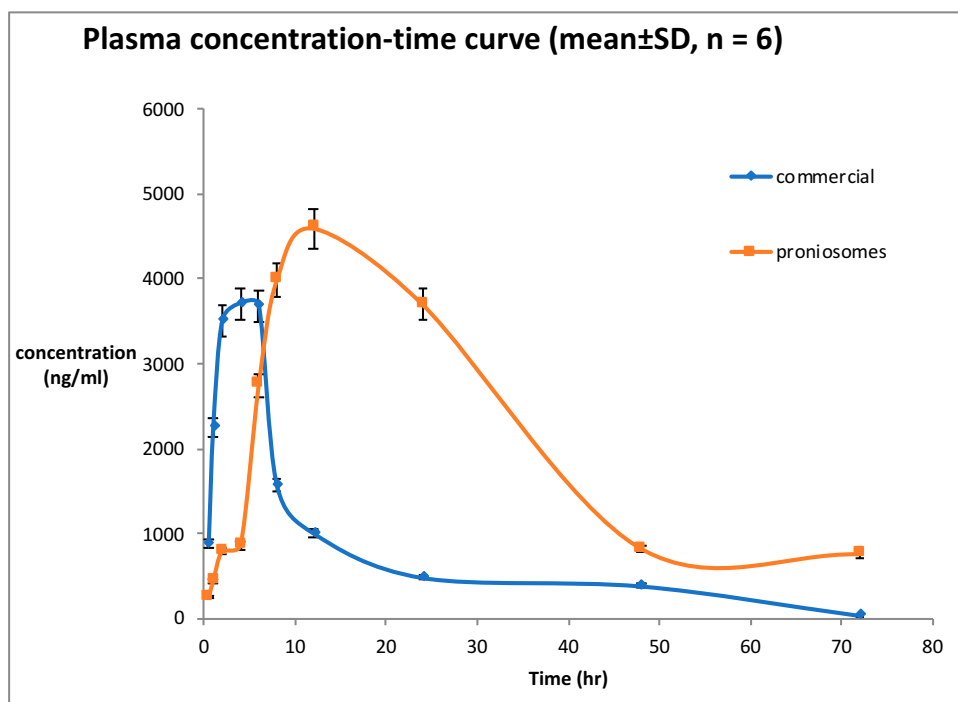**Figure 6** HPLC chromatogram of Telmisartan.

Figure 7 Comparative plasma concentration-time profile of Telmisartan from F6 and commercial product.

Table 5 Pharmacokinetic Parameters After Administration of TEL Commercial Tablet and TEL Proniosome-Loaded Tablet

PK Parameters	Proniosome Formula F6	Commercial Tablet
Cmax (ng/mL)	4592.42±3.1	3706.65±2.08
Tmax (hr)	12	4
AUC (0–72) (ng.hr/mL)	152572±112	53261±193
AUC (0–∞) (ng.hr/mL)	174911±201	53986±233
MRT	30.68±0.03	17.74±0.07
R.B	3.2	–

T_{max} (h) AUC0–72 (ng/mL/h), and AUC0–∞ (ng/mL/h) are summarized in Table 5.

The expanded bioavailability about proniosomal formulae might be expected with its lymphatic transport through transcellular pathway What's more improved dissolution profile because of diminished particle size. The fundamental rate-limiting step to medication regarding absorption/diffusion may be the solitary layer of intestinal epithelial cell. High content of surfactants and phospholipids could increase the permeability by disturbing the cell membrane.[33] Brij 35 What's more span 40 utilized within our investigation which have a polyoxyethylene and hydrocarbon chain. Its structural qualities confer both lipophilic and hydrophilic properties of the surfactant, permitting it to insert themselves between lipids What's more protein domains. Surfactant, additionally, exhibited a reversible impact on the opening about tight junction; it might connect for those polar head assemblies of the lipid bilayer, modifying hydrogen bonding Furthermore ionic powers between these bunches. It might additionally embed itself the middle of those lipophilic tails of the bilayer, bringing about a build in the absorption of the drug which has been affirmed for our in vivo examination.[34]

Conclusion

In our study, the dry, free-flowing proniosome formulae which strike the physicochemical issues connected with niosomes might have been perfectly prepared for oral intake. That proniosomal powder might have been smoothly transformed into tablets as a popular dosage form. Those proniosome-derived suspension exhibited reasonable and efficient entrapment efficiency from the homogenous nano-sized vesicle. In vivo pharmacokinetic investigation indicated that TEL-loaded proniosomes processed a noteworthy change in the bioavailability compared with TEL commercial tablets. Results obtained from male albino rabbits following oral administration suggested a controlled release profile. The

proniosomes might enhance the gastrointestinal absorption, also give an acceptable and exceptionally successful procedure of delivering poorly water-soluble drugs through the advantageous oral course for administration. Consequently, the proniosome powder has the chance to be a promising carrier system in modern pharmaceutical industry.

Disclosure

The authors declare that they have no conflict of interests.

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