



Research Article

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ENHANCED INTESTINAL ABSORPTION AND BIOAVAILABILITY OF MICROEMULSION BASED FORMULATION AS DRUG DELIVERY SYSTEM FOR GLICLAZIDE

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ABSTRACT

Purpose: The present study is intended to develop and evaluate oil in water (O/W) microemulsion based formulation for gliclazide as oral drug delivery system for the treatment of diabetes mellitus. Gliclazide, having sulphonyl urea moiety (Class II of BCS system) is a hydrophobic drug.

Methods: Oil in water microemulsion was formulated using water titration method. Viscosity, pH, conductivity, particle size and thermodynamic stability studies were carried out for optimization followed by In vitro drug release and in vivo pharmacokinetic study.

Results: The formulated O/W microemulsion had olive oil, tween 80 and propylene glycol as ingredients with an average particle size 14.3 nm. The developed formulation showed a drug release of 82.4% while the pure drug in powdered form showed a release of 32.19% as observed through in vitro drug release studies. The data obtained by these studies was fitted to zero order, first order Higuchi and Korsmeyer Pappas models. The in vivo pharmacokinetic parameters of the optimized microemulsion was significantly ($P < 0.05$) different when compared to the conventional tablet formulation. The peak serum concentration (C_{max}) for the microemulsion ($2.998 \pm 0.419 \mu\text{g/mL}$) was higher than that for the conventional tablet ($2.118 \pm 0.169 \mu\text{g/mL}$), and the time required to reach the peak serum concentration (T_{max}) was significantly shorter for the optimized microemulsion ($2.5 \pm 0.548 \text{ h}$) compared to the tablet formulation ($5.333 \pm 1.033 \text{ h}$).

Conclusion: Gliclazide O/W microemulsion was found to be stable and showed superior in vitro and in vivo release. The study promises improved clinical efficacy for gliclazide as O/W microemulsion in the management of type 2 diabetes.

KEYWORDS: Microemulsion, Gliclazide, Immediate release, Pharmacokinetics, Thermodynamic stability, in vitro diffusion.

INTRODUCTION

Diabetes Mellitus commonly known as hyperglycemia is a collection of disorders primarily due to defective insulin release (Type I Diabetes Mellitus) or insulin sensitivity (Type II Diabetes Mellitus). Type I diabetes or Insulin Dependent Diabetes Mellitus (IDDM) is predominantly known as genetic disorder seen in children while Type II diabetes or Non-Insulin Dependent Diabetes Mellitus (NIDDM) is known as lifestyle disorder seen in adults. IDDM is treated with insulin and its analogues while NIDDM treatment involves oral therapy with hypoglycemic agents.

Gliclazide, an oral hypoglycemic agent is chemically a sulfonylurea, specifically [1-[(4-methyl benzene)sulfonyl]-3-(octahydro cyclopenta[c]pyrrol-2-yl)] urea. This drug is an insulin secretagogue with the mechanism that stimulates β cells of pancreas which release insulin thus controlling the blood sugar levels. Gliclazide belongs to class II drugs in Biopharmaceutics Classification System (BCS) [1, 2] which comprises of poorly soluble and highly permeable drugs. The low water solubility of gliclazide results in a low dissolution rate with inadequate and variable bioavailability [3].

Poorly soluble drugs often offer challenge not only for the

formulation design and development but also for the screening studies. Among several strategies adapted to improve bioavailability, the major concern has always been on enhancing drug's water solubility [1, 4, 5]. Solubility of the active pharmaceutical ingredient (API) in the gastric medium is of prime significance as its fair absorption through the intestine and its bioavailability depends on this property. Beside solubility the API must also possess decent permeability through brush border epithelial cells of small intestine which decides the bioavailability factor. Since improving aqueous solubility is an important criterion in formulation development, several techniques such as pH adjustment, hydrotropy, micellar solubilization, micronization (reducing particle size), chemical modification (salts, complexes, pro-drugs), solid dispersion, complexation, cosolvency were explored [6, 7]. Enhancing permeability could be achieved by using certain surface active agents in the formulation design which would not only improve aqueous solubility but also disrupt the inside layer of epithelial cells of the intestine. Since gliclazide is poorly soluble in aqueous solvents, microemulsification technique is utilized to reduce the particle size and improve the solubility of this drug.

Microemulsions are thermodynamically stable, isotropic, transparent or translucent systems mostly covering size range of 50-200nm [8-10]. They have attracted great attention in oral drug delivery systems for new drug candidates which are poorly soluble in water. These drugs face challenges because they are poorly bioavailable, possess subject variability and pose challenge for dose proportionality. Microemulsion system largely consists of four components: lipophilic phase, hydrophilic phase, surfactant and co-surfactant. The nano sized droplets have large surface area that influences the passage of the drug in the biological system.

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The objective of the current study is formulation and evaluation of oil in water immediate release microemulsion system for gliclazide and study the in vitro release kinetics and in vivo pharmacokinetics.

MATERIALS AND METHODS

Materials:

Gliclazide was a gift sample from Bal Pharma (Bengaluru, Karnataka, India). Polyethylene glycol 400 (PEG 400), Polysorbate 80 (Tween 80), Isopropyl Myristate (IPM), propylene glycol, methanol were procured from Merck (Schuchardt, Germany). Almond oil, soyabean oil, rice bran oil, olive oil, coconut oil, arachis oil and castor oil were obtained from standard sources. Milli-Q-water (Millipore, USA) was used throughout the process.

Preformulation studies:

Solubility study:

For preparation of microemulsion, different components were selected through solubility study using equilibration method [11]. A known quantity of the drug was dissolved in each of the oils, surfactants and cosurfactants by vortexing in stoppered vials, followed by shaking at 100 rpm for 72 hr on an orbital shaker at $25 \pm 10^\circ\text{C}$. These mixtures were then centrifuged at 3000 rpm for 15 min and the supernatant was filtered through 0.45 μm membrane filter. The dissolved drug was diluted within the linearity range and was measured spectrophotometrically using double beam uv-spectrophotometer (Shi-madzu UV-1700) at 228 nm.

Drug-excipient compatibility studies:

Fourier Transform Infra-Red analysis (FTIR) was used to study drug-excipient interaction by scanning the samples in the range of 400-4000 cm^{-1} . The pure drug was mixed with surfactant, co-surfactant and oil and this mixture was analyzed. Spectral comparison was done with FTIR of pure drug to eliminate the possibility of important functional groups of the drug interacting with the excipients.

Pseudoternary phase diagrams:

Simple water titration method by varying the ratio of oil, surfactant and co-surfactant is used to prepare a series of mixtures. A mixture of surfactants and co-surfactants were prepared initially (1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:12) and fixed volume of oil was introduced into these mixtures by gentle shaking and vortexing. The resulted mixture was titrated with water slowly with constant stirring on magnetic stirrer to allow equilibration. The end point of the titration could be identified by the turbid solution becoming transparent. Appearance of milky white and turbid mixtures indicated unstable emulsions that sooner or later phase separated and thus termed bi-phasic. The clear, transparent or translucent, low viscous mixtures indicated that they are monophasic. They were kept under observation at room temperature for a day.

The different ratios of oil, surfactant, co-surfactant and water from the titrations that resulted in mono-phasic mixtures were plotted on three diagonals of the triangle to construct pseudoternary phase diagram (Chemix software CHEMIX School 3_60, Evaluation Copy). The shaded area represented monophasic emulsions and considered as the area of existence of stable microemulsions. All titrations were repeated twice to get reproducible results.

Drug loaded microemulsions prepared by solubilizing drug in the oil and further following the same procedure as described earlier for microemulsification, were also used for plotting pseudoternary Phase diagrams. The influence of the drug on microemulsion area was observed.

Evaluation of Microemulsion System: Thermodynamic stability studies:

The thermodynamic stability of gliclazide microemulsion was evaluated using following stress tests in series. Physical stability of the formulations was checked by centrifugation at 3000 rpm for 30 min. Those formulations which didn't cream, crack or separate into two layers were subjected to the next test.

The stability of the formulations at extreme temperatures was tested by storing them at 45°C and 4°C each for a period of 48 hr.

This heating and cooling cycle was repeated six times. The formulations which were stable at these temperatures were progressed on to the next test.

The next stress test is freeze-thaw cycle that involved storing the formulations between -21°C and $+25^\circ\text{C}$ each for a minimum period of 48 hr.

The formulations that passed these stress studies were considered thermodynamically stable and selected for further optimization.

Physicochemical characterization:

Conductivity measurement

Electrical conductivity (σ) of the drug loaded microemulsions was studied using a conductivity meter (Elico CM 180). This measurement was done to study the effect of the amount of water in the microemulsion and to ascertain the type of the system; oil-continuous, bi-continuous or water continuous.

pH:

The pH values of drug loaded microemulsions were measured using a calibrated pH meter (Mettler Toledo, pHcompact 220) at $25 \pm 1^\circ\text{C}$. The measurements were done in triplicate.

Viscosity:

Viscosity measurement of the microemulsions was done in triplicates using Brookfield viscometer (DV-III +, Programmable rheometer).

Droplet size, polydispersity index and zeta potential measurement:

The droplet size, polydispersity index and zeta potential of the optimized formulation was measured by dynamic light scattering (DLS) using Malvern Zetasizer (S-90 Nano series).

In-vitro diffusion study:

The drug permeability study was executed by using a Franz diffusion cell fitted with a 0.45micron cellulose membrane pre-hydrated in distilled water at 25°C for 24 hr [12]. The receptor compartment was filled with 6.8 pH phosphate buffer and the donor compartment was charged with 10 mg of pure drug or 5 mL of the microemulsions. The diffusion medium was continuously stirred with a magnetic stirrer at 100 rpm throughout the experiment (Remi 2MLH). 2 mL of the sample was withdrawn from the receptor compartment at 1 hr time interval till 8 hours and immediately replaced with an equal volume of fresh buffer. The samples withdrawn were diluted with diffusion medium and the absorbance was measured spectrophotometrically at 228 nm. The percentage cumulative drug release was determined for the pure drug as well as the formulated microemulsion.

Accelerated stability study:

The accelerated stability study was conducted as per ICH guidelines [13] at $25^\circ\text{C} \pm 2^\circ\text{C} / 60\% \pm 5\%$ relative humidity (RH) and $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\%$ RH in the stability chambers (Thermo labs). Approximately 5 mL of the formulation is stored in tightly screw capped bottle. This 6 month study involved collection of samples at the interval of one, two, three and six months. The formulation was evaluated for various parameters such as physical appearance, phase separation at accelerated gravitational force, active ingredient content and globule size determination. Globule size was determined microscopically (Jenoptics optical systems with software ProgResRCapturePro2.7.7) throughout the study period to ascertain uniformity.

Determination of drug content:

The drug was extracted from the drug loaded micro-emulsion using methanol and was appropriately diluted and the drug content was measured by recording the UV/Vis spectrum by absorption peak at 228nm as well as by HPLC. The HPLC method was developed in house and the Chromatographic conditions were optimized for assay were; Stationary phase as C18 $5\mu\text{m}$ 250 x 4.6mm (WatersXBridge), flow rate at 1 mL/min, mobile phase as Methanol: 0.1% Trifluoroacetic acid buffer (80:20), column temperature of 25°C , injection volume of 20 μL , detection wavelength at 227nm and run time of 8 min.

In-vivo pharmacokinetic study:

The study conducted was approved by Institutional animal ethical committee of Karnataka College of Pharmacy, Bangalore (No.1564/PO/a/11/CPCSEA).

Animals:

Albino rabbits of both sex and of 3 months of age were used as study animals. They weighed between 1.35 to 1.75 Kg. Two groups comprising six rabbits in each group were formed; one group was administered with conventional tablet and second group with microemulsion. The animal laboratory maintained the temperature of $25 \pm 2^\circ\text{C}$ and $50 \pm 15\%$ relative humidity. The rabbits were given standard pellet diet and had free access to water. They were fasted for 18 h prior to the experiment. Food and water were withdrawn during the experiment too.

Preparation of animal dose:

Gliclazide is an orally administered drug as anti-diabetic therapy. Human oral therapeutic dose of the drug was extrapolated to rabbit based on body weight. Gliclazide conventional tablets were crushed into powder and dose equivalent to 80 mg of human dose was suspended in 0.5% sodium carboxy methyl cellulose. Oral gavage was used to administer both the formulations to the respective groups.

Sample preparation:

The blood samples (about 400-500 μL) collected from marginal ear vein of the rabbits with the help of heparinized needle (24 size) at the fixed time intervals at 0.5, 1, 2, 3, 4, 6, 8 and 12 hr after oral dosing into the EDTA coated tubes. These tubes were kept on rotating rollers and mixed for 10 min. Then they were centri-fuged at 5000 rpm for 5 min. The supernatant clear plasma is separated and stored at -20°C

until analysis. Plasma samples were analyzed by HPLC for finding out various pharmacokinetic parameters [14].

Determination of gliclazide in rabbit plasma by Reverse Phase HPLC:

The plasma samples were analyzed for the determination of the concentration of gliclazide by a standardized reverse phase HPLC method with slight modification. The Agilent 1120 Compact LC-HPLC system with gradient pump (400barr), rheodyne injector, UV variable detector, standard cell and Agilent syringe (50 μL) was used. The separations were achieved on Water's XBridge column (5 μm 4.6 x 250mm) with UV detection at 228nm. Analytical weighing balance (Shimadzu AUX220) was used for weighing, sonicator (EQUITRON-230VAC,50Hz), vacuum pump (SUPERFIT110336), filtration kit (TARSONS) with PALL membrane for solvents and sample filtration were used throughout the experiment. The EZChrome Elite software performed the acquisition, evaluation and storage of the obtained chromatographic data. Acetonitrile: water: trifluoroace- from 0 to infinity (AUC $-\infty$). Half-life ($t_{1/2}$ as 0.693/Kel.

RESULTS AND DISCUSSION**Criteria for the selection of components:**

One of the factors involved for the choice of components in the microemulsion system was solubility of the drug, so that on dilution in the gut the drug should not precipitate. Therefore it is important that the drug has high solubility in all the components used in the microemulsion system.

The results from the solubility study showed that olive oil has highest solubility of 16.73 mg/mL among all the oils used (Figure 1). Tween 80 and propylene glycol had more solubility of 27.38 mg/mL and 20.31 mg/mL compared to tween 20 and PEG 400 (Figure 2). Thus olive oil, tween 80 and propylene glycol were chosen as the suitable components of microemulsion system.

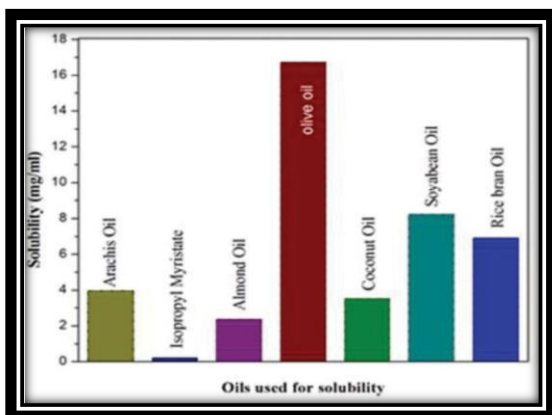


Fig. 1: Solubility of gliclazide in oils

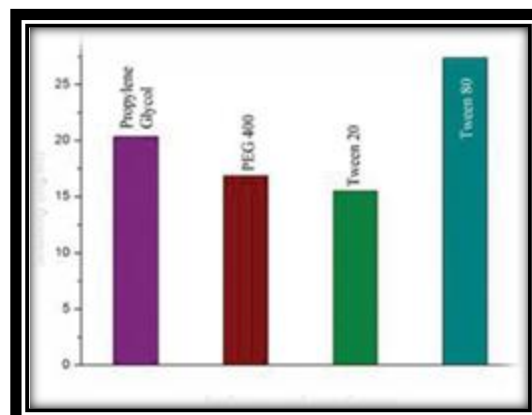


Fig. 2: Solubility of gliclazide in surfactants and cosurfactants

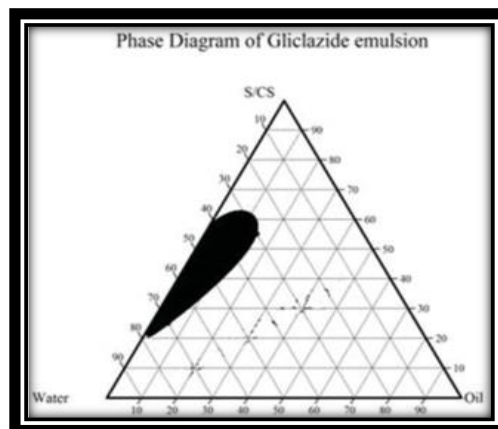


Fig. 3: Pseudoternary phase diagram for gliclazide with varying ratio of oil, surfactant, cosurfactant and water. Shaded area represents oil in water microemulsion region

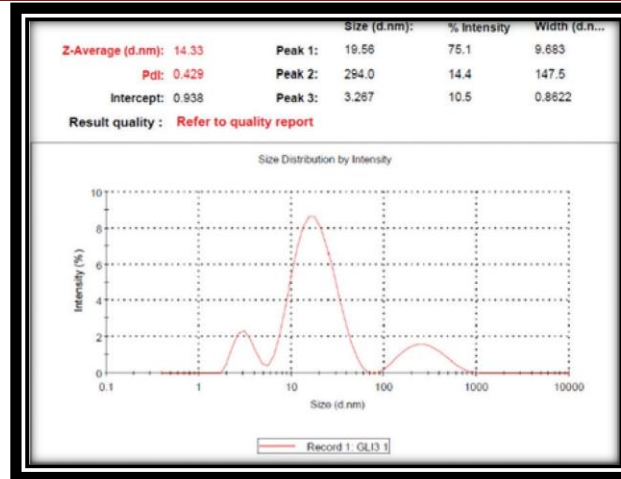


Fig. 4: Droplet size measurement of G3 microemulsion by dynamic light scattering technique

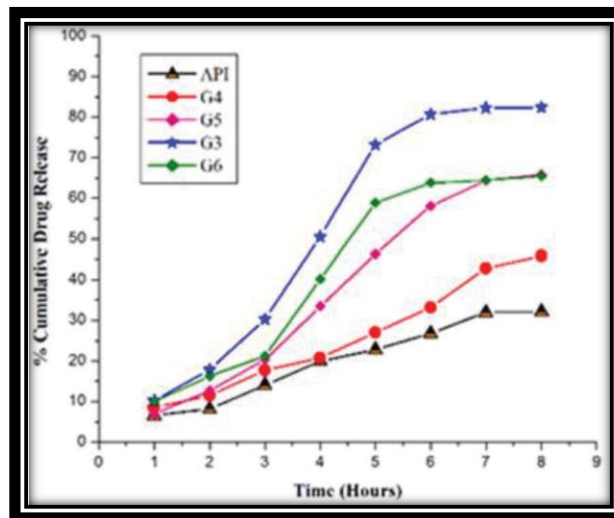


Fig. 5: *In-vitro* release profile of glizide in microemulsions

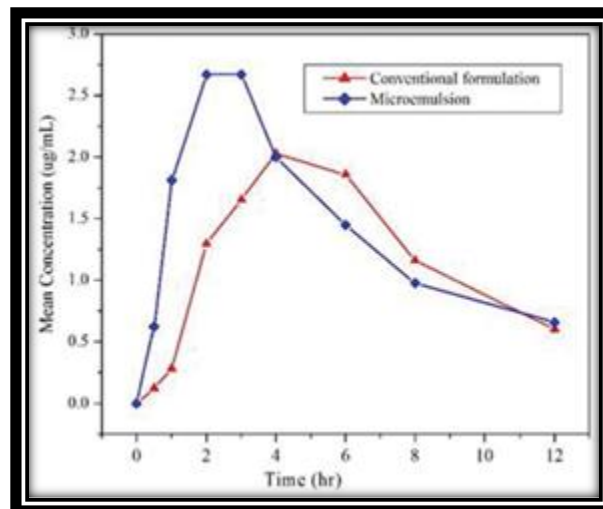


Fig. 6: Increase in plasma concentration of glizide after oral administration of microemulsion formulation in comparison with conventional tablet

Table No. 1: Formulations subjected to thermodynamic stability tests

Formulation Code	S _{mix} (%v/v)	Oil (%)	Appearance
G3	25	5	Clear and transparent
G4	35	7.5	Clear and transparent
G5	45	10	Clear and transparent
G6	55	15	Clear and transparent

Table No. 2: Regression values for different kinetic models

Formulations	% Cumulative Drug Release at 8 h	Regression coefficient (R ²)			
		Zero order	First Order	Higuchi	Korsmeyer Pappas
G3	82.4	0.9206	0.9356	0.9401	0.9672
G4	45.8	0.9826	0.9644	0.9386	0.9670
G5	65.8	0.9743	0.9722	0.9618	0.9854
G6	65.4	0.9305	0.9254	0.9875	0.9458
Pure Drug (API)	32.2	0.979	0.9824	0.9729	0.9679

Table No. 3: Accelerated Stability Study of G3 formulation

Temperature/Time period	Physical appearance	Phase separation	Centrifugation Test	Droplet size (nm)	Assay (%)
25 °C ± 2 °C / 60% ± 5% RH					
0 Month	Clear, transparent	monophasic	Pass	23	99.4
1 Month	No colour change/ cracking/ creaming	none	Pass	27	96.8
2 Months	Clear, transparent	none	Pass	32	97.2
3 Months	No colour change/ cracking/ creaming	none	Pass	36	98.2
6 Months	No colour change/ cracking/ creaming	none	Pass	37	96.8
40 °C ± 2 °C / 75% ± 5% RH					
0 Month	Clear, transparent	monophasic	Pass	23	99.4
1 Month	No colour change/ cracking/ creaming	none	Pass	42	98.4
2 Months	Clear, transparent	none	Pass	51	97.9
3 Months	No colour change/ cracking/ creaming	none	Pass	57	94.7
6 Months	No colour change/ cracking/ creaming	none	Pass	83	97.6

Table No. 4: Comparison of the Pharmacokinetic parameters of the conventional and microemulsion formulation

Parameters	Conventional formulation	Microemulsion Formulation
C _{max} (µg/mL)	2.118±0.169	2.998±0.419
T _{max} (h) *	6 (4-6)	2.5(2-3)
AUC _{0-t} (µg·h/mL)	14.436±0.657	17.006±0.966
AUC _{0-∞} (µg·h/mL)	18.077±1.837	22.247±2.731
T _{1/2} (h)	4.01±1.188	5.372±1.817
K _{el} (h ⁻¹)	0.188±0.062	0.138±0.033

*T_{max} is represented by median value (range)

Drug excipient compatibility studies:

The FT-IR spectrum shows the important functional groups present in the drug. Drug excipient compatibility studies are performed to eliminate any compatibility issues of any of the components in the microemulsion system with the drug. The spectrum indicated that none of the components interfere with the functional group of the drug.

Pseudoternary phase diagrams:

Construction of Pseudoternary phase diagrams taking variable concentrations of tween 80 (surfactant) with hydrophilic lipophilic balance (HLB) value of [15], pro-pylene glycol (co-surfactant), olive oil as oil phase and distilled water as aqueous phase gave crucial information (Figure 3).

It is clear that when surfactant and co-surfactant (S_{mix}) concentration is low the emulsion formed is biphasic and unstable. Such emulsions are turbid and milky white. As the S_{mix} ratio increases, the

clear, translucent to transparent microemulsions are formed which are stable and there is no phase separation. Another important factor is the concentration of oil in the microemulsion system which is required to solubilize the maximum quantity of drug. As the oil concentration increases, phase separation occurs. To prevent phase separation, S_{mix} ratio has to be increased which results in microemulsion system which may cause gastric irritation. Such formulations are highly viscous and not free flowing. Hence the pseudoternary phase diagram gives relevant information on the optimum ratio of oil, surfactant and co-surfactant that has to be used for preparation of a thermodynamically stable microemulsion system. To check the usefulness of the formulated microemulsion as suitable drug delivery system for glimepiride, the drug equivalent to one dose is incorporated into the oil phase and similar phase diagrams were constructed. The phase behavior of the drug loaded system did not change. The monophasic, clear and transparent formulations were further characterized for

thermodynamic stability as one of the criterion to optimize the best formulation (Table 1). The nonionic surfactants and cosurfactants; tween 80, propylene glycol and polyethylene glycol 400 used in the formulation reduce the interfacial tension between oily phase and aqueous phase that results in mono phasic microemulsion that remains stable over a period of time. Tween 80 is the commonly added pharmaceutical excipient that is considered non-toxic and inert, used to increase aqueous solubility.

Thermodynamic stability study:

The formulations which passed the visual tests and appeared clear and transparent were exposed to stress studies such as centrifugation, heating-cooling cycle and freeze-thaw cycle. G-3 and G-6 formulations cleared the stress tests and were further evaluated.

Physicochemical characterization:

Conductivity measurements:

The electrical conductivity was measured to understand the category of the microemulsion prepared as one among oil continuous, bicontinuous or water continuous. It was based upon percolation theory where conductivity was seen rapidly increasing with the increase in the amount of water. The swift increase of conductivity continues up to 40% (w/w) of aqueous phase addition and then onwards conductivity remained stagnant with further titration with water. A slight decrease in conductivity was observed on further dilution with water. These observations clearly point that the micro-emulsion prepared is water continuous type or oil in water microemulsion. When the conductivity measurement was done with drug-loaded microemulsion, the pattern followed was similar to that of drug unloaded microemulsion.

pH:

The pH of the selected formulations G3 and G6 was found to be 6.4 ± 0.100 and 6.8 ± 0.120 , respectively. It was observed that G6 has higher pH value due to higher surfactant content.

Viscosity:

The viscosity of G3 and G6 formulations was 50.0 ± 0.01 and 240.5 ± 0.08 cPs, respectively. With the increase in concentration of Tween 80 and the co-surfactant 1,2-propylene glycol, the viscosity also increased.

Droplet size measurement:

The size of the droplets in G3 was found to be 14.3 nm with a low poly dispersity index (PDI: 0.429) (Figure 4).

Zeta potential of microemulsion:

Zeta potential of G3 formulation was found to be 0.05 mV. Aggregation is not expected to happen, due to the slightly negative charge of the droplets.

In vitro release studies:

Release and diffusion of the drug from the micro-emulsion was calculated using the data of percentage drug diffused in the given time into the equations of zero order, first order, Higuchi and Korsmeyer Pappas model. Regression coefficients of all formulations in different orders were compared.

The in vitro drug release studies have shown the drug release for the optimized formulation across the cellulose membrane followed Korsmeyer Pappas model (Table 2). This was concluded by higher regression coefficient value in the curve fitting. Drug release from the G3 microemulsion and gliclazide suspension was found to be as 82.4% and 32.19% respectively (Figure 5). Surfactants and co-surfactants solubilize the oil by forming micelles thereby reducing the interfacial tension between oil and water. Hence the oil dissolved drugs solubility will be improved. Microemulsion showed higher drug release as compared to plain drug solution which may be due to solubility enhancing component of the surfactant and co-surfactant.

Accelerated stability study:

The results of the accelerated stability studies tabulated in Table 3 show that the microemulsion did not change significantly in the physical appearance, assay and droplet size. On microscopic

observation, no droplet aggregation was observed and the maximum globule size observed was 83 nm (<100nm).

Determination of drug content:

The amount of drug present in the stable microemulsion formulation G3 was found to be 99.4%.

In-vivo pharmacokinetic study:

The plasma concentration time profile of microemulsion and conventional tablet formulation in rabbit at dose equivalent to 80 mg of gliclazide is shown in Figure 6. Microemulsion administration resulted in swift rise of plasma gliclazide level up to C_{max} 2.998 ± 0.419 $\mu\text{g/mL}$ and AUC_{0-t} value was calculated to be 17.006 ± 0.966 $\mu\text{g}\cdot\text{h/mL}$ (Table 4). The observed pharmacokinetic parameters of gliclazide for the reference tablet formulation from this study, was in agreement with literature results [15]. Relative Bioavailability of gliclazide from microemulsion formulation was found to be greater than the bioavailability from that of marketed tablet formulation. The peak exposure of gliclazide was 1.42 fold higher and the extent of exposure was found to be 1.18 to 1.23 fold greater for microemulsion compared to the reference tablet formulation.

Microemulsions are known to have higher solubility in comparison to conventional formulations, and this strategy has been applied for improving solubility of drugs that have poor aqueous solubility [16]. Gliclazide is a BCS class II drug that is known for low solubility and high permeability. The effective surface area of this drug would directly influence its solubility and the dissolution rate. Thus high aqueous solubility at the site of absorption determines the rate of absorption.

The increased absorption of microemulsion can be attributed to nano sized fine droplets as observed in droplet size analysis. This increased surface area has direct impact on the improved contact with intestinal mucosa and thus better absorption. This is clearly indicated in reduced T_{max} for the microemulsion. Thus gliclazide microemulsion shows superior pharmacokinetic behavior owing to the improved aqueous solubility and enhanced surface area.

CONCLUSION

The efficient formation of drug loaded microemulsion of gliclazide with droplet size in the nanometer range has facilitated the incorporation of poorly water soluble drug gliclazide into the oil in water emulsion system. Effective solubilization of gliclazide was accomplished using the microemulsification method. It is evident that this novel formulation improves in vitro diffusion and systemic exposure that evidently points towards its better therapeutic efficacy to be used as oral drug therapy.

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