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Research Article

GLIBENCLAMIDE LOADED SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS): DEVELOPMENT AND OPTIMIZATION

RAJESH B. NAWALE, BHARAT N. MEHTA*

Government College of Pharmacy, Aurangabad 431005 (M.S.), India. Email: bharat.mehta.d@gmail.com

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ABSTRACT

Objective: The objective of the present study was to develop and characterize self-microemulsifying drug delivery system (SMEDDS) of anti-diabetic drug glibenclamide for filling into liquid filling hard gelatin capsules.

Methods: Solubility of glibenclamide was evaluated in various nonaqueous careers that included oils, surfactants, and cosurfactants. Pseudo ternary phase diagrams were constructed to identify the self-microemulsification region. Preliminary screening was carried out to select proper components combination. Glibenclamide SMEDDS was prepared using Peceol (oil), Tween 20 (surfactant), Transcutol P (cosurfactant), and evaluated for self-emulsification property, droplet size, polydispesity index, zeta potential, optical clarity, drug content, in-vitro dissolution study in pH 7.4 phosphate buffer compared with plain glibenclamide and marketed tablet.

Results: The optimized glibenclamide SMEDDS composed of 15% Peceol, 44% Tween 20 and 41% Transcutol P with droplet size 81.13 nm, PDI 0.270, zeta potential -55.12 mV and complete drug release within 15 min as compared with marketed tablet and plain glibenclamide, which showed limited dissolution rate.

Conclusion: The results from this study demonstrate the potential use of SMEDDS as a means of improving solubility, dissolution, and concomitantly the bioavailability of glibenclamide.

Keywords: Glibenclamide, SMEDDS, Dissolution rate, Pseudo ternary Phase diagram, Droplet size.

INTRODUCTION

Glibenclamide is a second-generation sulfonylurea used in the treatment of noninsulin-dependent diabetes. It is one of the most prescribed long-acting anti-hyperglycemic agents [1]. Glibenclamide is classified as BCS class II drug, which means it has high permeability and poor water solubility [2]. The poor water solubility of glibenclamide is responsible for its poor dissolution rate, which ultimately leads to variable absorption of glibenclamide. Furthermore, there are reports which have documented that glibenclamide shows large variations in interindividual bioavailability and bioequivalence of the marketed products [3,4]. Thus, it can be concluded that the bioavailability and in vivo performance of glibenclamide is dependent on its dissolution rate. In view of this, researchers have attempted various techniques to improve the dissolution rate and, ultimately, the in vivo performance of glibenclamide. To date, the potential of various drug delivery approaches, such as amorphization [5], solid dispersion [6-8], cyclodextrin complexation [9,10], and permeation enhancers [10], has been established in improving in vitro and/or in vivo performance of glibenclamide.

The potential of microemulsions and/or self-microemulsifying drug delivery systems (SMEDDS) or anhydrous form of microemulsion in the improvement of the bioavailability and therapeutic performance of the hydrophobic agents has been very well-established [11-14]. In view of this, the present investigation was aimed at developing SMEDDS for the delivery of glibenclamide with droplet size <150nm, PDI<0.3, Complete drug release within 15 min.

MATERIALS

Glibenclamide was obtained as a gift sample from Atra Pharmaceutical Ltd. (Aurangabad, India). Lauroglycol 90, Transcutol P, Plurol Oleique CC 497, Labrafil M 1944 CS, Labrafac Lipophile WL 1349, Peceol were obtained as a gift sample from Gattefosse India Pvt. Ltd. (Mumbai, India). Tween 80, Tween 20, and PEG-400 (all AR grade) were purchased from Merck (Mumbai, India). Capmul MCM was obtained as a gift sample from Indichem international (Mumbai, India). Liquid filling hard gelatin capsules were obtained as gift sample from Grace Drugs & Pharmaceuticals (Hyderabad, India). All other chemicals and reagents used were of AR grade.

METHODS

Solubility Studies

The saturation solubility of glibenclamide was evaluated in various oils, surfactants, and cosurfactants. In this study, an excess amount of glibenclamide (approximately 200 mg) was added to 2 ml of each of vehicle in screw capped glass vials and the mixture heated to 60˚C in a water bath under continuous stirring using a vortex mixture to facilitate drug solubilization. The mixture was kept at ambient temperature for 48 hours to attain equilibrium. The equilibrated sample was centrifuged at 5,000 rpm for 15 min. Undissolved drug was removed by filtering with a membrane filter (0.45µm) [15]. The concentration of dissolved Glibenclamide was determined by UV-VIS spectrophotometer (UV-1700, Pharmaspec, Shimadzu Ltd, Japan) at ƛ max 226.5 nm.

Pseudo ternary phase diagrams

Pseudo ternary phase diagrams of oil, surfactant/ cosurfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a drop wise manner. For each phase diagram at a specific ratio of S/CoS (i.e.1:1, 2:1 wt/wt), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 min. Then each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addition on the microemulsion boundary, phase diagrams were also constructed in the presence of drug using drug enriched oil as the hydrophobic component. Phase diagrams were then constructed using TRI-PLOT V-1.4 software by David Graham (Loughborough University).

Preparation of SMEDDS formulations

A series of SMEDDS formulations were prepared using Tween 20/ Transcutol P as the S/CoS combination and Peceol as the oil were given in Table 1. In all the formulations, the level of glibenclamide was kept constant (5 mg). Briefly, accurately

weighed glibenclamide was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated at 40ºC on a magnetic stirrer, until glibenclamide was perfectly dissolved. The mixture was stored at room temperature until further use.

Table 1: Formulations of Glibenclamide SMEDDS.

Formulation	ME1	ME2	ME3	ME4	ME5	ME6	ME7	ME8	ME9
Glibenclamide (mg)	5	5	5	5	5	5	5	5	5
Peceol (%)	15	15	15	20	20	20	25	25	25
Tween 20 (%)	36	40	44	36	40	44	36	40	44
Transcutol P (%)	49	45	41	44	40	36	39	35	31

Determination of Droplet Size distribution and Zeta Potential

Each batch of Glibenclamide SMEDDS was dispersed in 100 ml of distilled water, at25±0.5˚C. The resultant emulsions were prepared by gentle agitation for 10 min using a magnetic stirrer. Droplet size distribution of all batches and the zeta potential of the final microemulsions were determined immediately using, Delsa Nano C particle size and zeta potential analyzer (Beckman Coulter, USA). All studies were repeated in triplicate, with good agreement being found between measurements.

Visual Assessment of Self-emulsification

A visual test to assess the self-emulsification properties reported by Craig et al. [16] was modified and adopted in the present study. In this method, a predetermined volume of formulation (0.2 ml) was introduced into 100 ml of water in a glass beaker that was maintained at 37ºC, and the contents mixed gently using a magnetic stirrer at 100 rpm. The tendency to emulsify spontaneously and progress of emulsion droplets were observed. On the basis of dispersibility, appearance and time required to emulsify SMEDDS were categorize in different grades were given in Table 2.

Spectroscopic characterization of optical clarity

The optical clarity of aqueous dispersions of glibenclamide SMEDDS formulations was measured spectroscopically. The formulations were diluted to 50 times with double distilled water and 0.1N HCL. The absorbance of each solution was measured at λ max 400 nm, using double distilled water/0.1N HCL as a blank.

Table 2: Visual assessment of efficiency of self-microemulsification

Grade	Dispersibility and appearance	Time (min)
I	Rapid forming microemulsion, which is clear or slightly bluish in appearance	< 1
II	Rapid forming, slight less clear emulsion, which has a bluish white appearance	< 2
III	Bright white emulsion (similar to milk in appearance)	< 2
IV	Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify	> 3
V	Exhibit poor or minimal emulsification with large oils droplets present on the surface	> 3

Self-Emulsification and Precipitation Assessment

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessment as previously reported [17]. In brief, different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by drop wise addition of the preconcentrate (SMEDDS) into 100 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), non-clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours) [18].

Drug content

The content of glibenclamide in the each SMEDDS formulation was determined by UV Spectrophotometer at λ max 226.5 nm.

In Vitro Dissolution Study

Glibenclamide SMEDDS (equivalent to 5 mg of glibenclamide) were filled in size "0" liquid filling hard gelatin capsules. In vitro release profiles of glibenclamide SMEDDS, plain glibenclamide, and marketed glibenclamide tablet (Daonil, Aventis Pharma Ltd.) were studied using United States Pharmacopeia (USP) XXIII apparatus II (Paddle Type) at 37±0.5°C with a rotating speed of 50 rpm in buffer pH 7.4 as the dissolution media. During the study, 2 ml of aliquots were removed at predetermined time intervals (5, 10, 15, 20, 30, 45 and 60 min) from dissolution medium and replaced with fresh media. The amount of glibenclamide released in the dissolution medium was determined by UV-VIS spectrophotometer at λ max 226.5 nm.

RESULTS AND DISCUSSION

Solubility Studies

The self-emulsifying formulations consisting of oil, surfactants, co-surfactants and drug should be clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution [19]. The solubility of glibenclamide in various vehicles is presented in Table 3. Amongst the various oily phases that were screened, Peceol provided the highest solubility of glibenclamide so were chosen for further investigations. The surfactant, Tween 20, Tween 80 showed good solubilizing power for glibenclamide, therefore, the selection of the surfactants in the further studies was governed by their emulsification efficiency rather than their ability to solubilize the drug [20], Tween 20 has more emulsification efficiency in preliminary studies. Transcutol P, which is a solubilizer and absorption enhancer, was found to be a very efficient solubilizer for glibenclamide, and so was chosen as a cosurfactant in the development of SMEDDS formulations aiming to improve the drug loading capabilities.

Pseudo ternary Phase Diagrams

Self-microemulsifying systems form fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and cosurfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation [21, 22]. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion.

In the present study Peceol (oil) was tested for phase behavior studies with Tween 20 and Transcutol P as the S/CoS mixture. As seen from the ternary plot in Figures 1, Peceol gave a wider microemulsion region at both S/CoS ratios (1:1 & 2:1). The microemulsion area was higher in S/coS ratio 1:1 then 2:1. However, it was observed that increasing the surfactant ratio resulted in a loss of flowability and increase in surfactant toxicity. Thus, an S/CoS ratio 1:1 was selected for the formulation study.

Table 3: Solubility of Drug in Oils, Surfactants, and Cosurfactants (n=3)

Vehicles	Chemical Composition	Solubility (mg/ml) mean ± SD
Transcutol P	Diethylene glycol monoethyl ether	17.60 ± 0.017
Tween 20	Polysorbate 20 / Polyoxyethylene (20) sorbitan monolaurate	8.30 ± 0.012
Tween 80	Polysorbate 80 / polyoxyethylene (20) sorbitan monooleate	8.60 ± 007
Peceol	Glyceryl monooleate	7.31 ± 0.022
Labrafac Lipophile WL 1349	Medium chain triglycerides	3.34 ± 0.061
Labrafil M 1944 CS	Oleoyl macrogolglycerides	2.85 ± 0.029
PEG 400	Polyethylene glycol 400	3.36 ± 0.036
Plurol Oleique CC 497	Polyglyceryl-3 dioleate	2.36 ± 0.14
Capmul MCM	Glyceryl Caprylate / Caprate	3.21 ± 0.018
Lauroglycol 90	Propylene glycol monolaurate	2.75 ± 0.017

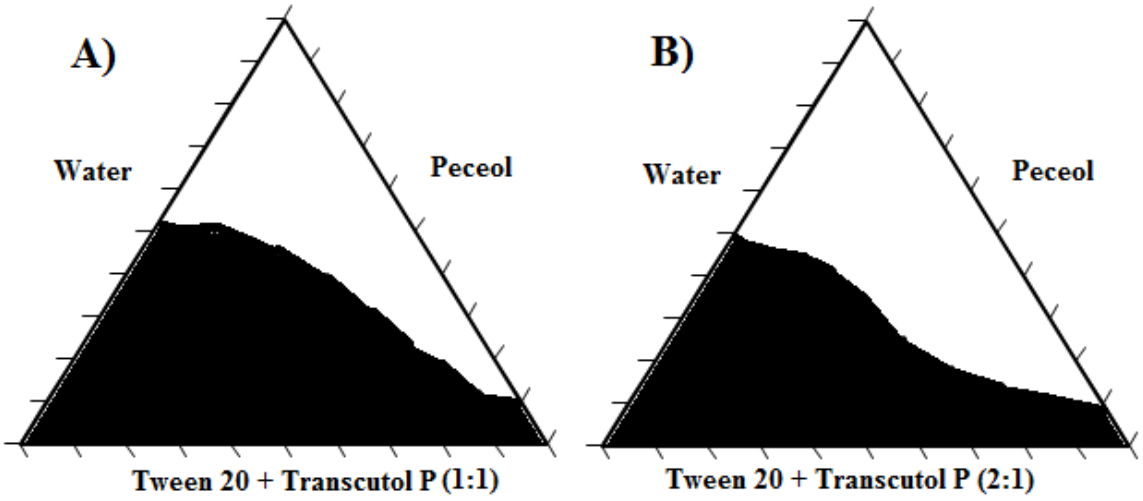

Fig. 1: Pseudo ternary phase diagram of system with the following components: oil = Peceol, surfactant =Tween 20, and cosurfactant = Transcutol P. S/CoS ratio of A) is 1:1, B) is 2:1.

Determination of Droplet Size and Zeta Potential

Droplet size distribution following self-microemulsification is a critical factor to evaluate a self-microemulsion system. Droplet size is thought to have an effect on drug absorption as has been illustrated in several papers. The smaller the droplet size, the larger the interfacial surface area will be provided for drug absorption [23]. The droplet size distribution and Polydispersity Index of various formulations is given in Table 4. An increase in the ratio of the oil phase (Peceol) resulted in a proportional increase in droplet size. Also, as increased in the surfactant (Tween 20) ratio, proportionally decreased in droplet size. It is well known that the addition of surfactants to the microemulsion system causes the interfacial film to stabilize and condense, while the addition of cosurfactant causes the film to expand; thus, the relative proportion of surfactant to cosurfactant has varied effects on the droplet size.

Zeta potential is the potential difference between the surface of tightly bound layer (shear plane and electroneutral region of the solution). The significance of zeta potential is that its value can be related to the stability of colloidal dispersions. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. For molecules and particles that are small enough, a high zeta potential will confer stability i.e. the solution or dispersion will resist aggregation. When the potential is low, attraction exceeds repulsion and the dispersion will break and flocculate. So, colloids with high zeta potential (negative or positive) are electrically stabilized. Zeta potential of optimized glibenclamide SMEDDS (ME3) was found to be -55.12 mV, which indicates that microemulsion was stable.

Spectroscopic characterization of optical clarity

As shown in Table 4, Absorbance of the studied aqueous dispersion of SMEDDS varied between 0.474 and 1.011. As expected, compositions with lower absorbance showed lowest droplet size since, aqueous dispersions with small absorbance are optically clear and oil droplets are thought to be in a state of finer dispersion [24]. The oil mixture provides the largest contribution to the absorbance of the diluted SMEDDS and consequently the droplet size of the produced microemulsion. On basis of dispesibility, appearance and time required to emulsify the SMEDDS formulation, results of Visual Assessment of Self-emulsification were also given in Table 4.

Drug content

Drug content in various SMEDDS formulations were presented in Table 4. The content of drug in various SMEDDS formulation varies from 95.50% to 100.28%. However, it was showed that as the surfactant increased in composition and oil decreased in composition of SMEDDS formulation, drug content was proportionally increased.

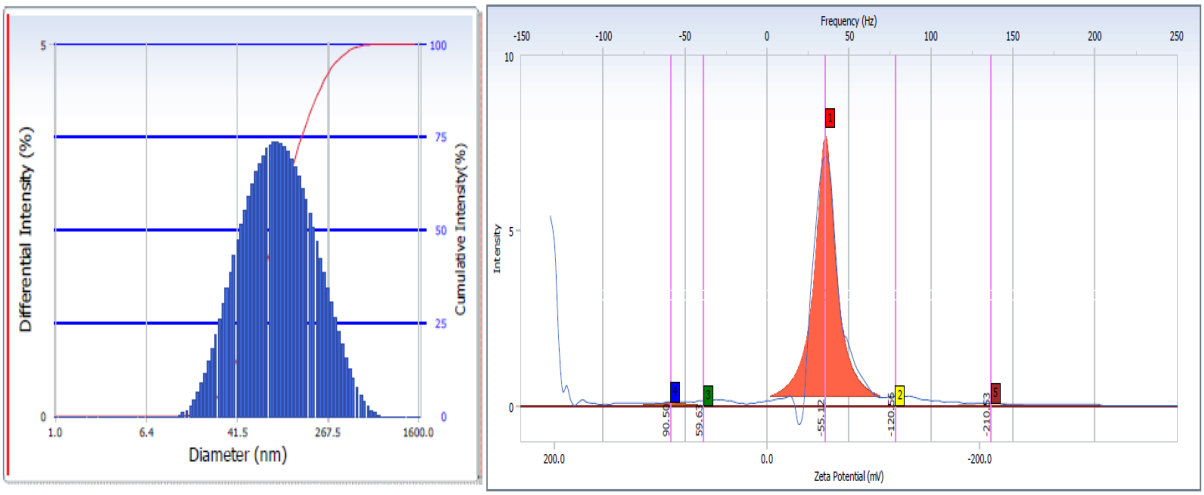

Fig. 2: Droplet size distribution (Intensity Distribution) and Zeta potential (Mobility Distribution).

Table 4: Droplet Size Distribution, Polydispersity Index (PDI), Optical Clarity, Drug Content, Visual assessment of Self-emulsification and % Drug Release after 15 min. (n=3).

Formulation	Droplet Size (nm) mean ± SD	PDI mean ± SD	Abs (water)	Abs (0.1N HCL)	Drug Content (%) mean ± SD	Grade	% Drug released after 15 min. mean ± SD
ME1	128.23±3.27	0.086±0.030	0.567	0.55	98.72±0.234	I	94.34±0.229
ME2	108.33±1.40	0.163±0.028	0.513	0.515	99.65±0.130	I	94.44±0.439
ME3	81.13±1.55	0.270±0.008	0.474	0.477	100.14±0.405	I	95.16±0.315
ME4	178.86±6.09	0.321±0.025	0.752	0.752	96.88±0.337	I/II	91.31±0.748
ME5	166.77±0.76	0.265±0.026	0.624	0.64	97.48±0.129	I/II	92.14±0.513
ME6	162.69±2.75	0.215±0.047	0.593	0.597	97.82±0.454	I/II	93.31±0.384
ME7	222.03±3.26	0.350±0.014	0.803	0.808	95.50±0.648	I/II	89.71±0.462
ME8	214.53±3.80	0.379±0.008	0.879	0.87	96.17±0.234	I/II	90.76±0.361
ME9	205.07±2.80	0.365±0.010	1.007	1.011	100.28±0.211	I/II	91.55±0.503

Self-Emulsification and Precipitation Assessment

The results of self-emulsification and precipitation studies are given in Table 5. It was seen that an increase in the proportion of oil (Peceol) and surfactant (Tween 20) in the composition resulted in increasing self-emulsification time. The increase in self-emulsification time can be assumed to be due the relative increase in oil and surfactant concentration, leading to increased viscosity of the formulation. However, it was found that ME4, ME5, ME6 showed precipitation and thus was not stable, because of the presence of Transcutol P. Transcutol P can be assumed to act as a cosolvent for glibenclamide (as seen from solubility studies), and thus it increases the solubilization capacity of the vehicle. However, in case of ME7, ME8, ME9, the precipitation is stable because there is low amount of Transcutol P which is unable to solubilized the precipitated glibenclamide.

Table 5: Evaluation of various formulations (n=3)

Formulation	Dispersion Time (sec) mean±SD	Clarity	Precipitation
ME1	18.33±0.577	Clear	Stable
ME2	20.00±1.000	Clear	Stable
ME3	20.33±0.577	Clear	Stable
ME4	24.33±0.577	Non Clear	Stable
ME5	25.67±0.577	Non Clear	Stable
ME6	28.33±0.577	Non Clear	Stable
ME7	32.00±1.000	Non Clear	Unstable
ME8	34.33±0.577	Non Clear	Unstable
ME9	37.33±0.577	Non Clear	Unstable

In Vitro Dissolution Study

Drug release from the all SMEDDS formulation was found to be significantly higher as compared with that of plain glibenclamide and marketed tablet as showed in Figure 3. All glibenclamide SMEDDS formulation released drug above 90% within 15 min as showed in Table 4. It could be suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain glibenclamide and marketed tablet. Thus, this greater availability of dissolved glibenclamide from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. It was also showed that increase in surfactant concentration and decrease in oil concentration in formulation increase in drug release.

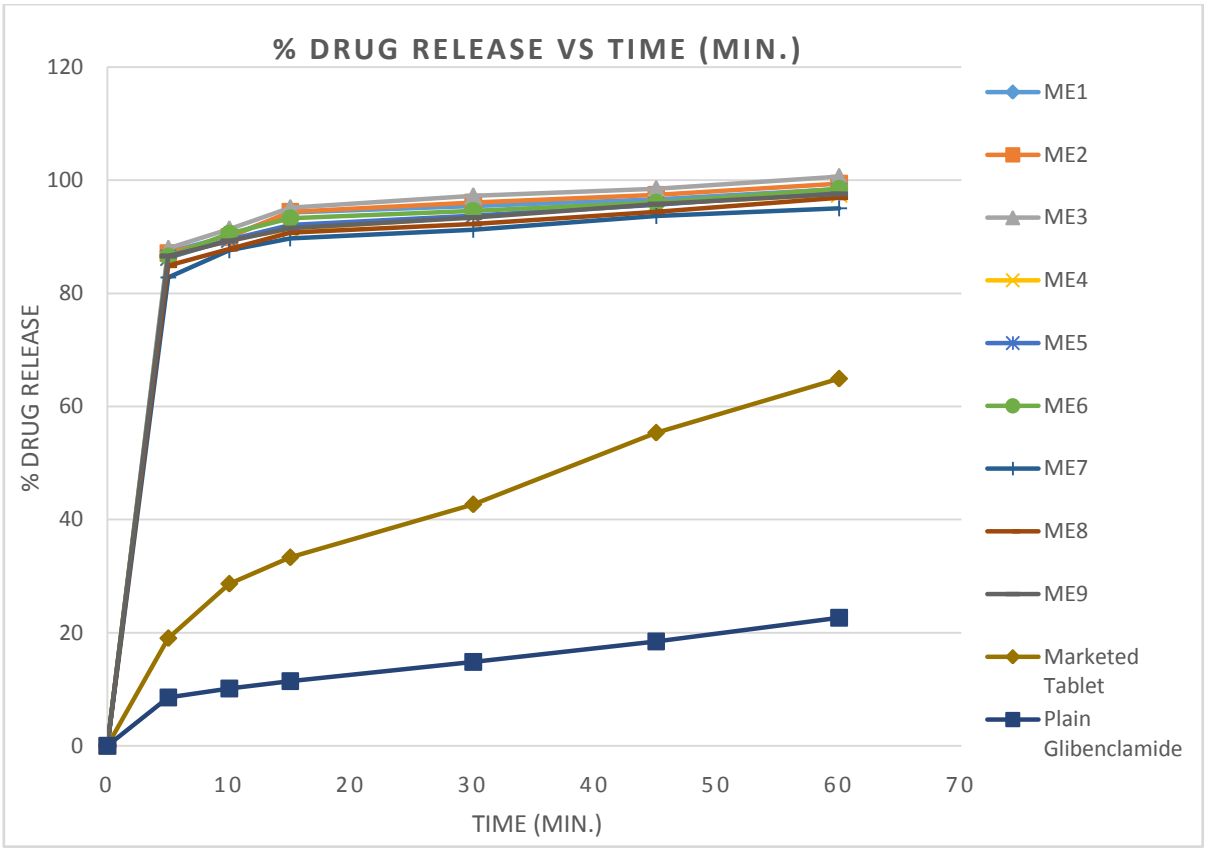

Fig. 3: Comparative dissolution profile of glibenclamide SMEDDS formulation with plain glibenclamide and marketed tablet.

CONCLUSION

A SMEDDS formulation of poorly water soluble drug, glibenclamide was formulated for directly filling in liquid filling hard gelatin capsules for oral administration. SMEDDS of glibenclamide was optimized by using parameters like Droplet size distribution, polydispersity index, zeta potential, self-emulsification property, optical clarity, drug content, and in vitro drug release. The optimized glibenclamide SMEDDS (ME3) composed of 15% Peceol, 44% Tween 20 and 41% Transcutol P with droplet size 81.13 nm, PDI 0.270, zeta potential -55.12 mV and complete drug release within 15 min as compared with marketed tablet and plain glibenclamide, which showed limited dissolution rate. The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like glibenclamide.

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