Preparation and evaluation a proniosomal gel for terbutaline sulfate as transdermal drug delivery system

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Abstract:

The rationale of the present study is to formulate and evaluate proniosomal formulations as transdermal carrier systems for terbutaline sulfate. Proniosomal formulations have been prepared from mixing of one or two types of surfactants (span 20, span 40 ,span 60 span 80 ,tween 20 , tween 40 , tween 60 and tween 80),cholesterol and soya bean lecithin . Different formulas of terbutaline sulfate proniosomal preparations were prepared by changing the surfactant type. The microscopic observations showed that proniosomal gel formulations immediately converted to niosomal dispersions upon hydration. Their morphological properties have been determined by optical microscopy and scanning electron microscopy. The vesicle system was evaluated in-vitro for vesicle size, polydispersity, encapsulation efficiency of drug and permeation of terbutaline sulfate through excised rabbit skin. Optical microscope and scanning electron microscope pictures showed spherical shaped for all niosomes formulations of terbutaline sulfate and the size range in micrometer were 8.82-0.294, while the encapsulation efficiencies were 88.06%-39.46%. In addition better permeation was obtained from proniosomal gel through rabbit skin.

تحضير وتقييم هلام البرونايوسوم لعقار كبريتات التربيوتالين كنظام اعطاء دواء تحت الادمة

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الخلاصة:

إن الغرض من هذه الدراسة المقدمة هي تحضير وتقييم صيغ البرونايوسوم كمنظومات ناقلة لعقار كبريتات التربيوتالين عبر الأدمة.تم تحضير صيغ البرونيوسوم من خلال خلط نوع أو نوعين من عوامل الفعالية السطحية(سبان 20، سبان 40، سبان 60،سبان 80، توين 20 ، توين 40، توين 60، توين 80) مع الكولسترول و اليسيثين أو دهن الصويا.عدة صيغ مختلفة من إعدادات البرونايوسوم لعقار كبريتات التربيوتالين تم تحضيرها بتغير نوع العامل الفاعل السطحي. إن المشاهدات المجهرية أظهرت بان الصيغ الهلامية للبرونايوسوم تتحول إلى النيوسوم المشتت بعد ترطيبها كما إن الصفات التشكيلية تم تعيينها بواسطة المجهر البصري والالكتروني الدقيق.إن منظومة الحويصلة قد قيمت في المختبر من خلال حجم الحويصلة، مقياس التشتت، كفاءة التحميل للعقار و نفاذية كبريتات التربيوتالين خلال جلد المستأصل من الأرنب. صور المجهر البصري والالكتروني الدقيق أظهرت الشكل الكروي لكل صيغ النايوسوم ألمحضره (الحويصلات) لعقار كبريتات التربيوتالين وان مدى الحجم بالمايكروميتر هو من

0,294 إلى 8,82 ونسبة كفاءة التحميل هي من 39,46% إلى 88,06% بالإضافة إلى نفاذية جيدة خلال جلد الأرنب.

Introduction:

Terbutaline sulphate is variably absorbed from the gastrointestinal tract and about 60% of the absorbed dose undergoes first-pass metabolism by sulphate conjugation in the liver and the gut wall [(1)]. The oral bioavailability of terbutaline is 14.8% and half-life is 3 to 4 h. [(2)] Hence, it was considered as suitable candidate for administration by transdermal route. Transdermal drug delivery offers many advantages over other traditional routes of administration. Unfortunately, the barrier nature of the skin presents a significant obstacle for most drugs to be delivered into and through its [(3)].Several approaches have been developed to weaken this skin barrier. One of the approaches for increasing the skin penetration of drugs and many cosmetic chemicals is the use of vesicular systems, such as liposomes and niosomes.

Now a day, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering [(4)]. Vesicles can play a major role in modeling biological membranes, and in the transport and targeting of active agents. The basic structure of vesicles is illustrated in figure (1). Vesicles are water-filled colloidal particles. The walls of these vesicles consist of amphiphilic molecules in a bilayer conformation. In an excess of water these amphiphilic molecules can form one (unilamellar vesicles) or more (multilamellar vesicles) concentric bilayers [(5)]. Hydrophilic drugs can be entrapped into the internal aqueous compartment, whereas amphiphilic, lipophilic and charged hydrophilic drugs can be associated with the vesicle bilayer by hydrophobic and/or electrostatic interactions [(6)]. A wide variety of lipids and surfactants can be used to prepare vesicles. Most commonly, the vesicles are composed of phospholipids or non-ionic surfactants[(7)].These are referred to as liposomes and niosomes or nonionic surfactant vesicles, respectively. The rational for using of vesicles in dermal and transdermal drug delivery, perhaps due to vesicles might:

(a) Act as drug carriers to deliver entrapped drug molecules into or across the skin; [(8)].

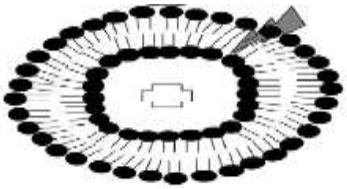

Figure (1): vesicle as drug carrier (Ref.8)

(b) Act as penetration enhancers owing the penetration of the individual lipid components into the stratum corneum and subsequently the alteration of the intercellular lipid lamellae within this skin layer;

(c) Serve as a depot for sustained release of dermally active compounds;

(d) Serve as a rate-limiting membrane barrier for the modulation of systemic absorption, hence providing a controlled transdermal delivery system.

Materials and Methods:

Terbutaline sulfates, span 80, tween 40 were purchased from Sigma-Aldrich comp. (Oma, Iraq).Span 20 and span 40 were from fluka chemie. (U.S.A). Span 60 and tween 60 were obtained from mereck- schuchardt (Germeny). Tween 80 was from Gainlind chemical comp. (UK). Tween 20 was obtained from Thomas baker (India) Cholesterol and soyabean lecithin were from BDH (Pool, UK). All other chemicals used were of analytical grade**.**

Preparation proniosomal gel for terbutaline sulfate:

Proniosomal gel was prepared by a coacervation-phase separation method as reported by Perrett et al. [(9)]. Different formula were prepared by mixing the specified amount of surfactant [Sorbitan esters (spans) and their ethoxylated derivatives (tweens)], lecithin, cholesterol and drug were taken in a clean and dry, wide mouth small glass tube with capacity about 5 ml. The composition of each formula is given in table (1). After mixing all the ingredients, the open end of the glass tube was covered with a lid to prevent loss of solvent from it and warmed on a water bath at 60–70^{0}C for about 5 min, until the surfactants were dissolved completely. The aqueous phase (0.1% glycerol solution) was added and warmed on a water bath till clear solution is formed which on cooling converts into a proniosomal gel .The gel obtained was remained in the same glass tube in dark for characterization.

Characterization of proniosomal gel:

The proniosomes and niosomes were characterized for following parameters

Observation (appearance of proniosomal gel):

The appearance for each formula was checked such as color, consistency and fluidity and comparison of each one with the other.

Encapsulation Efficiency (Entrapment):

The loading capacity of proniosomal systems for drug was evaluated by taking a 100mg of proniosomal gel and dispersed in distilled water then warmed by using water bath to ensure the formation of niosomes. Then the dispersion was centrifuged at 14000 rpm for 40 min at 5^{o}C (by using centrifuge with cooling) [(10)].The clear part (supernatant layer)was used for the determination of free drug .Sample was taken for analysis by suitable method The percentage encapsulation efficiency was calculated according to the following equation [(11)]:

$$\% \text{ Encapsulation Efficience} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug used}} \times 100$$

Microscopic evaluation of proniosomal gel:

A suitable sample of proniosomal gel was spread on microscope slide to form a thin layer. After placing the cover slip the sample was

observed under light microscope and compared with another sample after adding a drop of water to it .Photomicrographs were taken for both samples [12].

Visualization by scanning electron microscopy (SEM):

For SEM (This test also was done in the Anatomy department of Medicine school- Marmara university), one drop of dispersion system was mounted on a stub covered with clean glass. The drop was spread out on the glass homogeneously. A Polaron E5100 sputter-coater (Polaron, UK) was used to sputter -coat the samples with gold, and the samples were examined under a scanning electron microscope (JEOL, JSM-5200. Japan). At an accelerating voltage of 25 kV [13].

Vesicle Size Analysis:

Size and size distribution studies were done for niosomes prepared from proniosomes hydration with agitation (shaking) and without agitation size Analysis was done by adding saline solution (0.9% solution) to the proniosomal gel (100mg) in a small glass vial with occasional shaking for 10 min. After hydration, the dispersion of niosomes was observed under optical microscope (Olympus) at 100, 40 and 10x magnification. The sizes of 150-200 vesicles were measured using a calibrated ocular and stage micrometer fitted in the optical microscope [14].

Table (1): Different Formulas of Proniosomal Gel for Terbutaline Sulfate

formulation code.	Surfactant type	Ratio (mg)	Lecithin (mg)	Cholesterol (mg)	Terbutaline sulfate (mg)	Alcohol(ml) (Ethanol)	Water (ml)
F1t	**Span 20**	1000	100	100	10	0.5	0.2
F2t	**Span 40**	1000	100	100	10	0.5	0.2
F3t	**Span 60**	1000	100	100	10	0.5	0.2
F4t	**Span 80**	1000	100	100	10	0.5	0.2
F5t	Span20:span40	500:500	100	100	10	0.5	0.2
F6t	Span20:span60	500:500	100	100	10	0.5	0.2
F7t	Span20:span80	500:500	100	100	10	0.5	0.2
F8t	Span40:span60	500:50	100	100	10	0.5	0.2
F9t	Span40:span80	500:500	100	100	10	0.5	0.2
F10t	Span60:span80	500:500	100	100	10	0.5	0.2
F11t	**Tween60**	1000	1000	100	10	0.5	0.2
F12t	**Tween80**	1000	1000	100	10	0.5	0.2
F13t	**Tween20:span60**	500:500	100	100	10	0.5	0.2
F14t	**Tween40:span60**	500:500	100	100	10	0.5	0.2
F15t	**Tween60:span40**	500:500	100	100	10	0.5	0.2
F16t	**Tween60:span60**	500:500	100	100	10	0.5	0.2
F17t	**Tween60:span80**	500:500	100	100	10	0.5	0.2
F18t	**Tween80:span60**	500:500	100	100	10	0.5	0.2

In vitro skin permeation studies

Preparation of animal skin:

Male rabbit (animal's house, college of medicine, Kufa University). Weighing 2.5-3 kg was sacrificed by ether or chloroform inhalation. The abdominal skin was shaved lightly with an electrical clipper (before of which a depilatory cream was applied) taking care to prevent any damage to the surface of the skin, several centimeters in each dimension on abdominal skin(rectangular section) was excised from the animal using a sharp blade and surgical scissors. The skin was lifted easily from the animal after incision was made. The skin was defatted by wiping it with a cotton tip soaked in diethyl ether to remove the subcutaneous fat and scraping the dermal side to remove the muscle and blood vessels. The skin was wiped again with a cotton tip soaked in ether to prevent any adhering fat. The skin was kept in phosphate buffer pH 7.4 for about 1 hour in a water bath at constant temperature of 37 $^{\circ}$C to allow water soluble UV absorbing material to leach out. The skin was either used immediately or frozen until ready for use [15].

Drug diffusion studies:

The in vitro skin permeation of drug from different formulations was studied by using Franz glass diffusion cells [16]. The classic Diffusion cell consists of donor and receptor compartments separated by skin sample. The permeation rate of the drug from the donor chamber through the skin into the receptor is determined by measuring the amount of drug permeated over time.

The effective permeation area of the diffusion cell and receptor cell volume was 3 cm^2 and 5 ml or 17.5 ml, respectively. The temperature was maintained at 37°C ± 0.5°C. The receptor compartment contained phosphate buffer saline pH 7.4.Excised skin was mounted between the donor and the receptor compartment. The donor compartment left open and wrapped with cellophane to prevent contamination of the formulation from the atmosphere, the receptor chamber contents was magnetically stirred at 600 rpm .Sample formulation was applied to the surface of skin. Samples were taken from the receptor solution at suitable time intervals and analyzed by appropriate assay method.

Results and discussion:

Appearance of gel:

Table (2) shows the color, physical state and pH for each formula, these properties are differ from each other since they depend on the composition, for example, formula F2t gave a white semisolid appearance whereas F1t showed a brown liquid, this is due to the property of span 40 and span 20 for each formula respectively. The inspection of formula F5t offered the light brownish color with gel state at 37ºC which represents the combination of the two surfactants ,this means a change in the physical properties of surfactant after mixing and addition of alcohol with a few drops of water. In addition to the effect of high temperature since span 20 is liquid in nature at room

temperature and has a low phase transition point while span 40 is solid with higher phase transition point [17].these observations are similar to the results that obtained with proniosomal gel of captopril [18]. On the other hand, the pH of each formula was determined in order to investigate the possibility of any side effects in vivo. Due to acidic or alkaline pH which may irritate skin .The pH was found between 4.8(for F9t formula) and 6.4(for F12t, F14t and F18t formulas), this range is within the physiologically skin surface pH [19]. Changes in the pH are reported to play a role in the pathogenesis of skin diseases like irritant contact dermatitis and atopic dermatitis[20] Maintaining the skin's pH factor helps maintain a proper balance of the "acid mantle" which aids in protecting the body from bacteria and helps prevent moisture loss.

Table (2): Physical State and Appearance of Proniosomal Gel of Terbutaline Prepared By Different Compositions

Formula code	Observation	Physical state	pH
F1t	Brown	Liquid	5.3
F2t	White	Semisolid	5.4
F3t	White	Semisolid	
F4t	Brown	Liquid	5.4
F5t	Light brownish	Gel at 37ºC	5.3
F6t	Pale yellow	Gel at 37ºC	6.0
F7t	Brown	Liquid	5.4
F8t	White	Semisolid	5.9
F9t	Pale yellow	Gel at 37ºC	4.8
F10t	White	Gel at 25ºC	
F11t	Yellow	Gel	5.5
F12t	Yellow	Gel	6.4
F13t	White	Semisolid	6.2
F14t	White	Semisolid	6.4
F15t	Yellow	Semisolid	5.4
F16t	White	Semisolid	6.1
F17t	Yellow	Liquid	5.2
F18t	White	Semisolid	6.4

Microscopic evaluation of proniosomal gel:

By using different non-ionic surfactants. Various formulations of proniosomal preparation were prepared, and then proniosome was spontaneously transformed to the niosomal dispersion after hydrated by aqueous phase .The technique that was used in the preparation of noisome based on the principle of coacervation phase separation. A proniosome in these formulations are

a mixture of non- ionic surfactant, cholesterol, lecithin, alcohol and aqueous phase .Addition of excess amount of water acts as a vehicle for dispersion of niosomes [21].

The transformation of lamellar liquid crystalline proniosomes to niosomes may be explained by different degree of hydration of proniosome composition and change in shape of the hydrated molecules in the proniosome. When there is a limited vehicle system, the mixture of proniosome formed appears as lamellar liquid crystals resembling palisades and vesiculating lamellas stacked together which may be termed as compact niosomes. Further addition of water leads to swelling bilayers as well as vesicles due to interaction of water with polar groups of the surfactant. Above a limiting concentration of vehicle, the bilayers tend to form spherical structures randomly giving rise multilamellar, multivesicular structure. Then a complete hydration takes place leading to the formation of niosomes when shaken with excess aqueous phase [22] as shown in figure (2).

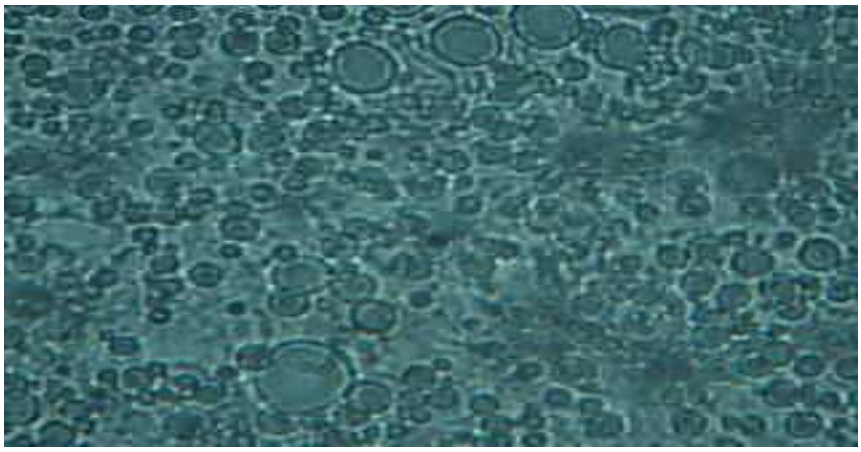

Figure (2): Niosomal dipersion of terbutaline sulfate (F7t) under scanning electron microscope at room temperature.

Scanning electron microscope examination

For an initial vesicle characterization, proniosomal gel prepared from span 20 and span 40 according to formula F5t was studied .Surface morphology and three-dimensional nature of vesicles prepared from different formulations were revealed by using scanning electron microscopy . As shown in figures (3), the image of the vesicles by scanning electron microscopy was confirmed the vesicular properties of these drug carriers, which formed from double layers.

Figure (3): Niosomal dipersion of terbutaline sulfate under scanning electron microscope at room temperature.

Size and size distribution:

Determination of vesicle size is important for the topical application of vesicles. Brian et al also demonstrated that vesicle more than 10 micrometer remains on skin surface and the vesicle of 3-10 micrometer concentrates in follicle and less than 3 micrometer penetrates the stratum corneum [23]. Size reduced when the dispersion was agitated. As shown in table (3), the size range of vesicles are decreased in an insignificant value in sequence of F1t>F2t>F3t>F4t that correspond to span 20, span40, span 60 and span 80 respectively, the results that obtained found that the mean size of the niosomes showed a regular increase with increasing the hydrophilic lipophilic balance (HLB) of the surfactant because surface free energy decreases with increasing hydrophobicity [24].These results are in good agreement with the results obtained by Yoshioka et al[25] and also with results established during determination the size of acyclovir niosomes[14] . Generally the surfactant with longer alkyl chains show a larger vesicles because the diameter of vesicles is depended on the length of the alkyl chains of surfactants [26] .The same reason was observed when compared the size range of formula F13t (tween 60) with F3t (span 60), the size of niosomes in the F13t is larger than F3t ,perhaps due to tween 60 which is more hydrophilic than span 60 and less hydrophobicity [27] .The size of the other formulas lies between the average size range for the combination of spans or between span and tween.

Uniformity of vesicles size is determined by polydispersity index values in which the low value means the more uniformity in size. Particle size distribution of the prepared niosomes reflects a wide size range, for example, the size range of formula F5t is from 5.145 to 2.94

μm as shown in figure 4. This finding may be owing to the influence of certain preparation conditions such as the hydration time, volume of medium, temperature and the degree of agitation. Smallest vesicles were achieved after agitation the dispersion of vesicles which may be due to the effect of applied energy during shaking resulted in breakage them into smaller vesicles.

Table (3): The Size Range and Encapsulation Efficiency of Niosomes for Selected Niosomal Gel Formulations of Terbutaline

Formulation code.	Size range (μm) before shaking	Mean vesicles size ±SD	Polydispersity Index SD/mean vesicle	Size range (μm) after shaking	Mean vesicles size ±SD	Encapsulation efficiency % ±SD
F1t	4.704-2.940	3.792±0.64	0.168	2.940-0.882	1.822±0.61	70.293±0.73
F2t	4.116-1.470	3.057±1.03	0.336	2.940-0.755	1.620±0.70	79.81±0.78
F3t	3.528-1.176	2.469±1.01	0.409	2.058-0.588	1.268±0.51	79.87±1.09
F4t	2.350-0.882	1.645±0.60	0.364	2.058-0.294	1.18±0.59	60.193±1.15
F5t	5.145-2.940	3.395±0.68	0.200	2.350-0.882	1.616±0.54	85.276±0.46
F6t	4.990-2.940	3.497±0.66	0.188	2.940-0.588	1.646±0.68	72.766±0.38
F7t	4.410-1.470	3.204±0.84	0.262	1.470-0.147	0.898±0.46	65.263±2.02
F8t	3.822-1.176	2.616±0.95	0.363	1.760-0.882	1.205±0.27	79.98±2.7
F9t	3.234-1.470	2.763±0.52	0.188	2.940-0.147	1.660±0.72	66.31±6.25
F10t	2.646-0.882	1.998±0.77	0.385	2.058-0.147	1.148±0.54	73.196±4.3
F11t	6.468-3.234	4.042±0.98	0.242	4.410-2.940	3.439±0.48	85.246±4.74
F12t	8.820-4.410	5.718±1.29	0.225	5.439-3.087	3.948±0.67	----------
F13t	5.880-1.470	3.395±1.37	0.403	5.586-1.764	2.94±1.19	39.43±2.75
F14t	6.174-1.470	3.630±1.60	0.440	4.410-1.176	2.822±0.96	74.633±4.10
F15t	-------	----------	-----	-------	----------	70.966±3.11
F16t	-------	---------	---------	-------	---------	88.066±4.11

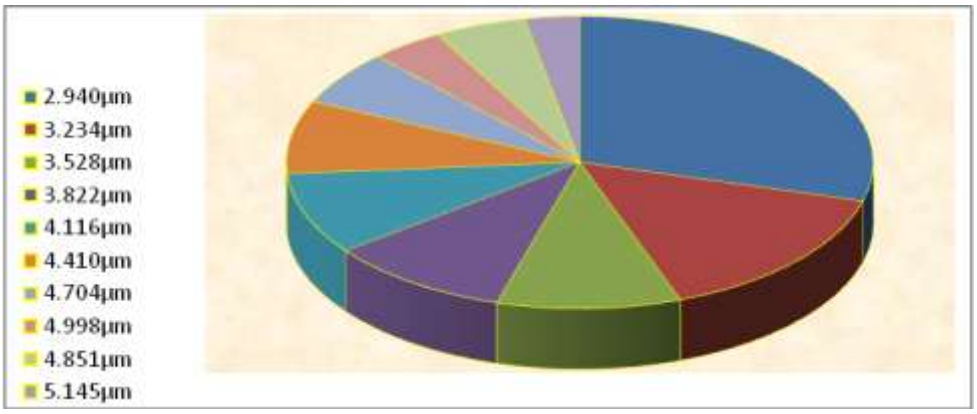

Figure (4): Particle size distribution of niosomal dispersion of terbutaline sulfate (F5t)

Encapsulation Efficiency (Entrapment):

The entrapment efficiency of the drug was defined as the ratio of the mass of niosome-associated drug to the total mass of drug. It was expressed as a percentage of the total amount of terbutaline sulfate used initially. To investigate the influence of surfactant structure on niosome properties, the encapsulation of different formulations of niosomes prepared from different surfactants compositions and constant additives was evaluated, the data are listed in table 2.From the table, it appears that the less fluid the bilayer (higher the gel to liquid phase transition temperature) the higher the encapsulation efficiency, for example the encapsulation efficiency followed the trend F3t>F2t>F1t>F4t. This may be attributed to the fact that spans 40 and span 60 are solids at room temperature and showed a higher phase transition temperatures [Tc] [28].The transition temperatures of surfactants increased from liquid at room temperature for span 20 to 46-47°C for span 40 and to 56-58°C for span 60 as the hydrocarbon length is increased .This stability decreases leakage of the vesicles and stabilizes against osmotic gradients [29].

The nature of the hydrophobic alkyl chain affects the encapsulation efficiency of drug. Span 20, span 40 and span 60 have the same head group with different alkyl chain but span 80 has an unsaturated alkyl chain so the double bond made the chain bend .This means that the adjacent molecular cannot be tight when they form the membrane of noisome and might be the reason for the lower entrapment efficiency of the span 80 system [30].The same results was obtained with encapsulation of 5[6]-carboxy-fluorescein [31] and doxorubicin [32]. The vesicles prepared with span 20 showed the most efficient entrapment, when compared with those prepared by span 80 because the size of vesicles may also responsible for high drug entrapment since terbutaline sulfate is water soluble drug. The large or intermediate sized unilamellar vesicles are the most appropriate types to achieve as a high value as possible for entrapped volume: lipid

ratio. This means a large core available for entrapping a large amount of drug mass, so that the entrapment efficiency is higher for larger vesicles prepared by span 20 than those prepared by span 80 [33] .
Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size [34].The encapsulation efficiency of terbutaline sulfate in vesicles prepared by tween 60 (F11t) was larger than those prepared by span 60(F3t) and it's about 85.246%±4.74 . Tween is more hydrophilic than span (span molecule + 20 molecules of ethylene oxide =tween) the balance of the hydrophilic and hydrophobic moiety of the surfactants/cholesterol mixture has been an important reflection for high entrapment of water-soluble substances. Surfactants with the larger hydrophilic head group such as tween 60 gave higher entrapment efficiency than those with the same alkyl chain ,but had the smaller hydrophilic head group [35].The same result was obtained from encapsulation of diclofenac diethylammonium in niosome [36] .
On the other hand formulations such as F14t, F15t and F16t that represent a combination between span and tween, the encapsulation efficiencies are higher than the others, for the same reason in which spans have high transition temperature, while formula F13t offered the lowest percentage of entrapment perhaps due to a non homogenous dispersion obtained between liquid nature of tween 20 and the solid powder of span 60 at room temperature.

In vitro permeation:

The effect of different surfactants on drug permeation profile was estimated (figures 5, 6 and 7) and the permeated value was variable from one to another. No considerable variation was observed at 8 hours in excised rabbit skin permeation profile of formulations containing span-40(58.8%) and span-60(57.585%).

On other hand span 20 shows 73.305% for drug-permeated percent at 8 hours, due to their higher phase transition temperature; this is responsible for their less permeable nature (37). 46.04% of drug permeated was found by means of tween 60(F11t) .This was probable due to the larger size of the vesicles and the less lipophilic nature of the tween, which makes it more difficult for these vesicles to go through or fuse with the skin .

On comparison with free dug solution, a low percent of drug permeated was obtained (15.06%). The adsorption and fusion of niosomes onto the surface of skin and the role played by the constituents of niosomes might facilitate drug permeation across skin. The interaction of niosomes with skin possibly leading to high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of drug [38] and alters the barrier properties of stratum corneum thus enhancing permeation. The higher flexibility of

this vesicle is responsible for the improved transdermal penetration. The different molecular shape of the amphiphiles molecule, render the membrane more flexible. Because of the flexibility of vesicle membrane these vesicles can changes its shape easily owing the stress , therefore such vesicle require significant less energy to pass through the small pores ,and penetrate into the deeper layer [39].

The data obtained from formulations prepared from different span and tween surfactants was evaluated and the correlation coefficients R^2 was calculated as showing in table (4). The all formulations gave a linear release with zero order mechanism (figures 5, 6 and 7).

Table (4): In Vitro Permeation of Terbutaline Sulfate from Selected Formulations

First order equation, $\log Q = \log Q_0 - kt/2.303$, Higuchi equation, $Q = k\, t^{½}$, Zero order equation, $Q = k\, t$, Korsmeyer-Peppas equation, $Q_t/Q_\mu = kt^n$

Formulation code	Zero order	First order	Higuchi model	Korsmeyer-peppas
F1t	0.990263	0.994613	0.956238	0.710455
F2t	0.997012	0.995824	0.926413	0.807802
F3t	0.999017	0.994591	0.923131	0.832430
F5t	0.997007	0.996334	0.934171	0.816498
F6t	0.973494	0.941314	0.962005	0.778365
F8t	0.999808	0.948811	0.920391	0.810031
F10t	0.996762	0.996541	0.934098	0.813877
F11t	0.981433	0.989803	0.962737	0.731389
F12t	0.975089	0.820261	0.957972	0.631944
F13t	0.991491	0.988258	0.946709	0.755808
F16t	0.992305	0.994659	0.962737	0.802237
solution	0.993790	0.994984	0.941354	0.934436

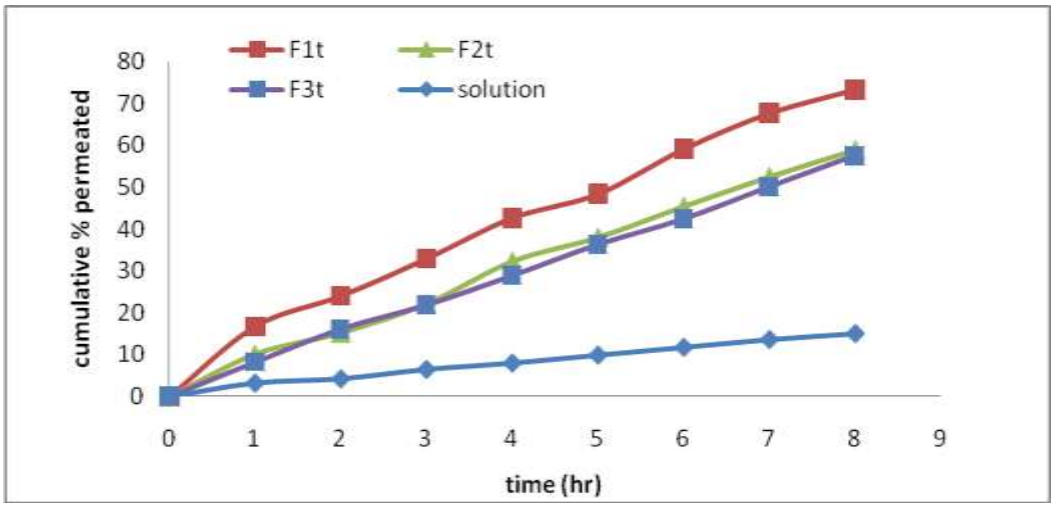

Figure (5): Effect of surfactant (single span) on in-vitro terbutaline sulfate permeation from **proniosomal gels** at pH 7.4 through rabbit skin in Franz diffusion cells at **37.5 ºC**.

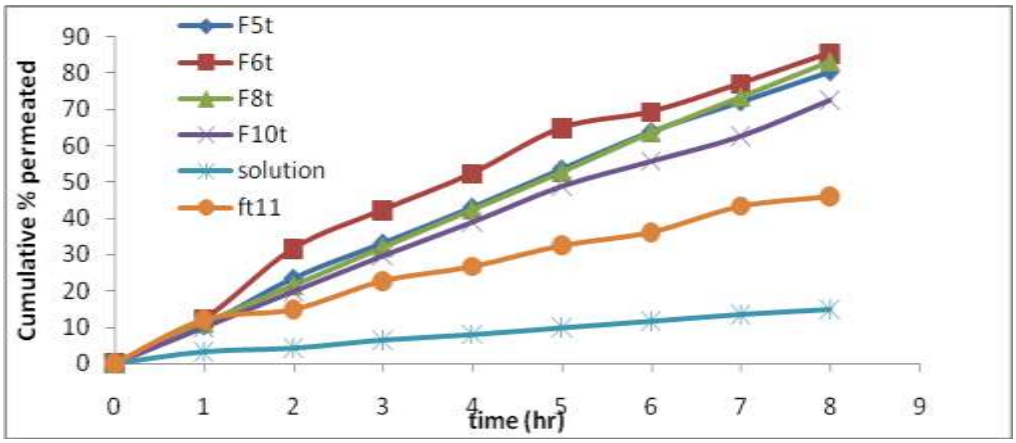

Figure (6): Effect of surfactants (mixture from two spans) on in-vitro terbutaline sulfate permeation from **proniosomal gels** at pH 7.4 through rabbit skin in Franz diffusion cells at **37.5 ºC**.

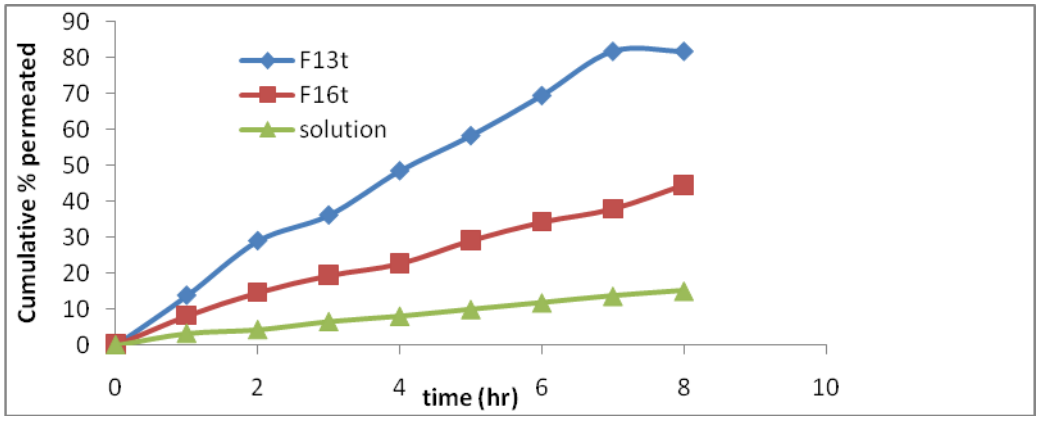

Figure (7):): Effect of surfactants (mixture of span and tween)on in-vitro terbutaline sulfate permeation from **proniosomal gels** at pH 7.4 through rabbit skin in Franz diffusion cells at **37.5 ºC**.

Conclusion:

Proniosome-derived niosome suspensions appear to be as good as or easier than the conventional niosome preparations. Also proniosomal gel can encapsulated hydrophilic drug such as terbutaline sulfate and possesses high entrapment efficiency. Experiments of the niosomes showed that the surfactant nature and vesicular size played an important role in enhancing permeation of drug. In addition, niosomal surfactants themselves act as penetration enhancers, due to interaction with liquid crystalline layers of stratum corneum.

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