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Microemulsion *versus* niosomes for the transdermal delivery of Repaglinide

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ABSTRACT

The antidiabetic drug, Repaglinide, was incorporated into a microemulsion and a niosomal carriers for transdermal administration to overcome the drawbacks associated with its oral formula. In the microemulsion formulation, pseudoternary phase diagrams were constructed to obtain the concentration range of the oil, surfactant (S) and co-surfactant (CoS) using three different S/CoS weight ratios. Microemulsion showed spherical particles with mean diameter ranging from 40.60 ± 13.04 to 58.94±0.02 nm and newtonian viscosity ranging from 58.94 ± 0.02 to 111.23±6.32 mPa.S. Compared to the marketed tablet, the release of repaglinide from microemulsion showed a zero order, controlled and continuous pattern. Repaglinide was also encapsulated in niosomal formulations. Niosomes showed vesicle size diameter ranging from 109 ± 6.2 to 263±11.9 nm with an entrapment efficiency of 77.9 ± 5.2 to 98.6±6.3 %. Compared to the oral tablet, release of repaglinide from niosomal vesicles showed a more uniform pattern however, a much slower rate. The microemulsion formulation (ME1) composed of triacetin as oil, Cremophor® RH40 and n-butanol as surfactant and co-surfactant, respectively, together with niosomal formulation (S) prepared using span 60 and cholesterol in ratio 1:1 were selected for the *ex-vivo* permeation. The permeation rate constant and permeation efficiency were found to be 65.5 µg/cm^2/h and 29.19%, respectively with micro emulsion ME1 and 11.42 µg/cm^2/h and 4.14 %, respectively with niosomal preparation S. It was concluded that the microemulsion transdermal delivery systems offered a controlled and more sustained drug release and permeation profiles compared to the niosomal formulations and to the commercial tablet.

INTRODUCTION

Diabetes mellitus is a universal disease that is associated with marked morbidity and mortality. First-line therapy usually comprises dietary control and weight loss, but 50-70% of patients will require an oral anti diabetic drug [1, 2]. Repaglinide is a new carbamoymethyl benzoic acid derivative which differs structurally from the sulphonylureas and belongs to the meglinitide group of drugs. Repaglinide shows a relatively low bioavailability (56-60% of oral administration) due to extensive hepatic first pass effect and low solubility [3]. Moreover, it has a low $t_{½}$, so it shows a dosing frequency of 3-4 times daily, this multiple oral administrations together with repaglinide being an insulin secretion stimulator lead to weakened blood glucose lowering action [4]. Traditional route of drug administration sometimes fail to optimize delivery of the correct concentration of medication. In such cases an alternative drug delivery carrier administered through an alternative route becomes a true requirement to overcome the drawbacks of the traditional ones [5]. Transdermal delivery offers many advantages over the oral route. Unfortunately, the barrier nature of the skin made it difficult for most drugs to be delivered into and through it. A number of delivery systems have emerged for transdermal drug administration, they are capable of achieving controlled and effecient drug delivery. Microspheres, nanotechnology, microemulsions, microcapsules and implantable pumps are considered appreciated systems [6], also,

vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and pharmacosomes were successfuly used.

Microemulsions (MEs) are able to encapsulate hydrophilic and lipophilic molecules.The administration of MEs offers a lot of advantages in dermal and transdermal drug delivery. They present a high solubilization capacity even for poorly soluble drugs. MEs have substantial penetration enhancing effects for extremely lipophilic drugs when using a lipophilic colloidal phase [7]. Up to date, however, main point of criticism is the need of large amounts of surfactants to form MEs. Therefore, a successful extended use of these colloidal carrier systems depends on the choice of well-tolerated surfactants and the restriction of their amounts.

Liposomes are unilamellar or multilamellar spherical structures consisting of lipid bilayers. Niosomes just like liposomes have attracted a great deal of attention in the delivery of dermal drugs because of being biodegradable, non-toxic, amphiphilic in nature, penetration enhancers and effective in the modulation of drug release properties[8]. In fact, if compared to liposomes, niosomes offer higher chemical stability, lower costs, and great availability of surfactant classes [8, 9].

The main objective of the present study was to develop a transdermal delivery system for repaglinide based on microemulsions and niosomes as drug carriers. Therefore, the development of repaglinide entrapped niosomal and microemulsion systems and their characterization to optimize the various formulations and process-related variables together with the assessment of the various characters, *viz.* degree of entrapment, size profile, *in vitro* release and their ability to carry the drug across the skin barrier (skin permeation studies) has been carried out.

To our knowledge, no work is done on repaglinide entrapped in transdermal carriers.

MATERIALS AND METHODS

Repaglinide was donated by Multipharma, (Egypt). Triacetin (glycerol triacetate), was obtained from Sigma Chemical Company, St. Louis, (USA). Dialysis tubing non-rate limiting cellulose membrane (molecular weight cut-off 12,000 g/mole), was obtained from Sigma Chemical Company, St. Louis, (USA). *n*-butanol, was purchased from BDH Laboratory Supplies, Poole, (England). Cremophor® RH40 (polyoxyl 40 hydrogenated castor oil), was kindly donated by BASF, (Germany). Potassium dihydrogen phosphate, disodium hydrogen phosphate, span 60, chloroform, ethanol and sodium chloride were purchased from Al Nasr pharmaceutical chemicals Co., ADWIC (Egypt).

Microemulsion

Construction of microemulsion phase diagram

The most significant problem associated with micro emulsion formulations is the difficulty inherent with excipients acceptability [10]. Triacetin, a synthetic triglyceride oil, often used in transdermal formulations [11] and oleic acid an oil known for its safety and high penetration enhancing abilities were used as short chain and long chain oil, respectively. In addition, two surfactants were used; Cremophor® RH 40 for being a non-irritant, safe and good emulsifier that is commonly used in microemulsion formulations [12] along with soybean lecithin. Whereas, *n*-butanol was selected as the cosurfactant. *n*- butanol is the most widely used cosurfactant in microemulsion preparation inspite of its possible irritation properties [13], in addition alcohols of short and medium chain length are necessary in preparation of lecithin based microemulsions to achieve the ultralow interfacial tension necessary for the formation of small droplets [14].

Pseudoternary phase diagrams were constructed in order to find out the concentration range of components that provide large microemulsion zones. Surfactant and co surfactant (S/CoS) were mixed at different weight ratios of 1:1, 2:1 and 3:1. At each specific S/CoS weight ratio, the ratio of oil to the S/CoS mixture was varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Each mixture of oil, surfactant and co surfactant, at specific weight ratio were titrated with water along water dilution lines [15, 16]. Following water addition, the microemulsion components were mixed using a vortex for 2-3 min then incubated at 25°C for 24h for equilibrium before second addition. Clear and transparent samples were marked as points in the phase diagrams and areas covered by these points were considered as the microemulsion region of existence, whereas, turbid and phase separated samples were considered unstable emulsion phases.

Preparation of microemulsion containing Ripaglinide

Drug loaded microemulsions were prepared as follows; the appropriate amount of oil, surfactant and co surfactant weight ratios were weighed in 5 ml glass vials and specified amount of Repaglinide was accurately weighed and added to the oily mixture, vortexed and then distillated water was added dropwise at ambient temperature. Drug loaded microemulsion was then sonicated for 1h and stored for 24h at room temperature for equilibrium before further investigations. Four microemulsion systems were prepared, in ME1 and ME2 triacetin was selected as the oil phase, n-butanol as co-surfactant and Cremophor RH40 and Soy Bean Lecithin (SBL) as surfactants, respectively. ME3 and ME4 were prepared using oleic acid as oil, n-butanol as co-surfactant and again Cremophor RH40 Soy Bean Lecithin (SBL) as surfactants, respectively.

Assessment and characterization of prepared microemulsions

Repaglinide content in microemulsion

Twenty four hours post preparation of the drug loaded microemulsion, the microemulsion formulation was centrifuged, filtered and the amount of drug was determined versus drug free microemulsion as blank at 283.2 nm after appropriate dilution with methanol using UV spectrophotometer (UV-vis spectrophotometer, Shimadzu, model UV-1601 PC, Kyoto, Japan).

Thermodynamic stability of Ripaglinide microemulsion

Thermodynamic stability was examined for microemulsions containing Repaglinide through the following procedures [15]:

(*i*) *Heating-cooling cycle* Six cycles were carried out between refrigerator temperature; 4°C and 45°C with storage at each temperature of no less than 48 h. The formulations that were stable at these temperatures were subjected to a centrifugation test. *(ii) Centrifugation test* Formulations passing test (i) were further centrifuged at 9000 rpm for 20 min (Refrigerated large capacity centrifuge, Union 32R, Korea). Those formulations that had no phase separation were used in a freeze-thaw stress test. (*iii*) *Freeze-thaw stress test* Three freeze-thaw cycles were carried out between 21°C and 25°C with storage of formulations at each temperature for not less than 48 h [17].

Physicochemical properties

Morphology and particle size

Morphology and particle size of the microemulsion droplets were studied using transmission electron microscope capable of point-to-point resolution (JEOL, JEM-1230 transmission electron microscope, Japan). One drop of the sample was deposited on a film- coated 200- mesh copper specimen grid and allowed to stand for 10 min after which any excess fluid was removed with filter paper. The grid was later stained with one drop of 3% phosphotungestic acid and allowed to dry for 5 min before examination. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the microemulsion droplets.

pH determination

The pH-values of microemulsions were determined in triplicate at 25°C using a digital pH meter (JENWAY 350, UK)

Viscosity measurement

The effect of water dilution on microemulsion viscosity was measured at 25ºC using a Brookfield viscometer (Brookfield DV Viscometer (model DV-II+; Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA).

Refractive index

Refractive indices of the prepared microemulsions were determined at 25°C (Higler and Walts refractometer, M46.17/ 63707, England).

***In vitro* release studies for Repaglinide microemulsion**

Release of Repaglinide, across a semi permeable; non-rate limiting; cellulose acetate membrane, from the drug loaded microemulsions was determined using a USP dissolution apparatus equipped with a rotating paddle (USP dissolution tester, model Hanson SE8-plus-85, USA). Half ml of the prepared microemulsion containing 1 mg drug was put in a clean dialysis bag. The bag was secured with two clamps at each end and placed into the apparatus containing 900 ml phosphate buffer pH 5.5. The buffer was kept at 32±0.5°C and stirred at 50 rpm. Aliquots of 5 ml at 0.5, 1, 2, till 8 h were sampled and replaced with fresh medium. The samples were analyzed for Repaglinide content spectrophotometrically (UV-vis spectrophotometer, Shimadzu, model UV-1601 PC, Kyoto, Japan) at 283.2 nm against a drug free microemulsion as a blank. The cumulative percentage of Repaglinide released across the semi permeable membrane was plotted as a function of time and the release rate was calculated from the slope of the straight line portion.

Niosomes

Preparation of niosomes

The niosomal formulations were prepared by lipid film hydration technique. [18]. Drug, Surfactant (S) and cholesterol (Ch) were weighed and dissolved in methylene chloride in a 100 ml round bottom flask. A thin lipid film was formed under reduced pressure in a rotary flash evaporator (Rotary evaporator, laboRota-4000 eco, Russia). The film was then hydrated by 10 ml of Phosphate Buffer Saline (PBS) pH 7.4 at room temperature with gentle shaking. The niosomal suspension was further hydrated up to 24 h at 2-8° C. The stabilized vesicles were used for further studies. Four niosomal formulations were investigated; S and S1 were prepared using Span 60 as surfactant in the ratio 1:1 and 1:4 S: Ch, respectively. Formula T and T1 were prepared using Tween 20 as surfactant in the ratio 1:1 and 1:4 S: Ch, respectively.

Assessement and characterization of niosomal formulations

Microscopy

All formulations were viewed under optical microscope to morphology of vesicles Optical micrographs were obtained with a Nikon TE-2000 inverted light microscope (magnification 900×).

Vesicle size determination

The vesicle sizes of niosomes were determined using the Malvern Mastersizer (Malvern, Model S, Ver. 2.15, UK).

Entrapment efficiency determination

The entrapment efficiency of niosomes was determined by the dialysis method (Hu and Rhodes, 2000). The unentrapped drug was removed by centrifugation at 9000 rpm (Refrigerated large capacity centrifuge, Union 32R, Korea). Residue were re-dispersed in 3 ml of phosphate buffer saline and placed in dialysis bag. The dialysis bag was then immersed in 25 ml of phosphate buffer saline solution (pH 5.5) maintained at 32°C and stirred with a magnetic stirrer. The receiver solution was completely withdrawn and replaced with fresh phosphate buffer saline (pH 5.5) at scheduled intervals of time, solution was measured spectrophotometrically at 283.2 nm (UV-vis spectrophotometer, Shimadzu, model UV-1601 PC, Kyoto, Japan) . This was repeated till the entire drug was removed from the niosomes. The difference between the amount dialyzed and the total drug incorporated was calculated and the entrapment efficiency determined.

***In vitro* release studies of Repaglinide from niosomes**

In vitro release pattern of niosome formulations was carried out by dialysis bag method. An amount of niosomes equivalent to 1 mg pure Repaglinide was weighed and filled in dialysis bag, the *in vitro* release experiment was then carried out as mentioned above under *in vitro* release of Repaglinide from microemulsion.

***Ex vivo* permeation studies of Repaglinide**

Permeation studies were carried out through hair-removed abdominal skin of male rat using Franz Diffusion Cell. The animals were sacrificed by an overdose of chloroform inhalation. The shaved part of the skin was separated from the animal and wiped off with a wet cotton swab soaked in isopropanol to remove any adhering fat material. The skin membrane surface area exposed to receptor phase was 3 cm diameter. In diffusion cell, phosphate buffer of pH 7.4 was used. Various Tested formulations (microemulsion and niosomes) each equivalent to 1 mg of drug was applied onto the prepared rat skin facing the donor chamber. An aliquot of 2 ml of samples was withdrawn at suitable time intervals up to 8 h and replaced with equivalent amount of medium to maintain the receptor phase volume as 50 ml. The samples were measured using UV spectrophotometer at 282 nm.

RESULTS:

Microemulsion

Phase diagram

Microemulsion systems were prepared with the oils, surfactant/co surfactant (S/CoS) combinations stated in table 1. Each system was prepared with S/CoS weight ratios of 1:1, 2:1 and 3:1. Pseudoternary phase diagrams were constructed using

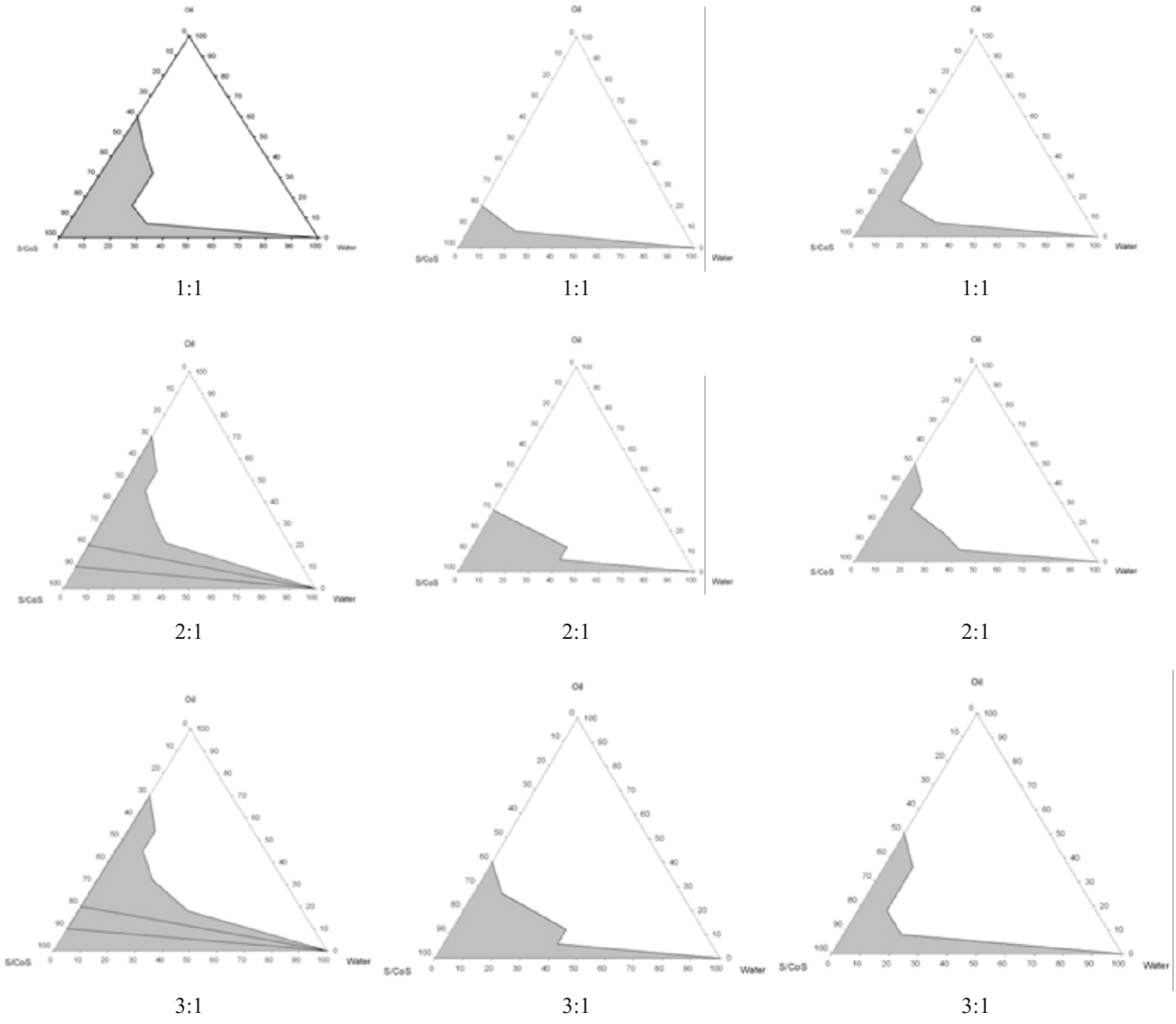

Figure 1. Pseudoternanry phase diagram of prepared microemulsion systems

water titration method at 25±1ºC, which corresponds to common conditions of preparation, storage and application of pharmaceutical microemulsions. In pseudoternary phase diagrams (figure 1) the grey areas represent the microemulsion regions. The rest of the regions on the phase diagrams represent conventional emulsion based on visual observations. Within the grey areas, microemulsions were formed with only gentle vortexing. This is possible as surfactant strongly localized on the surface of the emulsion droplets reduces interfacial free energy and provides a mechanical barrier to coalescence resulting in a thermo mechanically spontaneous dispersion.

The oil and S/CoS combination used in preparing system ME2 (table 1) didn't result in the formation of microemulsion monophasic system along its studied range. Increasing S/CoS weight ratio was generally accompanied by an increase in microemulsion existence area together with an increase in maximum amount of oil solubilised; this trend was observed in all of the prepared microemulsion systems. The increase in S/CoS ratio might have led to enhanced micelle formation which consequently, increased the solubilizing capacity of the microemulsion [19, 20].

Assessment and characterization of prepared microemulsions

Drug Content

Within the largest microemulsion region detected at S/CoS weight ratio 3:1 of phase diagram, a specific point was selected to compare the drug content and the physicochemical properties of the three prepared systems. This point contained the minimal amount of surfactant mixture capable of microemulsion formation (26% oil, 48% surfactant, 16% co-surfactant and 10% water).

One hundred *Percent* of repaglinide was entrapped in prepared microemulsions referring to the high solubility of the drug in the selected formulations**.**

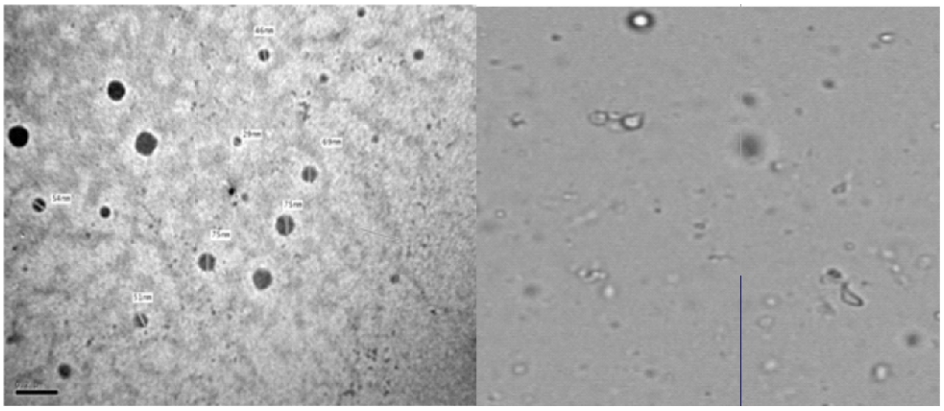

Figure (2): Transmission Electron Micrograph (TEM) photograph of microemulsion preparation (ME1, left), Optical micrographs of niosomal vesicles (S, right)

Thermodynamic stability

Thermodynamic stability differentiates microemulsions from conventional emulsions that have kinetic stability and will eventually phase separate [21].

Microemulsion formulae were tested for their thermodynamic stability utilizing heating cooling cycle, centrifugation and freeze thaw cycle - tests. All tests showed that microemulsions were thermodynamically stable with no phase separation, creaming or cracking.

Physicochemical characterization of microemulsion formulations

The Transmission electron microscopy (TEM) demonstrated clearly the spherical outlines of microemulsion droplets (figure 2). The diameter of formed micelles ranged from 40.60 ± 13.04 to 158.32 ± 8.14 nm as shown in table 3. This result are in accordance with a previous report stating that the co-surfactant molecules penetrate the surfactant film, lowering the fluidity and surface viscosity of the interfacial film, decreasing the radius of curvature of the micro droplets and forming transparent nanosized systems [22].

Microemulsion formulation, ME4, containing oleic acid and SBL/n-butanol showed the highest average particle diameter (158.32 ± 8.14 nm), the rigidity of the lecithin condensed film together with the electrostatic repulsion resulting from the presence of oleic acid at the level of the S/CoS film could lead to an increase in the microemulsion mean size.

pH values of the prepared microemulsion ranged from 5.32 ± 1.1 to 7.01 ± 0.09; these values are within the physiologic range accepted for dermal and transdermal preparations (4.5-7.0).It was recommended that microemulsion preparations should have refractive index not higher than 1.476 [17]. For the prepared microemulsions, the refractive index reading ranges were below this value proving that tested microemulsions were transparent and optically isotropic. The viscosity of tested microemulsion formulation followed a Newtonian behavior as expected for microemulsion [9].

The results of physicochemical characterization parameters are tabulated in table (1).

In vitro release studies for Repaglinide microemulsion

In Vitro release studies were carried out across a non-rate-

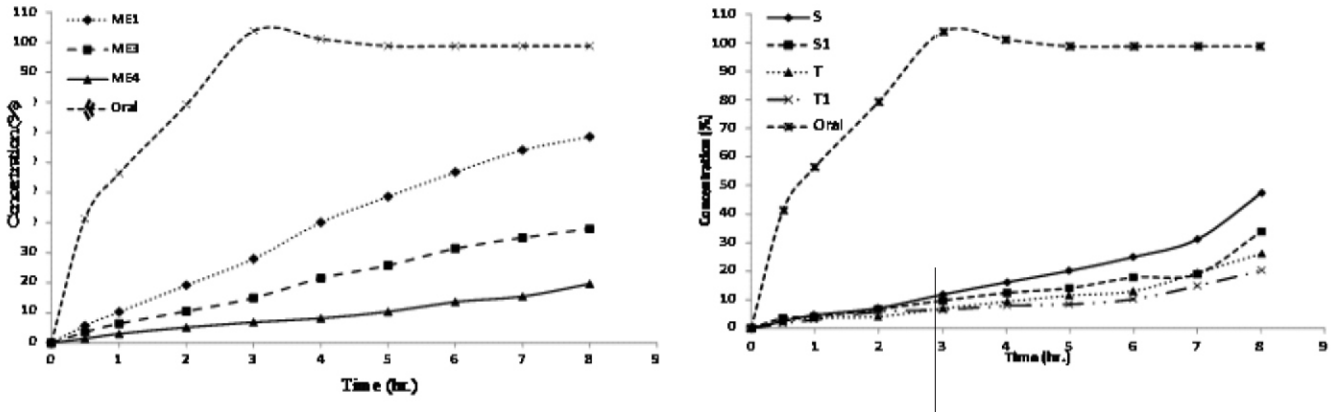

Figure (3): *In vitro* release of repaglinide from microemulsion formulations (left), *In vitro* release of repaglinide from niosomal formulations compared to the oral marketed product (right)

Table 1: Physicochemical characterization of Repaglinide microemulsion

Formula	Particle diameter* (nm)	pH*	RI*	Behavior	Viscosity *(mPa.s)
ME1	40.60 ± 13.04	7.01 ± 0.09	1.437 ± 0.02	Newtonian	58.94 ±0.02
ME3	96.32±11.25	6.02 ± 0.65	1.441 ± 0.02	Newtonian	94.66 ±10.41
ME4	158.32 ± 8.14	5.32 ± 1.1	1.439 ± 0.00	Newtonian	111.23±6.32

limiting cellulose acetate membrane to assess drug release profiles of the prepared Repaglinide microemulsion formulations. The release profiles of tested microemulsions were evaluated by fitting the experimental data to different order kinetic equations. It was found that Repaglinide release from all microemulsion systems followed zero order kinetics (R^2; 0.9931, 0.9950 and 0.9859 for ME1, ME3 and ME4, respectively). Compared to the oral marketed tablet, the release of repaglinide from the prepared microemulsion systems was controlled and continuous over the 8 hours of the experiment period. Oral tablet showed a biphasic release profile with 100% of the drug released within three hours. It was clear that the release results were highly correlated with the viscosity of the formulations. ME1 formulated with triacetin and Cremophor® RH40/n-butanol possessed the lowest viscosity and the highest percentage of drug released in 8 hrs time whereas, microemulsion ME4 containing oleic acid and SBL/n-butanol showed the lowest viscosity and the lowest percentage drug released in 8 hrs (68.55% *vs* 19.7%, respectively), figure 3.

Me1 containing triacetin as oil, Cremophor® RH40 as surfactant and *n*-butanol as co-surfactant was selected for the *ex vivo* permeation study for having the highest release rate together with low particle size, viscosity in addition to high existence range of microemulsion which would guarantee to a great extent its stability. Permeation properties of Repaglinide from selected microemulsion were compared with the trade product *(figure 5).*

Niosomes

Tween and Span were used in preparing niosomes for their interesting properties such as biodegradability, biocompatibility, low toxicity and derivation from easily available materials [21, 22]. They have been tested in various pharmaceutical drug delivery systems and have proved to be specially able to prepare highly stable niosomes [23]. Surfactants with single alkyl tail could normally form micelles however; they need cholesterol to achieve suitable molecular geometry and hydrophobicity for vesicle formation.

All studied niosomal formulations were able to form vesicles.

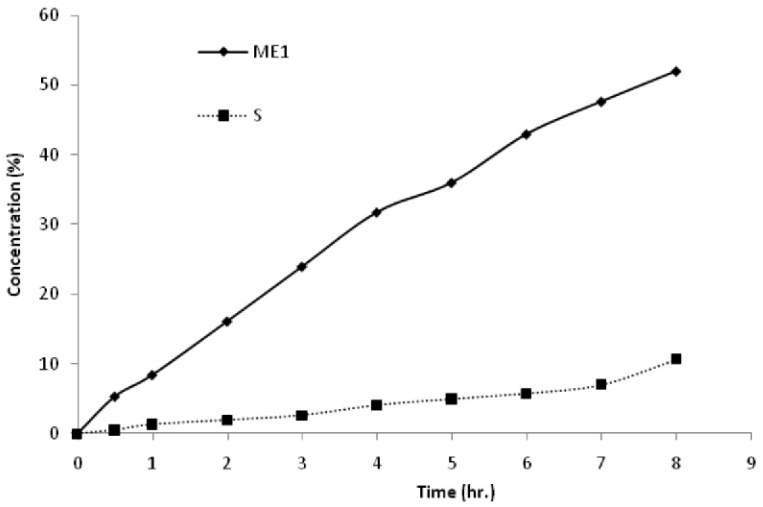

Figure (4): Ex vivo permeation of repaglinide through excised rat skin from microemulsion formulation (ME1) and niosomal formulation (S)

Table 1: Physicochemical characterization of Repaglinide microemulsion

Niosomal formulation	Vesicle size (nm)*	Entrapment (%)*
S	114±9.6	77.9±5.2
T	221±5.7	89.7±2.9
S1	109±6.2	83.3±7.0
T1	263±11.9	98.6±6.3

Niosomes appeared as translucent white dispersions that showed no sedimentation following extrusion. This appearance indicates their physical stability.

Morphology and vesicle size

All prepared niosomes showed a spherical morphology (figure 2). The mean vesicle sizes of the niosomal formulations are presented in table 2. Niosomes prepared with Span 60 were smaller than those prepared with Tween 20. The relationship observed between niosome size and Span hydrophobicity has been attributed to the decrease in surface energy with increasing hydrophobicity [24], resulting in the smaller vesicles. This would also explain the large vesicle size of niosomes prepared with Tween which have a much lower hydrophobicity than does Span.

Entrapment Efficiency

Niosomal formulations generally exhibited very high entrapment efficiency (table 2). This could be explained on the basis that the lipophilic portion of the drug is expected to be housed almost completely within the lipid bilayer of the niosomes. Similar observations have been previously reported [25].

In the case of niosomes, a correlation between amphiphile hydrophile lipophile balance (HLB) and vesicle size can be observed. In fact, niosomes made from span 60 (HLB = 4.7) showed a smaller mean size than those prepared with Tween 20 (HLB = 16.7). This behaviour can be explained because the higher the surfactant hydrophilicy, the higher the water uptake into the bilayer. Therefore, vesicle size increases as well as the amount of drug, which can be incorporated into the vesicular bilayers. In fact, the highest repaglinide incorporation efficiency (89.7 and 98.6 %) was observed for the large vesicles made with Tween 20. This improved incorporation of the lipophilic repaglinide is due to the increased capacity of the lipophile environment in the surfactant bilayer, which is capable of incorporating this amphipatic molecule to a higher extent. Therefore, the higher the surfactant HLB, the higher the amount of lipophilic drug, which can be intercalated into the niosomal bilayers. Therefore, repaglinide incorporation efficiency (E%) decreased with the decrease of the surfactant HLB as reported by [26] regarding nimesulide. The results are also consistent with the high entrapment efficiency of levonorgestrel in proniosomes incorporating Span 40 [27].

An increase in cholesterol concentration within the same lipid concentration in formulae S1 and T1 led to an increase in the entrapment levels of ripaglinide from 77.9% to 83.3% and from 89.7% to 98.6%, respectively. This might be attributed to the ability of cholesterol to cement the leaking space in the vesicle's membrane, which in turn allow enhanced entrapment [28].

***In vitro* release of Repaglinide from niosomes**

Compared to the oral marketed tablet, release of repaglinide from niosomal vesicles showed a more uniform however a much lower rate. Niosomal formulation S1 and T1 formed of 1:4 surfactant: cholesterol ratio showed lower amounts of released repaglinide in 8 hrs time (33.9% and 20.25%, respectively) compared to formulations S and T (47.3% and 26.12%, respectively), respectively . Increasing the cholesterol content might have resulted in a more intact lipid bilayer as a barrier for drug release and in turn decreasing its leakage by improving the fluidity of the bilayer membrane thus, reducing its permeability, which led to lower drug elution from the vesicles [29], (Figure 3).

Owing to their lower entrapment efficiency, niosomal formulations S and S1 showed a tendency towards releasing higher amounts of the drug from the vesicle compared to formulations T and T1, respectively.

Niosomal formulation S formed of 1:1 span 60: cholesterol was selected for the *ex vivo* permeation studies for its small vesicular size in addition to its high percentage drug released compared to other niosomal formulations.

***Ex-vivo* permeation study**

During this study, we compared the permeation data obtained from niosomal repaglinide formulation; S with those obtained from microemulsion formulation ME1 of the drug. The drug-flux was obtained by plotting the cumulative amount of ripaglinide in the receptor phase per square centimeter against time. Figure 4 describes the permeation flux of repaglinide from microemulsion (formula ME1) and niosomes (formula S). The permeation rate constant and permeation efficiency were found to be 65.5 $\mu g/cm^2/h$ and 29.19%, respectively with microemulsion ME1 and 11.42 $\mu g/cm^2/h$ and 4.14 %, respectively with niosomal preparation S. The skin penetration of drug and the consequently drug-transport abilities of microemulsion and niosomes can be explained on the basis of the presence of drug molecules in a solubilized state. This is achieved due to the aqueous and non-aqueous nature of the studied systems, most ideally suited for drug penetration. The prevailing hydrodynamic condition provides proper ground for better drugskin partitioning. Further, the permeation of repaglinide is observed to be more pronounced in case of microemulsion over niosomes. The higher drug permeation through mice skin achieved in case of microemulsion

proves its merit over niososmes. This reflects the impact of composition of formulation. The microemulsion content of water, oil, surfactant and co-surfactant proved to be better in generating and retaining the required physico-chemical state of the skin for enhanced permeation. Moreover, it results in their capacity to produce long lasting effect. Niosomes require components like cholesterol for CPP (critical packing parameter) to acquire the shape, and once deformed during the penetration process may not regain the same required structures. This explains that niosomes are comparatively less efficient in sustaining the suitable skin status for drug transfer.

In particular, niosomes seem an interesting drug delivery system in the treatment of dermatological disorders. However, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties, both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids [30].

CONCLUSION

Novel drug delivery systems have the ability to mend the drawbacks of conventional drug formulation. Thereby offering a good tool of developing disease treatment whilst minimizing the cost of discovering new drug entities.

Microemulsion formulation and niosomal preparation were used as novel drug delivery systems for the oral antidiabetic Repaglinide to overcome the drawbacks associated with its conventional oral tablet formula especially extensive hepatic first pass effect and high dosing frequency.

Microemulsion and niosomal systems of Repaglinide proved to be a good substitution for the oral form in the market due to its uniform controlled release action. So it is recommended to formulate Repaglinide microemulsion and niosomal systems in suitable topical transdermal preparations. Also it is recommended to investigate the in-vivo release of these formulated microemulsion and niosomal systems.

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