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# FORMULATION AND EVALUATION OF SOLID-SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM (S-SNEDDS) FOR GLIBENCLAMIDE

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## ABSTRACT

Glibenclamide (GBD) is one of the most prescribed long-acting anti hyperglycaemic agent used in the treatment of treat Type 2 diabetes mellitus. GBD is a poorly soluble drug which results in low bioavailability. Hence, the objective of the study is to develop a solid self-nano emulsifying drug delivery system (S-SNEDDS) to improve the solubility and dissolution rate of GBD. Liquid SNEDDS was prepared using Maisine-35-1 as oil, Cremophor RH40 as surfactant, and PEG 400 as cosurfactant. Ternary phase diagrams were constructed to identify the self-nano emulsification region. Based on the phase diagrams, few formulations containing 10-25% of oil were prepared by simple mixing and vortexing. These formulations were adsorbed onto Neusilin US2 to produce solid SNEDDS and were evaluated for drug content, globule size, zeta potential and in vitro drug release. DSC and FTIR studies were also performed and the results indicated that there were no incompatibilities between GBD and the components in the SNEDDS. The prepared formulations exhibited a globule size ranging from 14.14 to 45.36 nm. *In vitro* dissolution profiles showed that dissolution rate of Glibenclamide from liquid and solid SNEDDS was much greater when compared to the pure drug and the marketed tablet. Thus, this study indicated that the solid SNEDDS could be used as a potential drug carrier for GBD with improved solubility and dissolution rate.

**KEYWORDS:** Glibenclamide, SNEDDS, Neusilin US2, Maisine-35-1, Cremophor RH40, PEG400.

## INTRODUCTION

Diabetes mellitus, commonly referred to as diabetes, is a metabolic disorder in which there are high blood sugar levels over a prolonged period. Currently, an alarming statistic show that 425 million are suffering from diabetes worldwide.[1] When diabetes is not controlled by lifestyle modifications, such as diet and exercise, and insulin injections are not desired, oral hypoglycaemic agents are used. Glibenclamide is a preferred hypoglycaemic agent which is used to lower blood sugar levels by increasing insulin secretion.

Glibenclamide (GBD) or also known as glyburide (GLY) is a second-generation of sulfonylureas used in the treatment of Type 2 diabetes mellitus. Glibenclamide is classified as Biopharmaceutical Classification System (BCS) class II drug, having high permeability (log P = 4.7) and poor water solubility (2.06 mg/L).[2] For BCS class II drug, the absorption of drug is often limited by the rate of dissolution of the drug. The dissolution rate of a drug is affected by a few factors such as surface area of undissolved solid and solubility of solid in dissolution medium.[3] In this case, GBD has low water solubility, therefore, it has poor dissolution rate, leading to erratic drug absorption profile. This results in high inter-subject and intra-subject variability in bioavailability. Problems of GBD in terms of its solubility and dissolution are major concerns to achieve good bioavailability of the drug.

Different strategies have been employed to overcome solubility issue of poorly soluble drugs such as solid dispersions, eutectic mixtures, emulsion systems, cyclodextrin inclusion complex, liposomes, salt formation and solid liquid nanoparticles[4] However, these strategies have their own limitations.

Self-emulsifying drug delivery system (SEDDS) is a promising approach to improve the solubility of poorly water-soluble drugs. SEDDS are isotropic mixtures of oils, surfactants and cosurfactants, which spontaneously form an oil-in-water microemulsion/nanoemulsion upon mild agitation in aqueous gastrointestinal fluid. Small droplet size produced by this formulation provides a large interfacial surface area for drug release and absorption.[5,6] This is further supported by the Noyes-Whitney Equation which shows that the rate of dissolution increases with increasing interfacial surface.[7] Considering the advantages of SEDDS, it is planned to improve the solubility of Glibenclamide using SEDDS technology.

Liquid SEDDS poses problems such as low stability and portability, low drug loading and gastrointestinal irritation.[8] To overcome the above problems with liquid SEDDS, it is

planned to convert the liquid SEDDS to solid SEDDS and filled it in a hard gelatine capsules. This can be done by adding a carrier or inert adsorbent to the liquid SEDDS for instance, colloidal silicon dioxide, which is then filled into hard gelatine capsule which has a simple manufacturing process. This solid dosage form enables better patient compliance compared to liquid dosage form.

## METHODOLOGY

### Materials

Glibenclamide was a gift sample from Y.S.P Industries, Malaysia. Maisine® 35-1, Transcutol P, Labrafac® PG and Labrafac®Lipophile WL1349 were gift samples from Gattefosse®) whereas Neusilin® US2 was a gift sample from Fuji Chemical Industry Co. Ltd.). Poly(ethylene glycol) 400 and Cremophor® RH 40 were purchased from Sigma® Life Science. All other chemicals were of analytical grade and were used as received.

### Solubility Studies

An excess amount of GBD (approximately 100mg) was added into stoppered tubes containing 2ml of individual oils, surfactants and cosurfactants respectively. The mixture was vortexed initially and then allowed to agitation on a shaking water bath for 48 hours maintained at 40˚C. After reaching equilibrium, each tube was centrifuged at 4000rpm for 15 minutes at 40˚C. Then, the mixture was filtered and excess insoluble GBD was removed by filtration using a membrane filter of 0.45µm pore size. The concentration of dissolved GBD was determined by measuring the absorbance at $\lambda_{max}$ = 229 nm using UV-Visible spectrophotometer. Suitable dilution was carried if necessary.[9]

### Phase diagram studies, visual assessment, emulsification time and turbidity determination

Based on the solubility studies, the oil, surfactant and cosurfactant which were able solubilize the largest quantity of GBD were used for phase diagram studies to explore the possible self-emulsification region. Maisine® 35-1 as the oil phase, Cremophor® RH40 as the surfactant and PEG 400 as cosurfactant were mixed at various proportions as shown in the Table 1. Then, the mixtures were vortexed and were added to a conical flask containing 50ml of distilled water placed on a magnetic stirrer. The time taken to emulsify, and the final visual appearance were tabulated. The resultant emulsion was left to stand for 24 hours at ambient conditions. When no precipitation was observed at the end of 24 hours, the formulations were categorised as stable.[10] Only visually transparent or slightly bluish formulations were

accepted and different ratios for these formulations were used to construct the phase diagram using ProSim ternary phase diagram software.[11] In the phase diagram, each of the vehicle was represented as an apex of triangle. Using a turbidimeter (Eutech TN-100), the turbidity of the resultant emulsion was measured in nephelometric turbidity unit (NTU). Each formulation (0.5ml) was diluted to 50ml and transferred to the sample vials for measurement.[12] Turbidity measurement was repeated to obtain triplicate readings.

**Table 1: Concentration of Maisine® 35-1, Cremophor® RH40 and PEG 400 for phase diagram studies.**

| Series | Maisine® 35-1 (mg) | Cremophor® RH40 (mg) | PEG 400 (mg) | Series | Maisine® 35-1 (mg) | Cremophor® RH40 (mg) | PEG 400 (mg) |
|---|---|---|---|---|---|---|---|
| U1 | 100 | 800 | 100 | X3 | 200 | 100 | 700 |
| U2 | 100 | 700 | 200 | X4 | 200 | 500 | 300 |
| U3 | 100 | 600 | 300 | X5 | 200 | 400 | 400 |
| U4 | 100 | 500 | 400 | X6 | 200 | 300 | 500 |
| U5 | 100 | 400 | 500 | X7 | 200 | 200 | 600 |
| U6 | 100 | 300 | 600 | Y1 | 250 | 700 | 50 |
| U7 | 100 | 200 | 700 | Y2 | 250 | 600 | 150 |
| U8 | 100 | 100 | 800 | Y3 | 250 | 500 | 250 |
| W1 | 150 | 800 | 50 | Y4 | 250 | 400 | 350 |
| W2 | 150 | 700 | 150 | Y5 | 250 | 300 | 450 |
| W3 | 150 | 600 | 250 | Y6 | 250 | 200 | 550 |
| W4 | 150 | 500 | 350 | Y7 | 250 | 100 | 650 |
| W5 | 150 | 400 | 450 | Z1 | 300 | 600 | 100 |
| W6 | 150 | 300 | 550 | Z2 | 300 | 500 | 200 |
| W7 | 150 | 200 | 650 | Z3 | 300 | 400 | 300 |
| W8 | 150 | 100 | 750 | Z4 | 300 | 300 | 400 |
| X1 | 200 | 700 | 100 | Z5 | 300 | 200 | 500 |
| X2 | 200 | 600 | 200 | Z6 | 300 | 100 | 600 |

**Formulation of SEDDS**

Based on the results of solubility studies and phase diagram studies, four formulations were prepared with varying compositions of the selected oil (Maisine® 35-1), surfactant (Cremophor® RH40) and cosurfactant (PEG 400) as shown in the Table 2. The amount of GBD was weighed and kept constant at 5mg in each formulation in an 2ml Eppendorf tube. Oil, surfactant and cosurfactant were added to GBD and mixed by vortex mixing. Then, the mixture was heated at 40˚C until GBD is completely dissolved.

**Table 2: Concentration of Oil, Surfactant and Cosurfactant for the Formulation of SEDDS.**

| Sample | LF1 | LF2 | LF3 | LF4 |
|---|---|---|---|---|
| Maisine® 35-1 (mg) | 50 | 75 | 100 | 125 |
| Cremophor® RH40 (mg) | 200 | 250 | 250 | 350 |
| PEG 400 (mg) | 250 | 175 | 150 | 25 |
| Total mass (mg) | 500 | 500 | 500 | 500 |

**Preparation of Solid SEDDS of GBD**

Optimized formulations of liquid SEDDS of GBD (LF1, LF2, LF3 and LF4) were converted to solid SEDDS of GBD by adsorption onto Neusilin® US2 (magnesium aluminometasilicate). In drop wise manner, liquid SNEDDS of GBD was added onto Neusilin® US2 in the ratio of 2:1 by physical mixing. The resulting damp mass of solid SEDDS of GBD was uniformly homogenized, passed through sieve No. 100 and dried at ambient temperature.[13] The formulations were stored in a desiccator until further use. The resulting solid SEDDS of GBD was filled into hard gelatine capsule size '00' and stored for further studies.

**Drug Content**

The formulations (liquid and solid) containing 5 mg of the drug was transferred in to a volumetric flask and the volume was made to 10 ml with methanol. The flask was mixed on a sonicator for 15 minutes. Then it was filtered and suitably diluted if necessary. The concentration of dissolved GBD was determined by measuring the absorbance at λmax =229nm using UV-Visible spectrophotometer. Each formulation was analysed three times.

**Differential Scanning Calorimetry (DSC)**

DSC is a type of thermal analysis which provides qualitative and quantitative information about the physical state of the drug in a formulation. The physical state includes crystal and amorphous. A Perkin Elmer DSC8500 was used for DSC analysis. 5mg of pure GBD was placed in standard aluminium pan and sealed with a lid. Thermal analysis was performed under purge of dry nitrogen gas (20ml/min) at an increment of 10°C/min in terms of heat flow[14]. The analysis was repeated using GBD solid SNEDDS. Empty aluminium pan was used as a reference. The DSC curve of each sample was obtained.

**Fourier Transform Infrared spectroscopy (FTIR)**

Molecular confirmation of a material, including the information on drug-excipient interactions, was deduced using FTIR based on characteristic molecular vibrations that absorb in the infrared region. FTIR analysis was done using Perkin Elmer Spectrum 100 spectrometer. Solid SEDDS of GBD was blended into potassium bromide (KBr) at the concentration of 1%w/w GBD in potassium bromide and ground well using mortar and pestle. The mixture was compressed into KBr disc at a pressure of 1,000 psig.[15] The KBr disc was inserted into the sample holder for analysis. The sample was scanned in the wavelength region of4000-400cm$^{-1}$. Any incompatibilities of ingredients in the formulation was determined from overlain spectrum analysis. The analysis was repeated using pure GBD and Neusilin® US2 in the same method.

**Determination of droplet size and zeta potential**

Dynamic light scattering (DLS) technique was used to measure the globule size, polydispersibility index (PDI) and zeta potential using Malvern zetasizer. 0.1 ml of the formulation was added into a conical flask and diluted to 20ml using double distilled water[16]. 1ml of the resulting emulsion was transferred to a cuvette and the measurements were carried out at 25$^{o}$C.

**In-vitro drug release studies**

In-vitro drug release study was performed using USP XXIV, dissolution apparatus II (paddle) with 900 ml of pH1.2 hydrochloric acid solution at 37 ± 0.5°C and paddle speed set at 50rpm. The tested formulations were liquid SEDDS, solid SEDDS, marketed glibenclamide tablet (Daonil, Aventis Pharma Ltd.) and pure glibenclamide. The formulations were placed into the dissolution tester in each separate vessel. An aliquot (5mL) was extracted at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and filtered. 5ml of fresh media was added to replenish the dissolution medium. The extracted sample was analysed for GBD content by measuring the absorbance at $\lambda_{max}$=229 nm using UV-Visible spectrophotometer.

## RESULTS

### Solubility Studies

**Table 3(a): Solubility data of oils.**

| Oils | Solubility (mg/ml) |
|---|---|
| Maisine 35-1® | 10.92±0.72 |
| Sunflower seed oil | 9±2.14 |
| Sesame oil | 5.975±1.73 |
| Labrafac® PG | 3.357±0.04 |
| Labrafac® Lipophile WL1349 | 3.346±0.02 |
| Olive oil | 2.695±0.17 |
| Isopropyl myristate | 2.593±0.51 |
| Palm oil | 2.337±0.01 |
| Coconut oil | 2.222±0.44 |
| Ethyl oleate | 1.743±0.06 |

**Table 3(b): Solubility data of surfactants.**

| Surfactants | Solubility (mg/ml) |
|---|---|
| Cremophor® RH40 | 21.29±2.80 |
| Cremophor®HS15 | 16.81±7.69 |
| Cremophor® EL | 12.23±6.98 |

**Table 3(c): Solubility data of cosurfactants.**

| Cosurfactants | Solubility (mg/ml) |
|---|---|
| PEG 400 | 34.01±18.4 |
| Transcutol®HP | 28.58±2.13 |

### Ternary phase diagram studies

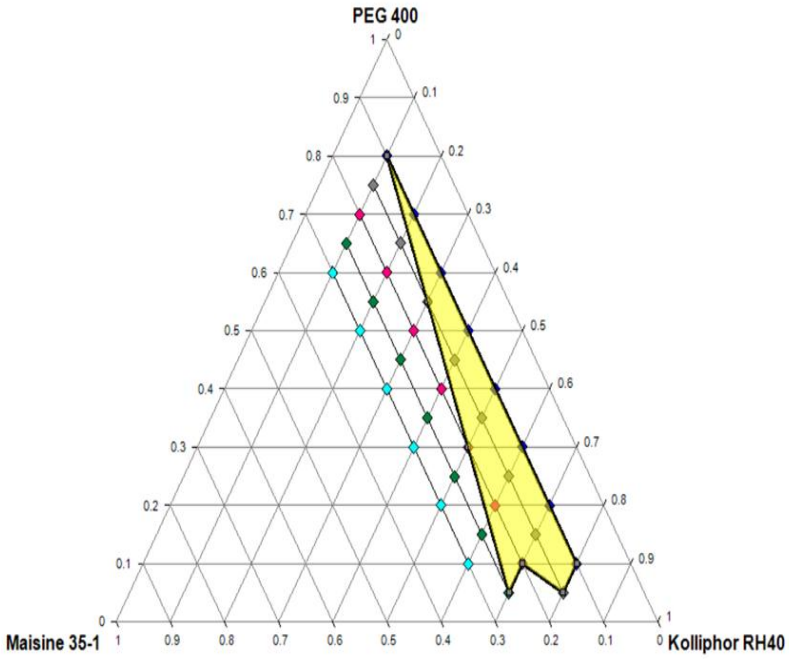


**Fig. 1: Ternary phase diagram of Maisine® 35-1, Cremophor® RH40 and PEG 400.**

**Table 4: Visual appearance, emulsification time and turbidity of the resultant emulsions.**

| Series | Appearance | Time to emulsify (sec) | Turbidity (NTU) | Series | Appearance | Time to emulsify (sec) | Turbidity (NTU) |
|---|---|---|---|---|---|---|---|
| U1 | Transparent | 19.91 | 6.35±0.05 | X3 | Transparent | 14.07 | 18±0.20 |
| U2 | Transparent | 17.25 | 6.43±0.09 | X4 | Slightly turbid | 28.94 | 195±0.58 |
| U3 | Transparent | 15.22 | 5.94±0.05 | X5 | Milky | 37 | 651±5.03 |
| U4 | Transparent | 16.53 | 7.69±0.22 | X6 | Milky | 38.72 | 566±1.53 |
| U5 | Transparent | 29.35 | 6.88±0.08 | X7 | Milky | 35 | 951±2.65 |
| U6 | Transparent | 26.06 | 11.6±0.17 | Y1 | Transparent | 22.65 | 13.1±0.18 |
| U7 | Transparent | 25.05 | 7.42±0.03 | Y2 | Slightly turbid | 23 | 216±5.29 |
| U8 | Transparent | 26 | 24.1±0.38 | Y3 | Slightly turbid | 44.08 | 200±2.08 |
| W1 | Transparent | 16.78 | 10.8±0.05 | Y4 | Milky | 35 | 673±12.1 |
| W2 | Transparent | 11.85 | 14.7±0.51 | Y5 | Milky | 44 | 718±18.6 |
| W3 | Transparent | 12.6 | 11.1±0.23 | Y6 | Milky | 43.22 | Error |
| W4 | Transparent | 21.75 | 21.8±0.42 | Y7 | Milky | 33.88 | 981±8.08 |
| W5 | Slightly bluish | 21.84 | 17.43333 | Z1 | Slightly turbid | 44.88 | 158±3.79 |
| W6 | Slightly bluish | 22 | 44.8±0.32 | Z2 | Slightly turbid | 33.98 | 183±1.53 |
| W7 | Slightly turbid | 23 | 417±1.15 | Z3 | Slightly turbid | 45.65 | 282±1.53 |
| W8 | Milky | 24 | 814±1.15 | Z4 | Milky | 43.78 | 987±3.51 |
| X1 | Transparent | 14.63 | 12.8±0.14 | Z5 | Milky | 53 | Error |
| X2 | Transparent | 14.6 | 15.7±0.22 | Z6 | Milky | 43.68 | Error |

**Table 5: Percentage drug content of liquid and solid SEDDS.**

| Formulation | Percentage drug content (±SD) |
|---|---|
| LF1 | 101.4±0.43 |
| LF2 | 98.7±0.43 |
| LF3 | 98.6±0.28 |
| LF4 | 103.8±0.43 |
| SF1 | 100±0.28 |
| SF2 | 98.2±0.43 |
| SF3 | 98.9±0.57 |
| SF4 | 102.8±0.59 |

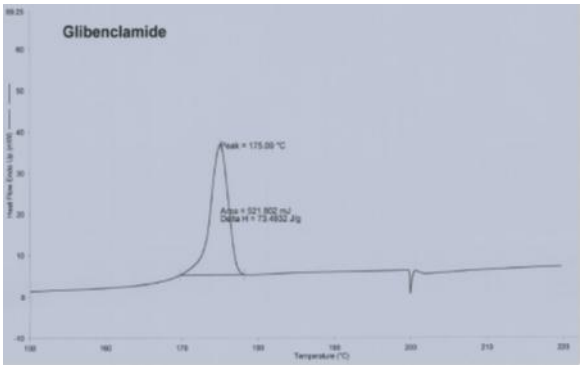


**Fig. 2 (a): DSC graph of pure GBD**

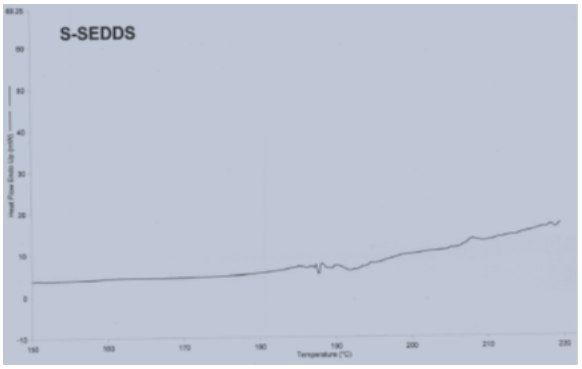


**Fig. 2 (b): DSC graph of S-SEDDS**

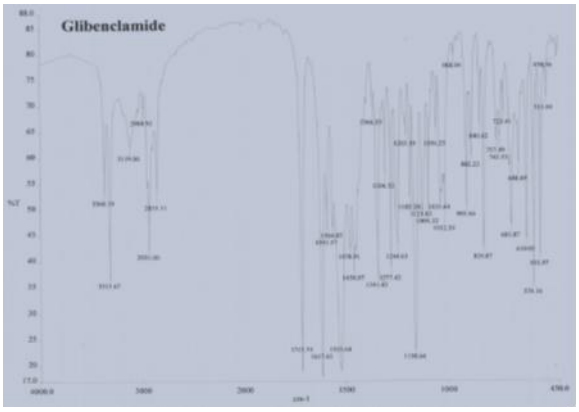


**Fig. 3 (a): FTIR spectra of pure GBD**

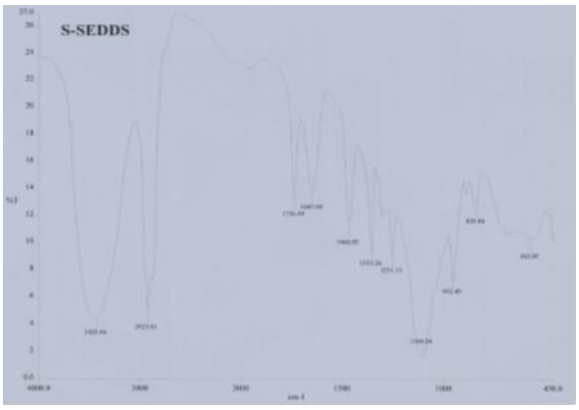


**Fig. 3 (b): FTIR spectra of S-SEDDS**

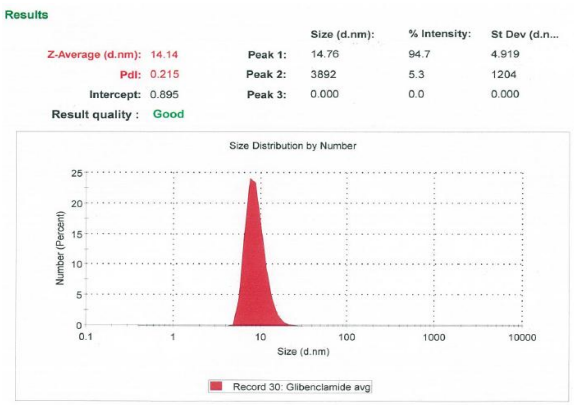


**Fig. 4(a): Droplet size of SF1**

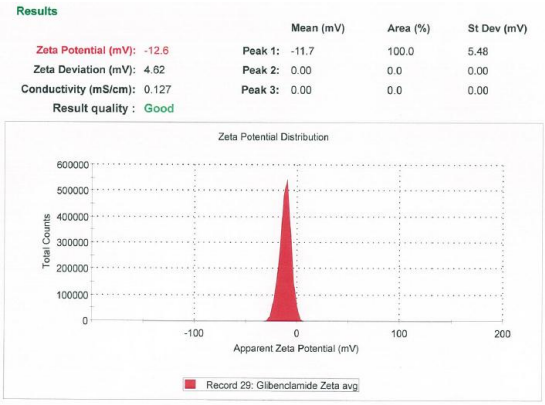


**Fig. 4 (b): Zeta Potential of SF1**

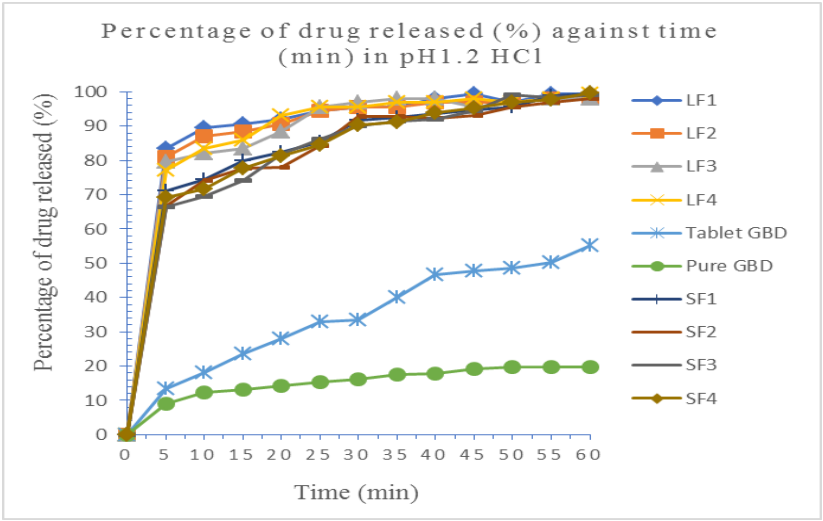


**Fig. 5: Dissolution profile of GBD SEDDS in pH 1.2 HCl.**

## DISCUSSION

### Solubility studies

Screening of oil, surfactant and cosurfactant is an imperative step for the formulation of SEDDS. These three components determine the maximum amount of drug which could be

solubilized in minimal volume of vehicle by having maximum solubilizing power. Among all the oils studied, Maisine® 35-1 had shown highest solubility (10.92±0.72mg/ml) and hence this oil was selected in the study (Table 3(a)). Similarly, Cremophor® RH40 and PEG 400 had shown highest solubility among surfactants and cosurfactants (Table 3(b) and 3(c)) and hence they were selected. The selected oil, surfactant and cosurfactant were further studied using ternary phase diagram.

**Phase diagram studies**

Ternary phase diagrams are used to express the three components which define the system and each component is represented at the triangle apices, whereby all the components add up to 100%. By constructing such diagram, the phase behaviour in the system is visualised and the concern of this study is to determine the region which is transparent or slightly bluish for the selection of self-emulsification zone. The optimal blends of oil and surfactant having the optimal compatibility is crucial for the formation of emulsion system as it is to provide the lowest interface tension between the oil and aqueous phase (gastrointestinal fluid). And this further improve the stability of the system as solubilisation is at the maximum and smallest globules are formed.[17] The shaded region shown in the phase diagram above is the region of self-emulsification (Fig 1).

**Visual assessment, emulsification time and turbidity determination**

Based on the observations, the resultant emulsion appearance, time to emulsify and turbidity values were determined and are stated in Table 4. Emulsification time was noted, and it was found that none of the formulations exceeded 1 minute to emulsify. When the resultant emulsion appeared to be transparent or slightly bluish, the turbidity ranged from 5.94±0.05NTU to 44.8±0.32NTU. The turbidity values were found to be higher when the resultant emulsion appeared to be slightly turbid, ranging from 158±3.79NTU to 417±1.15NTU. Milky emulsion was among those with highest turbidity, 566±1.53NTU and above. Error was displayed on the turbidimeter when the turbidity of emulsion exceeded the instrument detectable range of turbidity 0-1000NTU. There was no phase separation observed in any of the resultant emulsion after 24 hours at ambient temperature.

**Drug content**

The drug content of liquid SEDDS ranged from 98.6%±0.28 to 103.8%±0.43 whereas solid SEDDS ranged from 98.2%±0.43 to 102.8%±0.59 (Table 5). There was no significant difference in drug content despite the different compositions between the formulations. There

was no significant difference in drug content between liquid SEDDS and solid SEDDS. Therefore, using a solid carrier to convert liquid SEDDS to solid SEDDS would not affect the available drug content in the formulation.

**Differential scanning calorimetry**

According to British Pharmacopeia Commission 2018, the melting point range of GBD is from 169$^{o}$C to 174$^{o}$C[18]. DSC was run using pure GBD and the melting point was noted at 175.09$^{o}$C as shown in Fig. 2(a). The sharp endothermic peak was indicative of the highly crystalline structure of GBD. GBD peak of melting point in Fig. 2(a) was not present in Fig. 2(b), that is, DSC graph of S-SEDDS. This may be since GBD had become dispersed in the matrix. It had undergone change in its melting behaviour and being molecularly dissolve in oil, surfactant and cosurfactant.

**Fourier Transform Infrared spectroscopy (FTIR)**

The sample was scanned in the wavelength region of 4000-400cm$^{-1}$ as most of the inorganic and organic compounds is detectable within this region. The obtained FTIR spectra of GBD (Fig. 3(a)) and S-SEDDS (Fig. 3(b)) were shown above. Pure GBD showed characteristics band at 3368.19, 3315.67 cm$^{-1}$ (NH (amide)), 2931.0, 2855.11 cm$^{-1}$ (C=C (ring)), 1341.83, 1306.52cm$^{-1}$ (S=O2), 1366.23, 1123.83, 1035.64, 1012.24, 574.16, 541.97cm$^{-1}$ (C-C, C-N, C-O). The characteristics bands of pure GBD were present in solid SEDDS FTIR spectra. However, the corresponding peaks were sometimes broadened or reduced in intensity probably because of the mixing or the loss of crystallinity. This had confirmed that there was no incompatibility between GBD and excipients used in the formulation.

**Droplet Size and Zeta Potential**

It was noted that solid SEDDS droplet size ranged 14.14 to 45.36nm (Fig.4(a)). As the droplet size range was not exceeding 100nm, the formulations depicted that it was a self nano-emulsifying drug delivery system (SNEDDS). Based on the droplet size results, there is a positive correlation between droplet size and concentration of oil. Polydispersibility index (PDI) ranged from 0.215 to 0.478. A PDI value of <0.5 indicates a good uniformity of dispersion in the SNEDDS; A PDI value of >0.5 indicates heterogeneity in the particle size distribution. Higher PDI indicates a large variation of droplet sizes. As the results showed PDI <0.5, the formulations were rated as good. Zeta potential is a measurement of colloidal stability. Zeta potential of solid SEDDS ranged -12.6 to -16.2mV. It is common to have a negative zeta potential for oil-in-water emulsion due to the fatty acids. High zeta potential

would be indicative that the particles repel and do not aggregate, resisting flocculation. As the zeta potential of the selected formulations were >±5mV, hence, the formulations were considered relatively stable (Fig. 4(b)).

**Drug release studies**

Based on the results above, in pH1.2 HCl, there was no significant difference in dissolution between the liquid formulations of SEDDS. Around 90% of the drug was released within 20 minutes from all the liquid formulations. Similarly, solid SEDDS released around 90% of drug within 30minutes (Fig. 5). Both pure GBD and tablet GBD showed poor dissolution profile with less than 60% and 20% of drug released respectively in 60minutes. From the above results, it could be inferred that smaller droplet size is attributable to the distinguished improvement of the dissolution GBD in SEDDS compared to conventional tablet and plain drug. Smaller droplet size provides a larger interfacial area in contact with the dissolution media, allowing faster dissolution and thus rapid absorption and improved bioavailability. Furthermore, there is a more rapid rate of dissolution in liquid SEDDS compared to solid SEDDS.

## CONCLUSION

In this study, a self-emulsifying drug delivery system for GBD was developed and evaluated with an aim to improve its solubility and dissolution rate. The formulations were prepared using Maisine®35-1 as oil, Cremophor®RH40 as surfactant, PEG 400 as cosurfactant and Neusilin® US2 as a solid carrier. When diluted with distilled water, GBD-loaded SNEDDS could spontaneously form small globules with a mean droplet size of about 14 nm-46 nm in less than one minute. From the comparative *in vitro* dissolution studies performed, it was being concluded the liquid and solid SNEDDS formulations showed improved solubility and dissolution behavior than pure drug and the conventional marketed formulation. Thus, this study confirms that the SNEDDS formulation can be used as a possible alternative to traditional oral formulations of GBD to improve its solubility and dissolution rate.

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