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Original Article

FORMULATION AND EVALUATION OF GLIPIZIDE MICROEMULSION

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ABSTRACT

Objective: The aim of the present study was to formulate a microemulsion for the oral delivery of Glipizide.

Methods: Microemulsion systems composed of oleic acid, isopropyl myristate as oils; tween 80, span 20 and cremophor EL as surfactants; propylene glycol, isopropyl alcohol as cosurfactants were investigated as potential drug delivery vehicle for delivery for glipizide. Pseudo-ternary phase diagram of the investigated system at constant surfactant concentration and varying oil/water or oil/cosurfactant ratios was constructed at room temperature by titration method. This allowed studying structural inversion from oil-in-water to water-in–oil microemulsion. Furthermore, electrical conductivity, *in vitro* dissolution studies, pH, centrifugation, % transmittance, viscosity, particle size, polydispersity index, zeta potential, DSC and accelerated stability studies were conducted.

Results: The results of electrical conductivity clearly indicated the structural inversion. Based on these values oil/water microemulsions were selected. The plain drug has shown only 40% of dissolution, while the drug from all the o/w microemulsions has shown>90% dissolution. Based on *in vitro* release studies f3, f12, f22 formulations were chosen. Particle size values of f3, f12, f22 formulations are 202.4 nm, 83.3 nm, 315.3 nm respectively. Viscosity results showed that the formulations follow the Newtonian flow.

Conclusion: The 3 formulations f3, f12 and f22 were successful in increasing the dissolution of glipizide in GIT and capable of sustaining the release of the drug for 8 h. From the viscosity, particle size, polydispersity index values, f12 was considered as the optimized formulation. Further, centrifugation, zeta potential and accelerated stability studies also indicated that the formulations were stable. DSC studies revealed no drug-excipient interaction in the optimized formulation. Owing to the above results microemulsion can be thus considered as a suitable oral delivery system for glipizide.

Keywords: Microemulsion, Oral delivery, Glipizide, Pseudo-ternary phase diagram, Dissolution, DSC studies

INTRODUCTION

During the recent decades, various colloidal systems have been investigated as suitable pharmaceutical vehicles for oral delivery of the active substance. Microemulsions are thermodynamically stable isotropically clear systems in which two immiscible liquids (i.e., water and oil) are mixed to form a single phase with an appropriate surfactant or its mixture. Hoar and Schulman introduced the word microemulsion, which they defined as a transparent solution obtained by titrating a normal coarse emulsion with medium-chain alcohols [1]. The short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and co-surfactant in the system makes the interfacial tension very low.

A microemulsion is considered as a suitable candidate for the oral delivery of poorly water-soluble drugs. It has the ability to improve drug solubilization, protection against enzymatic hydrolysis and enhance the potential for absorption of hydrophilic, hydrophobic and amphiphilic substances in the gastrointestinal tract (GI), caused by surfactant-induced permeability changes [2-6]. After oral administration, it readily disperses in the stomach to a small droplet of the microemulsion, which promotes a wide distribution of the drug throughout the GI tract. Microemulsion comprises structures such as water in oil (w/o), oil in water (o/w) and bicontinuous systems. These help in the release of the drug. The microemulsion can also sustain the release the drug if the partitioning of the drug between water and oil phases strongly affects the drug release [7-9]. It can be formulated as an oil in water and water in oil microemulsion. Oil in water microemulsion is considered as a promising approach to improve the solubility and oral bioavailability of hydrophobic drugs such as cyclosporine [10] and also to sustain the release. Hydrophobic drugs will be solubilized in the dispersed phase and the thick layer of an emulsifying agent that surrounds the dispersed phase helps in sustaining the release of the drug. On the other hand, water in oil microemulsion is considered as an approach to improve the bioavailability and to sustain the release of hydrophilic drugs across the intestinal mucosa [11]. Therefore, it is important in our study to formulate oil in water microemulsion to improve the oral delivery of a hydrophobic drug, glipizide.

Glipizide, a second generation sulfonylurea, is used for patients with non-insulin dependent diabetes mellitus who have failed diet and exercise therapy. It appears to be the most effective insulin secretagogue both in first phase insulin secretion and in sustained stimulatory response during long-term administration. It is a sparingly water-soluble drug with a solubility of 37.2 mg/l. The percentage release and the bioavailability of glipizide given orally are low [12]. The novelty in the work is to develop a novel oral formulation of poorly water soluble drug, glipizide, which was not reported earlier with the used ingredients. A vast *in vitro* study was also performed. So, in the present study, a microemulsion of glipizide was developed and evaluated *in vitro* to increase the percentage of drug release in GIT and also to sustain the release with a hope of improving the bioavailability and half-life of the drug in further studies.

MATERIALS AND METHODS

Glipizide was provided as a gift sample from Aurobindo laboratories Ltd, Hyderabad, India. Cremophor EL was obtained from Signet chemical corporation, Mumbai, India. Oleic acid, isopropyl myristate, isopropyl alcohol, propylene glycol, ethanol, tween 80, span 20, sodium chloride were obtained from SD fine chemicals Private Limited, Gujarat, India. Solvents and all the reagents were of analytical grade.

Construction of phase diagram

Phase diagrams were used to construct different regions of microemulsion formation, from which a large number of potential microemulsions could be determined [13]. The pseudo-ternary phase diagram was constructed by titration of homogeneous liquid mixtures of oil, surfactant, and water with a cosurfactant at room temperature. Oil, glipizide, surfactant and water blend were prepared and cosurfactant was added drop by drop, under mechanical stirring. In this experiment, the contents of oil and water were varied in the ratio of 90:10 to 10:90. Transparent, single-phase, low viscous mixtures were designated as a microemulsion. After the cosurfactant titration, in order to establish the microemulsion regions, phase diagrams were constructed for the following 3 systems.

System I-Oleic acid: Tween 80: Propylene glycol.

System II-Isopropyl myristate: (Tween80-Span20): Isopropyl alcohol.

System III-Oleic acid: Cremophor EL: Isopropyl alcohol

Preparation of glipizide microemulsion

Microemulsions were prepared by cosurfactant titration method [14]. In this method about 2.5 mg of glipizide for 5 ml formulation was accurately weighed and taken in a beaker. It was dissolved in an appropriate amount of oil. To this required amount of surfactant and water were added. The preparation was then gently stirred with a mechanical stirrer until all the components were mixed properly. Cosurfactant was then added dropwise to this preparation until the solution was clear. The samples were then stirred for 15 min to allow equilibration.

Characterization of microemulsion

Conductivity measurements

The electrical conductivity of the samples was measured using a Digital pH/conductivity meter (model DI-707, Digisun electronics, Hyderabad). Conductivity was measured by using 0.01N sodium chloride solution instead of using water. The measurements were performed in triplicate at 25 °C

***In vitro* drug release studies**

Dialysis tube method was used for performing the dissolution process. In this method, a boiling tube was taken which was opened at both the ends [15]. To this tube, a cellophane membrane was attached at one end, which was previously soaked in 7.4 pH buffer for 24 h. 5 ml of microemulsion was taken from the other end of the tube. This setup was attached to the paddle of the dissolution apparatus. The dissolution medium consisted of 50 ml of freshly prepared phosphate buffer of pH 7.4. The release study was performed at 37±0.5 ^{o}C, with a rotation speed of 50 rpm. Samples of 3 ml were withdrawn at 1, 2, 3 up to 8 h at regular one-hour intervals and replaced with fresh medium. Dissolution of placebo microemulsion was performed in the same manner and samples were utilized as blank for the respective drug loaded microemulsion. The samples were analyzed by UV-Visible spectrophotometer at 276 nm. The release studies were performed in triplicate.

pH determination

The pH values of the samples were measured by a Digital pH meter (model DI-707, Digisun electronics, Hyderabad) at 37±1 ^{o}C.

Centrifugation

In order to eliminate metastable systems, the selected drug-loaded microemulsions were centrifuged (Research Centrifuge, R-24, Remi Instruments Limited, Mumbai) at 4000 rpm for 4 h.

Percent transmittance

The percent transmittance of the system was measured using UV-Visible double beam spectrophotometer (model-2201, Systronics) at 560 nm using distilled water as a blank.

Rheological studies

The viscosity of the samples was measured using Brookfield Viscometer LVDV-II+P (Brookfield Engineering Laboratories, Inc. Middleboro, United states) fitted with an S-32 spindle. A Sample volume of 15 ml was used. All the microemulsions studied were subjected to shear stress of 0-20 Pa at different rpm (3, 6, 12, 30 and 60) and the rheological behavior of the disperse systems were examined by constructing rheograms of shear stress *vs.* shear rate.

Particle size, Polydispersity index and Zeta potential measurement

Measurements were made on a Zetasizer Nano ZS instrument at 25 °C at a wavelength of 633 nm and incorporate non-invasive backscatter optics (NIBS). At a detection angle of 173 °C measurements were made.

Differential scanning calorimetry measurements (DSC)

DSC measurements were performed with DSC TA Q100 instrument equipped with a refrigerated cooling system. Nitrogen with a flow rate of 50 ml/min was used as purge gas. Approximately 4 to 13 mg of sample was weighed precisely into hermetic aluminum pans. An empty hermetically sealed pan was used as a reference. Samples were cooled from 25 ^{o}C to −50 ^{o}C at a cooling rate of 5 ^{o}C/min, held for 3 min at −50 ^{o}C and then heated to 25 °C at a heating rate of 10 ^{o}C/min. All measurements were performed in triplicate.

Stability studies of optimized formulation

Stability studies were carried out for optimized formulation for 6 mo at 37±2 °C and 04±2 °C according to ICH guideline in a controlled chamber. The sample was analyzed periodically for physical appearance, rheological properties, pH and percentage release by UV-Visible spectrophotometer at 276 nm.

RESULTS AND DISCUSSION

Oleic acid, isopropyl myristate were lipophilic permeation enhancers and can be used to improve the membrane permeability of microemulsion [16, 17]. Tween 80, span 20, cremophor EL were nonionic surfactants and categorized as generally recognized as safe (GRAS) excipients, which were widely used in pharmaceutical preparations [18-20]. Surfactants were used in microemulsion preparation such that their hydrophilic lipophilic balance value is greater than 10. Cosurfactants propylene glycol, isopropyl alcohol were used in the concentration which was safe for oral use.

Pseudo-ternary phase diagram

A pseudo ternary phase diagram was constructed to determine the composition of the aqueous phase, oil phase, and surfactant: a co-surfactant phase that will yield a microemulsion. Among the various phases formed by these four components a field with clear and transparent liquid microemulsions was identified. A pseudo ternary phase diagram of microemulsions prepared with system I was represented in fig. 1(a). At low concentrations of water, clear microemulsions were obtained. But at concentrations>18%, gel-like preparation was formed. Replacement of water with 0.01N sodium chloride solution produced the same microemulsions as that obtained with water. This was not surprising, as the various components of microemulsion were non-ionic and thus unaffected by the ionic strength of the dispersed aqueous phase. It was clear from the pseudo-ternary phase diagram that, microemulsions in this system was formed with less than 18% of water, 2.84-32.73% of oleic acid, 45% of tween 80 and 17% of propylene glycol.

The pseudo-ternary phase diagram of system II was shown in fig. 1(b). In this system the ratio of tween 80:span20 was 1:1. This combination of surfactant produced a broader range of microemulsions as compared with the other microemulsion systems. It appears that stable microemulsions were formed with 3-47% of water, 3-42% of isopropyl myristate, 27% of tween80: span20 (1:1) and 25% of isopropyl alcohol. A representative phase diagram of system III was shown in fig. 1(c). Water concentration of up to 32% was used. Above this concentration, gel-like preparation was observed. Stable microemulsions were formed with<32% of

water, 2-28% of isopropyl myristate, 45% of cremophor EL: tween 80 and 22% of isopropyl alcohol.

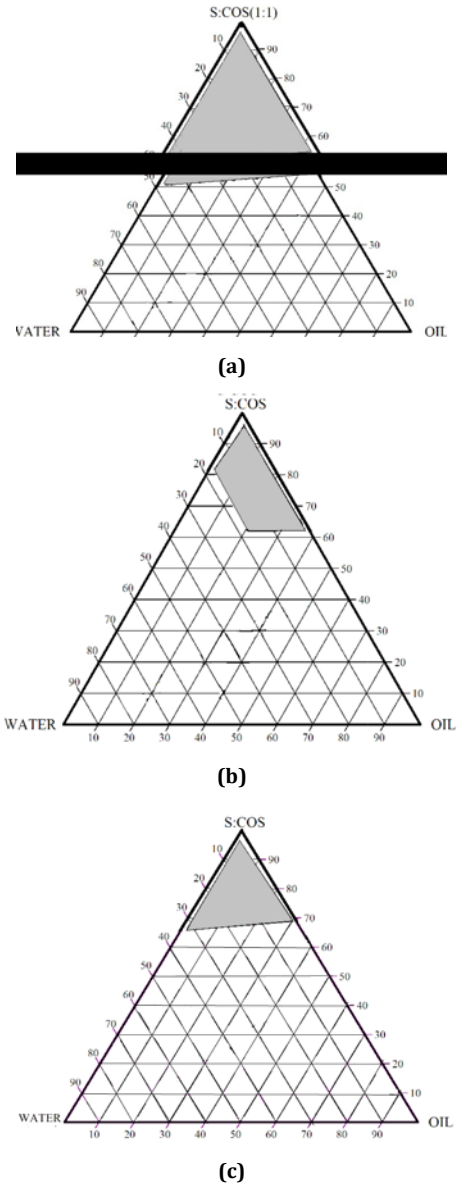


Fig. 1: Pseudo-ternary phase diagrams of a) system I b) system II c) system III

Characterization of microemulsion

Conductivity studies

Conductivity studies were performed by including sodium chloride solution in microemulsion instead of water. The electrical conductivity (σ) of the system I, as a function of percentage water content (Φw), was presented in fig. 2 (a). At concentrations of water<5% the conductivity of system I was 126mv. During water titration of>5%, the conductivity was suddenly increased to 176 mv. From Φw 6.66-17.75% (w/w), the conductivity of the system was not significantly affected by the further addition of water. After 17.75% there was no addition of water, a further addition of water lead to the formation of a gel. The increase in water incorporation was because of the presence of propylene glycol. When the volume of water increases, the electrical conductivity slightly increases until the critical Φw was reached where a sudden increase in conductivity was observed. This phenomenon was called as percolation, and the percentage of water at which it occurs is known as percolation threshold (Φp) [21]. The percolation threshold was observed at 13.2% water, where a network of conductive channels exists, which corresponds to the formation of water cylinders or channels in an oil phase due to the attractive interactions between the spherical microdroplets of the water phase in the w/o microemulsion. The Percolation threshold of up to 20% was observed in piroxicam microemulsion [22]. For the Φw>16.64% (w/w) the conductivity data can be explained by the dilution of microemulsion with the added water, which decreased the concentration of the dispersed oil droplets and increased conductivity. Thus, this σ–Φw curve illustrates the occurrence of the three structural regions: W/O (Φw<13.2% (w/w)), nonspherical W/O–bicontinuous–non-spherical O/W (13.2% (w/w)<Φw<16.64% (w/w)), and O/W (Φw>16.64% (w/w)).

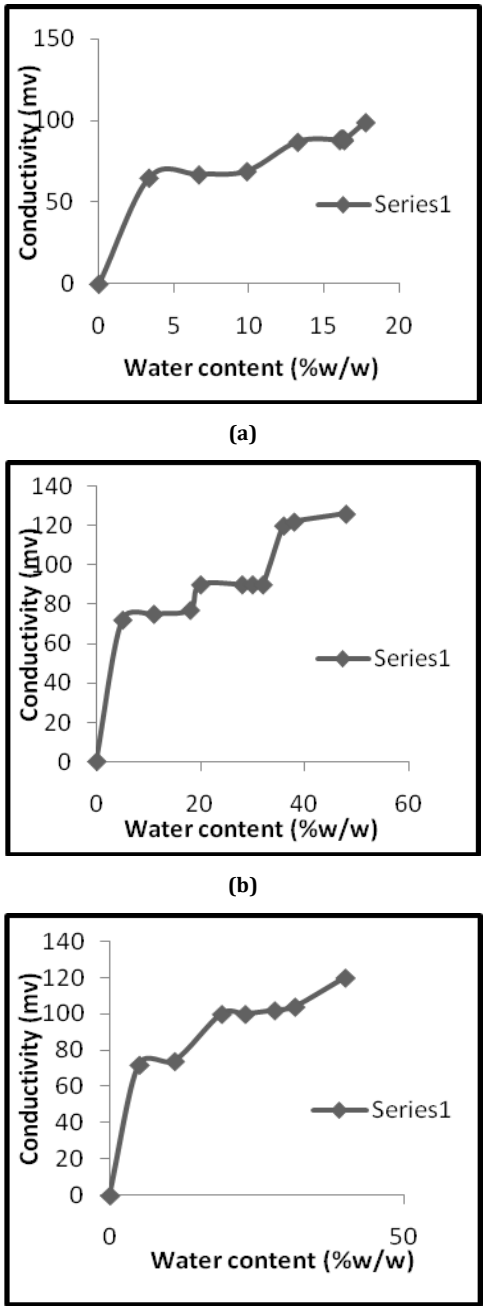


Fig. 2: Conductivity vs Φw profile of a) system I b) system II c) system III

The electrical conductivity of system II was presented in fig. 2 (b). At low fractions of water, i.e.<18%, the conductivity slowly increased from 72mv to77mv. After *Φ*w ~18% there was an increase in conductivity. From 18 %<*Φ*w<32% there was no significant increase in conductivity with the addition of water. At *Φ*w>32% there was again a raise in the curve. Further addition of water caused no significant increase in the conductivity of water. Thus, this *σ*–*Φ*w curve illustrates the occurrence of the three structural regions: W/O (*Φ*w<18% (w/w)), nonspherical W/O–bicontinuous–non-spherical O/W (18% (w/w)<*Φ*w<32% (w/w)), and O/W (*Φ*w>32% (w/w)). The electrical conductivity of system III was illustrated in fig.2 (C). At low levels of Φw<19% (w/w), there was a slow increase in the conductivity of water. After *Φ*w>19%, there was a steep increase in the conductivity of the formulation. After that, there was a slow increase in the conductivity of water until *Φ*w ~ 31.45%. Then a sudden increase in the conductivity was observed with the added water. Thus, this *σ*–*Φ*w curve illustrates the occurrence of the three structural regions: W/O (*Φ*w<19% (w/w)), nonspherical W/O–bicontinuous–non-spherical O/W (19% (w/w)<*Φ*w<31.45% (w/w)), and O/W (*Φ*w>31.45% (w/w). The observed conductivity curves of the 3 investigated systems as a function of water content enumerates the use of conductivity to measure the structural changes in microemulsions [23].

From the conductivity studies, O/W microemulsions were selected for carrying out *in vitro* dissolution studies [table 1].

In vitro dissolution studies

The dissolution studies of these microemulsions were compared with the dissolution profile of the plain drug. The release percentages at regular intervals were calculated and represented below in fig. 3.

Table 1: O/W microemulsions of glipizide selected from conductivity studies

Formulations	Oleic acid (%w/w)	IPM* (%w/w)	Tween 80 (%w/w)	Span 80 (%w/w)	C EL* (%w/w)	IPA* (%w/w)	PG* (%w/w)	Water (%w/w)
F1	2.84	_	44.81	_	_	_	34.37	17.75
F2	5.71	_	45.02	_	_	_	32.22	17.03
F3	11.53	_	45.45	_	_	_	26.79	16.26
F10	_	2.98	14.6	14.6	_	22.04	_	46.36
F11	_	9.09	14.77	14.77	_	22.27	_	39.07
F12	_	12.18	14.85	14.85	_	22.39	_	35.7
F20	2.90	_	_	_	43.6	21.95	_	31.53
F21	5.99	_	_	_	43.84	22.06	_	28.10
F22	9.03	_	_	_	44.06	22.17	_	24.71

*IPA-Isopropyl alcohol, *PG-Propylene glycol, *IPM-Isopropyl myristate, *CEL-Cremophor EL

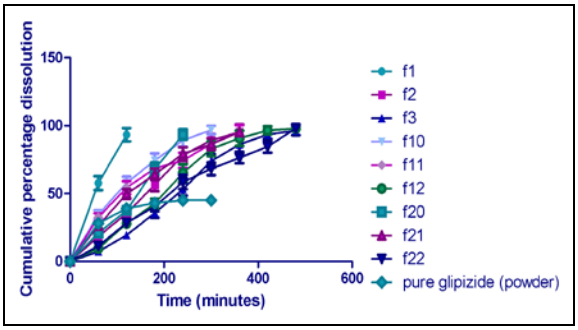


Fig. 3: *In vitro* release profile of o/w microemulsions data represents mean±SD (n=6)

Dissolution studies of pure glipizide have shown only 40% release owing to its poor dissolution and solubility in water. Formulation f1 have shown 93% release within 2 h, but not able to sustain the release. The fast release may be because of more amount of propylene glycol in the formulation which enhances the permeability of drug and also the presence of less oil content. This formulation can be suggested as immediate release formulation of glipizide. Formulations f2, f10, f11, f20, f21 showed good percentage release but are not capable of sustaining the release. However the formulations f3, f12, f22 showed>95% release and also sustained the release for 8 h. This may be because of the more internal oil phase and more solubilization of the drug in the oil phase. So, it takes time for the drug to diffuse through oil phase, surfactants, enter into the water phase and then reach the surrounding buffer. Hence, the formulations f3, f12, f22 were chosen taken for further studies. S. N. Deepak has shown similar dissolution profile for guaifenesin and phenylephrine microemulsion (100% drug release in 6 h), where oleic acid, tween 80, water and 2-propanol were used as formulation ingredients.

The cumulative percentage release of each optimized formulation at different time periods was fitted in various kinetic models [table 2]. The r^2 values>0.976 reveals that the drug follows zero order release profile. The value of n>0.8 indicates super case II transport of glipizide from microemulsion. This shows that the rate-limiting step in the release of glipizide was dissolution controlled release and not diffusion controlled release.

Table 2: Release kinetics of microemulsions selected

Formulation code	Parameters	Zero order	First order	Hixson crowell ($Q^{1/3}$-Qt)	Koresmeyer peppas (n)
F3	slope	0.125	-0.0001	3.736	0.825
	r^2	0.9760	0.961	0.970	0.977
F12	slope	0.141	-0.001	4.122	1.031
	r^2	0.979	0.923	0.930	0.892
F22	slope	0.137	-0.001	4.003	0.922
	r^2	0.994	0.865	0.936	0.992

pH studies were performed for the three formulations and found that the formulations have a pH near to neutrality. This indicates that they are not too acidic nor too basic, thus safe to take it orally. Centrifugation studies were done at 4000 rpm for 4 h and no phase separation was observed in all the optimized formulations which show that the samples were not metastable forms, which undergo phase separation easily, but were stable. Percentage transmittance studies were performed at 560 nm by using UV-Vis spectrophotometer. The results have shown>99.90% transmittance, which indicates that the microemulsions were transparent which is

considered as the primary property of a microemulsion [table 3]. The rheological studies of chosen formulations were investigated at 4 different shear rates at 303 °K which was shown in fig. 4. It was observed that viscosity was constant with an increase in the shear rate for all the compositions. This indicates that the sample follows the Newtonian flow. The results of the rheological study also have shown low viscosity values. So, it is considered that the other characteristic property of microemulsion, i.e., the low viscosity was met. Hence, Newtonian flow and lower viscosity values help in easy packaging, handling of the microemulsion and also helps to increase patient compliance upon oral administration. Out of the three formulations, f12 has viscosity very much lower than the other two formulations. Particle size analysis indicates that the size and polydispersity index (PDI) of f12 is much lower than formulations f3 and f22 [fig. 5]. Lower the particle size; greater is the permeation of microemulsions through the gastrointestinal tract and greater will be the bioavailability. PDI values of f12 indicate that droplet size in the formulation was uniform. The results of zeta potential showed that all the optimized formulations have good physical stability. The values confirm a net negative charge on the surface of the globule. From the above results of viscosity, particle size, PDI and zeta potential f12 formulation was optimized as a final microemulsion. Further differential scanning calorimetric studies (DSC) were performed to determine its stability and drug entrapment.

Table 3: Evaluation studies of selected o/w formulations

Formulations	pH	%Transmittance	Viscosity(cps)	Particle size(nm)			PDI	Zeta potential
				Peak1	Peak2	Peak3		
F3	6.87±0.05	99.93±0.01	210±2.3	10±0.2	25±0.31	315.3±2.9	0.608±0.04	-27.2±0.2
F12	6.72±0.15	99.99±0.01	30±0.67	10±0.09	83.3±0.45	-	0.120±0.01	-29.8±0.1
F22	6.98±0.04	99.98±0.2	150±0.45	30±0.11	183±1.6	-	0.452±0.02	-25.7±0.4

Data represents mean±SD (n=3).

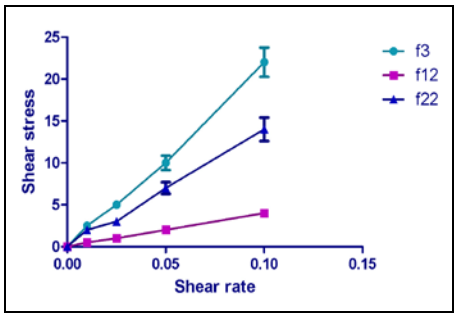
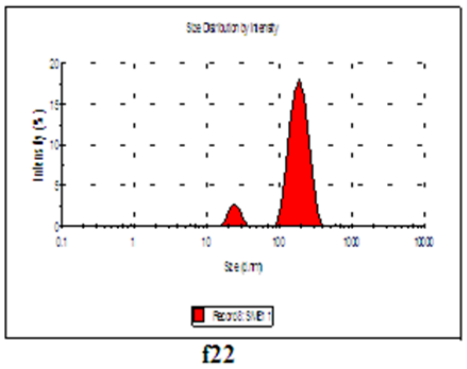
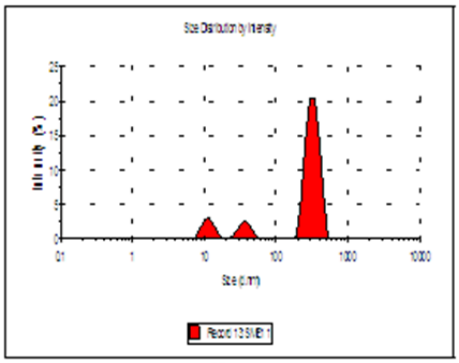


Fig. 4: Effect of shear stress on different rates of shear. Data represents mean±SD (n=3)

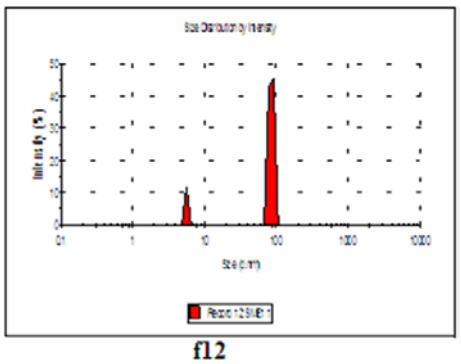


f22

Fig. 5: Particle size distribution of selected formulations



f3



f12

Differential scanning calorimetric study

Formulation f12 showed endotherms at 124.4 °c and 247 °C. Formulation f12 placebo showed endotherms at 128.6 and 254.2 °C [fig. 6]. Isopropyl myristate (IPM) oil showed endotherm at 212 °C. The endotherm of f10 at 247 °c and endotherm of placebo at 254.2 °C was due to the presence of IPM in the formulations. In f12, no peak for the drug was observed indicating that the drug was completely solubilized in the formulation.

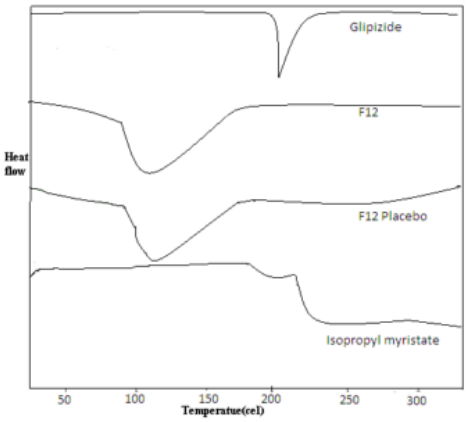


Fig. 6: DSC thermogram of glipizide, isopropyl myristate, f12 and f12 placebo

Further, stability studies were carried out for optimized formulation as per ICH guidelines at 37±2 °C, 4±2 °C in a controlled chamber. In periodic time intervals samples were withdrawn and retested for physical appearance, viscosity, pH and *in vitro* release for 6 mo. The physical appearance of the preparation was good without any phase separation or turbidity. The average pH of 6.8, viscosity of 40 cps and no considerable change in the percentage release, i.e., 95% was observed for 6 mo.

CONCLUSION

Pseudo-ternary phase diagram for the three microemulsion systems was delineated. Conductivity studies depicted the structural changes from w/o to o/w via bicontinuous phase. Particle size, viscosity, % transmittance, zeta potential studies were performed on selected formulations. From the three selected microemulsions, f12 was optimized. DSC, stability studies indicated that the formulation was stable. It was concluded the microemulsion f12 can be considered as a useful dosage form for oral intake of glipizide. Further *in vivo* tests have to be carried out to know the pharmacokinetic and pharmacodynamics parameters of the optimized formulation.

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CONFLICT OF INTERESTS

Declared none

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