AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Formulation, Characterization and *In Vitro* Evaluation of Solidified Self emulsifying Drug Delivery System of Glimepiride

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ABSTRACT

The aim of this study is to develop and characterize a solidified self-emulsifying formulation of glimepiride, and to compare its *in vitro* drug release profile to a commercially available tablets. Several self-emulsifying formulations (SEF) were prepared by selecting different combination from constructed pseudoternary phase diagram. Selected formulations SEF1, SEF2 and SEF3 were solidified using crospovidone and evaluated. Following emulsification, the optimized formula was selected to have the smallest mean particle size and the highest absolute zeta potential, which should yield the formation of a stable emulsion and its superiority in dissolution characteristics**.** Particle size and distribution of SEF1, SEF2 and SEF3 were 423.36nm, 159.128nm and 115.899nm respectively. Zeta potential analysis revealed that SEF3 had highest zeta potential – 43.78mV followed by -39.2mV (SEF2) and -39.08mV (SEF1). *In vitro* drug release in 30 min of formulation SEF1, SEF2 and SEF3 were 75.31%, 83.48% and 93.03% respectively. Which indicated superiority of SEF3. *In vitro* studies were also performed to compare the optimized formula, SEF3, to a commercially available Betaglim tablet. $T_{50\%}$ of glimepiride in SEF3 and betaglim was found to be 7 min and 22 min respectively. Which indicated a significant improvement in glimepiride release characteristics. SEF3 was found to be stable under stressed conditions. However slightly increased globules size of sample stored at accelerated storage condition for 12 weeks was observed.

Keywords: Self-emulsifying drug delivery system, glimepiride, crospovidone, *in vitro.*

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Received 21 July 2015, Accepted 27 July 2015

Please cite this article as: Babar I *et al*., Formulation, Characterization and *In Vitro* Evaluation of Solidified Self emulsifying Drug Delivery System of Glimepiride. American Journal of PharmTech Research 2015.

INTRODUCTION

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for BCS class II drugs, therefore by improving the *in vitro* drug release profile of these drugs, it is possible to enhance their bioavailability[1-2]. Glimepiride belongs to BCS class II drug and exhibits pH dependent poor aqueous solubility[3]. It is more soluble in alkaline medium (0.02 mg/ml at 37°C) as compared to acidic and neutral media (<0.004 mg/ml). However, it is well absorbed in body but takes 2-3 hours for onset of action (long lag time) and hence longer T_{max}. This is because absorption of it is limited by dissolution[4]. Therefore a promoted action oral dosage form of glimepiride has emergence potential for development and commercialization exploitation[3]. Several approaches have been attempted to increase the dissolution rate and thereby oral efficacy of BCS class II drugs. Some of these techniques include solid dispersion, complexation with cyclodextrin, and lipid-based formulations[5-7] etc**.** Self-emulsifying drug delivery systems is a commercially viable formulation approaches for improving the oral bioavailability of BCS class II drugs[8]. In which drug dissolved in oils and their blending with suitable solubilizing agents. It can be defined as isotropic mixtures of drug, oil / lipid, surfactant, and / or cosurfactant, which form fine emulsion / lipid droplets, ranging in size from approximately 400 nm to less than 50 nm, on dilution with water/physiological fluid. Since drug remains in solution in the gut so avoiding the dissolution step that limits the absorption rate of hydrophobic drugs from the crystalline state[9]. Furthermore they represent an attractive alternative to orally administered emulsions since they are physically stable lipid solutions or dispersions[10]. Self emulsifying formulation can be solid or liquid. Spray drying, melt granulation, melt extrusion and adsorption to solid carrier techniques have been exploited by researchers to solidified the liquid self emulsifying formulation[11-16]. Glimepiride was selected for the study as it is practically insoluble in water and hence take 2 -3 hours in absorption. In the present investigation an attempts was made to develop solidified self –emulsifying formulation of glimepiride. Labrafac, tween -20 and Labrasol which were selected as oil, surfactant and co-surfactant respectively on the basis of criterion of drug solubility in various oils, surfactant and co-surfactants[17]. For selected oil and surfactant –cosurfactant mixture, a pseudoternary phase diagram was constructed to define the existence zone for micro/nano emulsion[18]. Optimized formulation was solidified using crospovidone as adsorbent carrier. Followed by comparative evaluation of glimepiride loaded SEF and betaglim tablets were performed for *in vitro* drug release.

MATERIALS AND METHOD

Chemicals and reagents

Glimepiride was received as gift sample from Ranbaxy (Haryana, India), Labrafac® CC and Labrasol were received from Gattefosse (Mumbai, India). Tween-20 was kindly supllied by Colorcon Pvt. Ltd. (Mumbai, India). Crospovidone CL supplied by S.D. Fine Chemical Ltd. (Mumbai, India) All other chemicals were of analytical reagent grade and were used as received.

Preparation of SEF formulation

The excipients were selected on the basis of solubility of glimepiride and their ability to form translucent emulsions upon mixing with water with mild agitation. Existence zone for nanoemulsion was determined by construction of pseudoternary phase diagram. Pseudo-ternary phase diagrams of composition labrafac CC (Oil), tween -20 (Surfactant) and labrasol (Co-surfactant) in different surfactant/co- surfactant ratio of 1:0 1:1, 2:1, 1:2, 3:1, 4:1 were constructed using water titration method (Figure 1). The volume of water used was recorded for the observations such as clear region, bluish tint region, bluish region, clear gel region, bluish gel region, milky gel region and the milky emulsion region. Several formulations in various combination were prepared by dissolving glimepiride either in labrafac or labrafec , labrasol and tween-20 mixture in a water bath at temperature 50 ˚C ± 5 ˚C with frequent shaking. After complete dissolution of glimepiride, rest oils and excipients were added. Thereafter formulations were allowed to cool at room temperature and solidified using crospovidone (Figure 2). Exact composition of selected formulations are tabulated in table 1.

Table 1: Composition of selected SEF formulations

Formulation Code	Labrafac (% W/W)	T20 (% W/W)	labrasol (% W/W)	Glimepiride (% W/W)
SEF 1	12	40	40	8
SEF2	12	57.4	20	8
SEF3	12	52.8	27.2	8

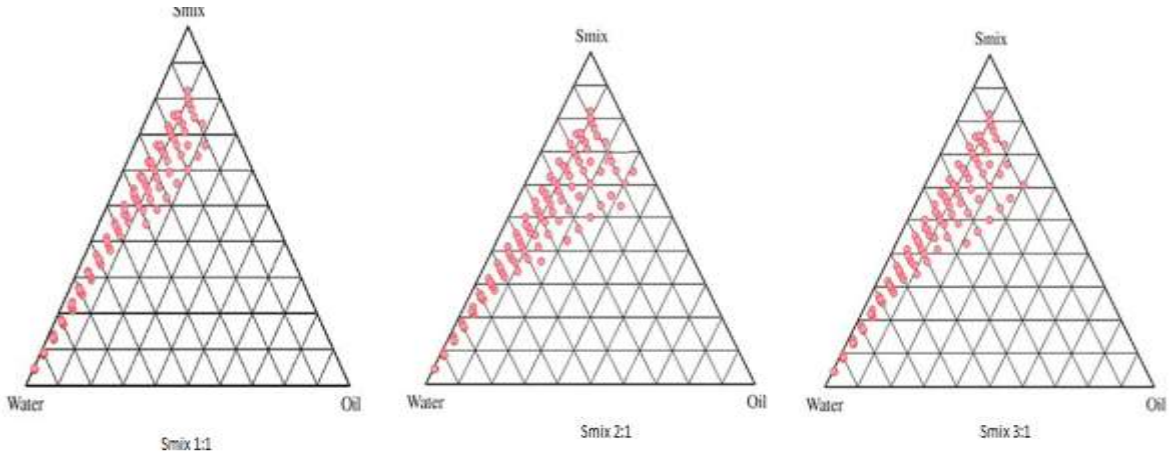

Figure 1: Pseudoternary phase diagram for existence zone of nanoemulsion

Figure 2: Liquid SEF of glimepiride (A) and solidified SEF3 using crospovidone as adsorbent carrier (B)

Assessment of self-emulsification of SEF

Assessment of the self-emulsifying of selected formulations, were carried out using 0.1% lipid soluble dye Sudan Red. Which was incorporated into lipid phase and then 1g of dye loaded granules were gently agitated in 100 ml 0.1N HCl. Agitation was provided by gentle shaking on a shaking water bath at 50 oscillations per min and a temperature of 37°C. The beaker was observed for intensity of pink color[11].

Particle size determination

The particle size distribution of the diluted SEF were measured using Transmission Electron Microscopic (TEM) [Philips CA10 Eindhoven, Netherlands]. A drop of the SEF was suitably diluted with water and applied on a carbon-coated grid, then treated with a drop of 2% phosphotungstic acid and left for 30s. The coated grid was dried and then taken on a slide and covered with a cover slip and observed under the microscope[19].

Zeta potential determination

The zeta potential determination was performed using photon correlation spectroscopy with in-built Zeta sizer (model: Nano ZS, Malvern Instruments, Westborough, MA, USA) at 633 nm. Formulation was diluted with a ratio of 1:2500 (v/v) with distilled water and mixed for 1 min using a magnetic stirrer. Zeta potential of each SEF was determined in triplicate[20].

***In vitro* dissolution**

The dissolution studies were performed for prepared formulation by filling the dry powder in hard gelatin capsule size 2. Dissolution were performed in 900 ml simulated intestinal fluid (SIF) 7.4 pH using USP apparatus – II (Paddle apparatus) at 37 ± 0.5°C and 50 rpm. All dissolution studies were run in triplicate. Samples of 3 mL of the media were collected and replaced with equal

volume of fresh media. The samples were filtered through 0.22 m Millipore filters and analyzed using UV Spectrophotometer (Shimadzu, Kyoto, Japan).

Stability studies

The optimized formulation selected on basis of desired particle size, optimum zeta potential and good *in vitro* drug release, was subjected to stability studies by storing it at 40 ± 2 °C, 75% ± 5% humidity for three months[21-22]. Sample was withdrawn at end of 3 months and evaluated for any physical change in the formulation, change in globule size and *in vitro* dissolution.

RESULTS AND DISCUSSION

SEF preparation

Several SEF formulations with the ability to dissolve 8mg/mL of glimepiride were prepared and evaluated. Formulations that were failed to self-emulsify upon mixing with water under mild agitation or produced an unstable emulsions were rejected. Few formulations were eliminated due to detection of oil globules on the surface of the diluted formulation and formation of milky emulsion. Since transparency of diluted emulsion reflects the proximity of the droplet size in micro to nano range so milky emulsions which reflect a relatively large mean droplet size were rejected. Moreover, micro emulsions and nanoemulsion are advantageous in ease of emulsification, stability, increased drug release and absorption rates[23]. Composition of selected liquid SEF are described in Table 1.

Assessment of self emulsification of SEF

SEF1, SEF2 and SEF3 were assessed for self emulsification by observing the intensity of pink colour. It was found that none formulation failed in test and completely emulsified within the first few minutes following gentle agitation. Moreover, pink colour intensity of the solution reflects the proximity of extent and rate of self emulsification (Figure 3).

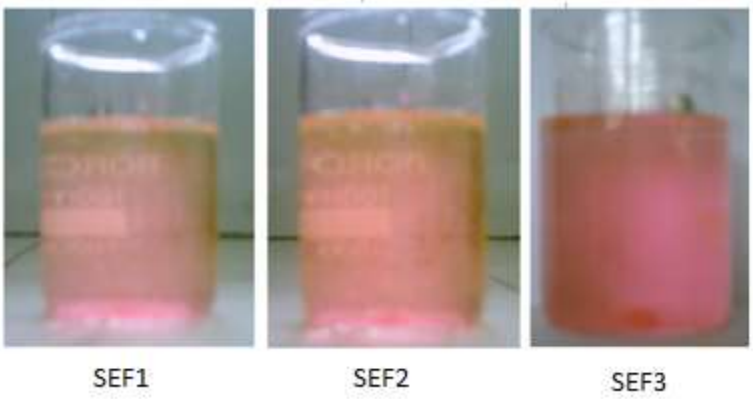

Figure 3: Photograph showing the release media of self-emulsifying granules after gentle agitation for 2 minutes.

Particle size analysis

The droplet size of diluted formulations SEF1, SEF2 and SEF3 were measured by TEM. The mean particle size of diluted SEF3 was significantly smaller than the mean particle size of the two other compositions. The mean particle size of the diluted SEF are shown in Table 2. It was noticed that droplets size depends on concentration of both tween-20 and labrasol. Moreover, ratio of them decided particle size of globules on emulsification. Tween-20 and labrasol in 2: 1 ratio was found optimum for the formulation of desired characteristics (Figure 4).

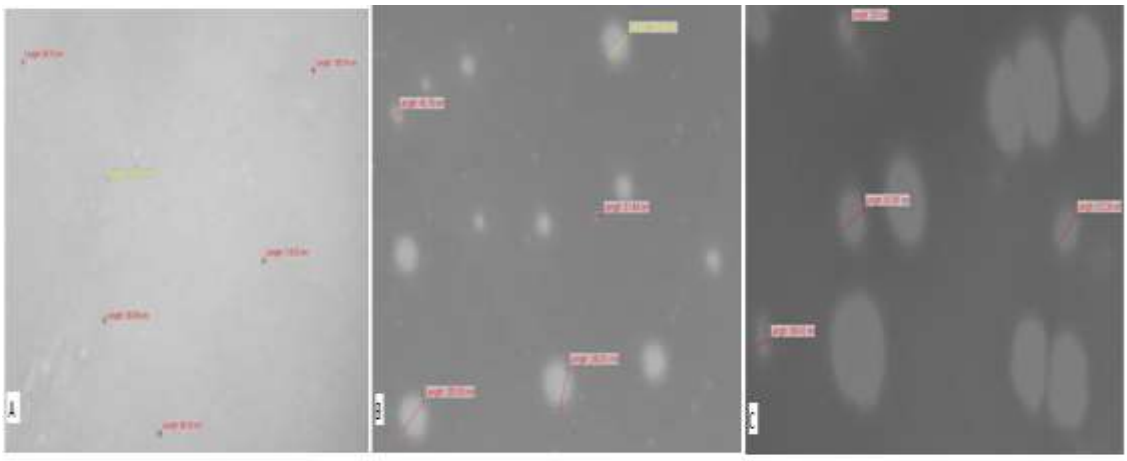

Figure 4: TEM image of SEF3(A), SEF2 (B) and SEF1(C)

Zeta potential

Diluted formulation SEF3 had a significantly higher zeta potential followed by SEF2, and SEF1 (Table 2). Higher value of zeta potential indicates that upon the emulsification SEF 3 produces a more stable emulsion than SEF1 and SEF2.

Table 2: Zeta potential and mean particle size of diluted formulations

Formulation Code	Zeta potential (mV) ± SD, n=3	Mean particle distribution (nm) ± SD, n=3
SEF1	- 39.08 ± 2.09	423.367 ± 49.65
SEF2	- 39.2 ± 3.1	159.128 ± 13.06
SEF3	- 43.78 ± 3.42	115.899 ± 9.73

***In vitro* dissolution study**

The cumulative percentage glimepiride release profile of SEF1, SEF2 and SEF3 in intestinal fluids were performed to compared the all three formulations. Significant difference was observed in dissolution of glimepiride among the different formulation (Figure. 5). Formulation SEF 3 showed relatively high glimepiride release (93.03%) while SEF 1 showed relatively low glimepiride release (75.31%). In addition to this comparative cumulative percent drug release profile of SEF3 and marketed formulation (Betaglim tablet) were also performed. $T_{50\%}$ of glimepiride in SEF3 and

betaglim was found to be 7 min and 22 min respectively which indicated that SEF3 resulted in significant improvement in dissolution rate as compared to the commercially available formulation (Figure 6). Since SEF 3 have highest absolute zeta potential, the smallest mean particle size and good glimepiride release as compared to SEF 1 and SEF2. Hence SEF3 was selected for stability studies.

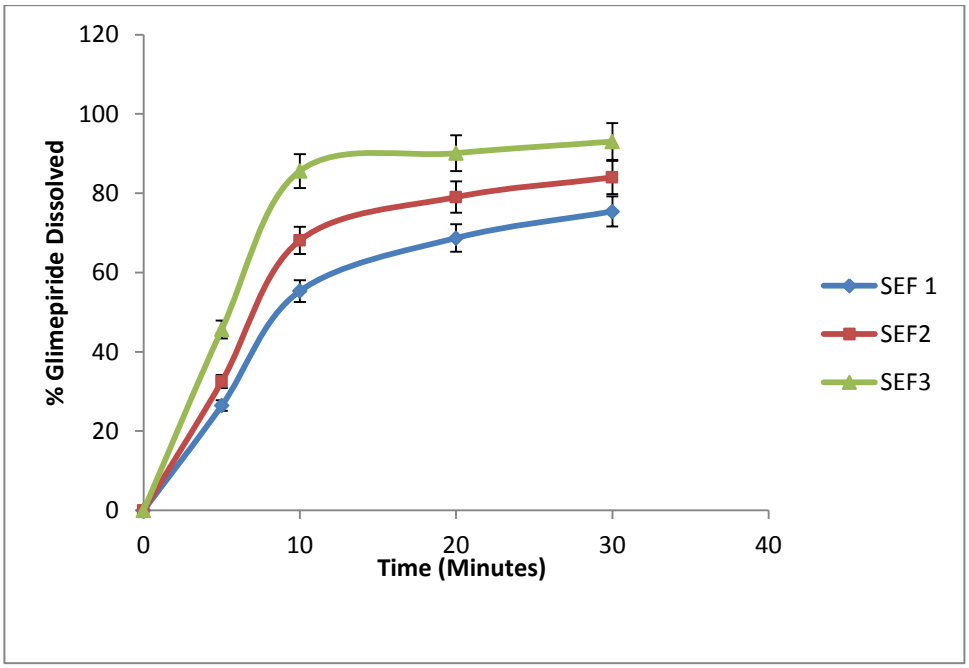

Figure 5: Dissolution profile of the mean percentage glimepiride dissolved of SEF1, SEF2 and SEF3.

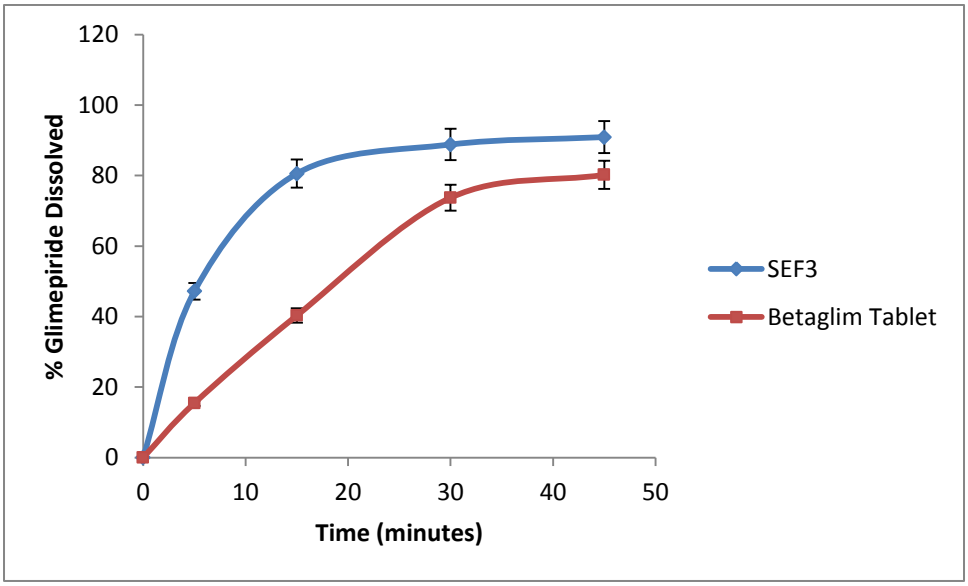

Figure 6: Dissolution profile of the mean percentage glimepiride dissolved of SEF3 and Betaglim tablet

Stability study

During the 12 weeks of stability study, none of the sample of SEF3 stored at 40 ˚C ± 2 and RH 70% ± 5 showed any change in color or appearance. The dissolution testing was performed after 12 weeks and zero time interval was considered as control and was found to be 88.37 (Figure 7). There was a 2.78% decrease in the dissolution rate of the SEF3 of glimepiride as compared to control. Furthermore, globules size slightly increased with storage temperature at end of three months (Figure 8). Which may be reason for decreased dissolution.

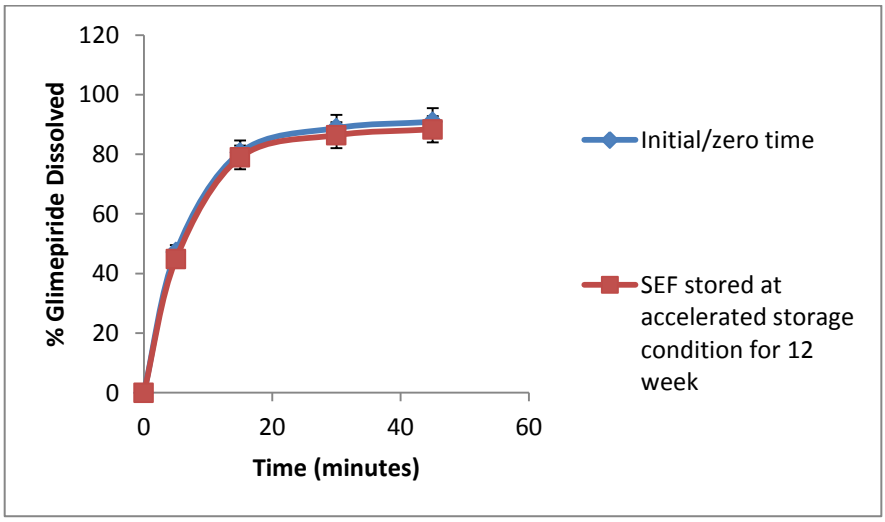

Figure 7: Percent glimepiride released from SEF3 stored for three month at accelerated storage conditions

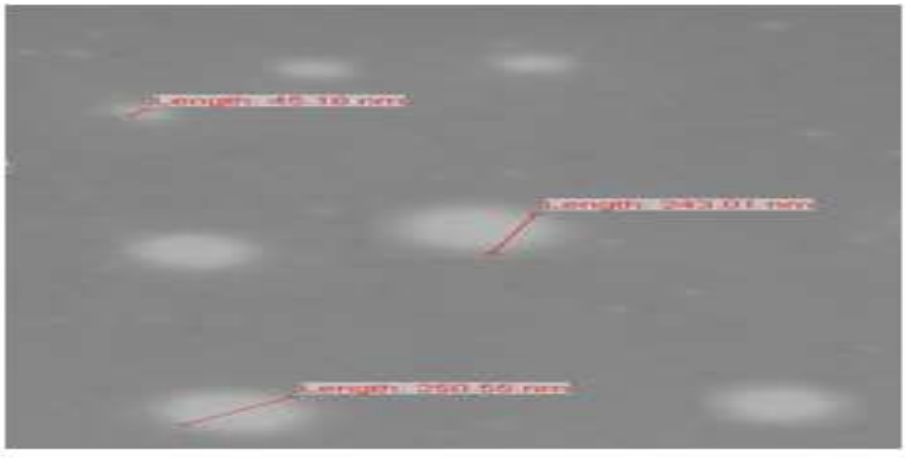

Figure 8: TEM image of SEF3 at the end of three months stored at 40± 2°C

CONCLUSION

SEF of glimepiride was successfully prepared, optimized and evaluated for cumulative percent *in vitro* drug release and physical stability. There was a significant improvement in the *in vitro* dissolution rate of drug when formulated as SEF as compared to Betaglim tablet.

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