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Research Article

Development and Characterization of Spray Dried Solid Self Emulsifying System of Glibenclamide

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ABSTRACT

Glibenclamide is BCS class II drug used in the treatment of NIDDM. It has low aqueous solubility and poor bioavailability. Hence, the aim of this study was to increase the solubility of glibenclamide by developing as solid self-emulsifying delivery system. Self-emulsifying region was determined by ternary phase diagram. The optimized formulation contained glibenclamide (5mg), linseed oil (28.80%), Tween 80: PEG 200 (43.19%). and further solidified by adsorbing it on Aerosil 200 using spray dryer. The formulations were evaluated for percent transmittance, emulsification time, percent drug content, *in-vitro* dissolution study, globule size and zeta potential. The optimized solid formulations showed 96.02% drug release with droplet size 178 nm and emulsification time of 39.27 sec. Optimized formulations showed more release than pure drug. Characterization of the solid SEDDS revealed no interaction among the drug and excipient. DSC study revealed presence of drug in dissolved state while XRD indicated that the drug was in amorphous state. The solid SEDDS which emulsifies rapidly and had very small droplet size can be a promising approach for delivery of poorly water- soluble drugs having low bioavailability.

INTRODUCTION

Lipid-based formulation is one of the well known approaches to enhance solubility and oral bioavailability particularly the self- emulsifying drug delivery system (SEDDS). The SEDDS formulations are isotropic mixtures of oil, surfactant, co-surfactant and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsion under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the GI tract presents the drug in a solubilized form and the small size of the formed droplet provides a large interfacial surface area for drug absorption [1]. Further the presence of oil phase in the formulation helps improve bioavailability by affecting the drug absorption. SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule shell resulting in either brittleness or softness of the shell [2]. To overcome this problem SEDDS need to convert into solid SEDDS.

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Numerous reports states that, the major techniques for converting SEDDS to solid SEDDS (S-SEDDS) are spray cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization[3]. Glibenclamide (GBM) belonging to long-acting anti hyperglycemic agents. It is classified as BCS class II drug having low solubility and high permeability. It is a second-generation sulfonylurea used in the treatment of noninsulin-dependent diabetes. The poor water solubility of the drug is responsible for its poor dissolution, which ultimately leads to variable absorption. Furthermore, there are reports which have documented that GBM shows large variations in inter individual bioavailability and bioequivalence of the marketed products. Thus, it can be concluded that the bioavailability and in vivo performance of GBM is dependent on its dissolution rate [4, 5]. The solubility of GBM in aqueous medium is very low with half-life of 1.4-1.8 hours (unchanged drug only) which is very low and the duration of effect is 12-24 hours which results into poor bioavailability after oral administration [6]. So it was necessary to enhance

dissolution of GBM. Hence the prime objective of this study was to develop and characterize SEDDS formulation using oil and mixture of surfactant and co-surfactant and compare its behavior with marketed formulation.

MATERIALS AND METHODS

Materials

Glibenclamide was obtained as gift sample from Cipla Ltd., Mumbai. The linseed oil was obtained from local market, Nashik. Tween 80, PEG 200 was obtained from Lobachemie, Mumbai and Aerosil 200 was obtained from Thomas baker, Mumbai. All other chemical and reagents used were of analytical grade.

Methods

Saturation Solubility Study

Saturation solubility of glibenclamide in various oils, surfactants and co-surfactants was determined by rotary orbital shaker. In this study an excess amount of glibenclamide was added to each vehicle. The mixture was mixed using cyclo mixer to get uniform dispersion and further clamped in flask shaker and stirred for 72 hrs. The samples were centrifuged at 3000rpm for 15 min to separate the supernatant. Aliquots of supernatant were taken and filtered through a membrane filter (0.45µm). The concentration of GBM in various vehicles was determined by UV spectrophotometer (Shimadzu 1800) at 301 nm using respective vehicle as a blank [7].

Pseudo Ternary Phase Diagram

Based on the observations of solubility studies, components of emulsion viz. oil, surfactants and co-surfactants showing highest solubility of GBM were selected. The surfactants and co-surfactants were blended together in 1:1, 2:1, 3:1 proportions respectively. These blends of surfactants: co-surfactants (S_{mix}) were mixed with oily phase by adding small amounts with constant stirring. The proportions of oil: S_{mix} were varied as 9:1, 8:2, 7:1, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. The resultant blends were titrated with distilled water (0.5% (w/w) increment) with proper stirring. Systems were allowed to reach equilibrium and the samples were checked visually for clarity. The pseudo ternary phase diagrams were constructed for each system of oil, surfactant, and co-surfactant. The point indicating the clear and isotropic mixtures were considered to be within the microemulsion region [8, 9].

Preparation of SEDDS

Based on the phase diagram, oil and S_{mix} ratio were selected as vehicle at which wide microemulsion region is observed and selected as the vehicle for the development of SEDDS.

Glibenclamide was added to the oil phase and sonicated for 10 min. To this dispersion surfactant and co-surfactant were added and agitated for 15 min.

Characterization of SEDDS

Percent Transmittance

Glibenclamide SEDDS were reconstituted with distilled water and the resulting microemulsion was observed visually for turbidity. Thereafter its % transmittance was measured at 301nm using UV–VIS spectrophotometer against distilled water as a blank [10].

Emulsification Time

The efficiency of self-emulsification was assessed using dissolution test apparatus. In 250ml of water maintained at 37±0.5^{0}C; about 1ml of SEDDS was dissolved. Gentle agitation was provided by paddle rotating at 50RPM. The system was assessed visually according the rate of emulsification and the final appearance of the emulsion. Also any precipitation was observed visually [11].

Percent Drug Content

Glibenclamide SEDDS (equivalent to 5mg) was dissolved in 10 ml of methanol in a volumetric flask. Accurately 0.1 ml of stock solution was measured and transferred to 10 ml volumetric flask, diluted with methanol and filtered through Whatman filter paper (0.45µm). The above solutions were analyzed by UV Spectrophotometer at λmax 301nm.

In-Vitro Drug Release

Drug release studies from liquid and solid SEDDS were determined using USP dissolution test apparatus II with 900 ml of phosphate buffer (pH 7.4) as a dissolution medium maintained at 37 ± 0.5°C. The speed of the paddle was adjusted to 50 rpm. GBM loaded liquid SEDDS (equivalent to 5 mg of GBM) and 5 mg of powder GBM (Pure) were placed in a vessel. At predetermined time intervals of 5, 10, 20, 30, 45 and 60 min, an aliquot (5 ml) of the sample was collected, filtered, diluted and analyzed spectrophotometrically at 301 nm.

Globule Size of Analysis

The globule size and distribution was determined by dynamic light scattering technique(Malvern Zeta sizer Nano ZS 170 version 7.02).The optimized SEDDS formulation was diluted 250 times with 0.1N HCl / distilled water under gentle stirring. After achieving equilibrium, the emulsions were analyzed by Zeta sizer [12].

Zeta Potential

The surface charge on emulsion droplets and their mean zeta potential were determined using Malvern Zeta sizer (Malvern Instruments, UK, and Model: Zeta sizer Ver 7.02). The magnitude of zeta potential gives an indication of potential stability of the formulation. The 1 ml of SMEDDS was diluted by 10 times and 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. Zeta potential and electrophoretic mobility of the formulation was determined [13].

Development of Solid Self Emulsifying Drug Delivery System (SEDDS)

A lab scale spray dryer (Labultima LU 222 advanced, Mumbai) was used for the preparation of solid SEDDS. Aerosil 200 was used as inert carrier. Aerosil 200 was added in 250 ml ethanol, followed by magnetic stirring to form a suspension. Liquid SEDDS (equivalent to 5 mg of glibenclamide) was added to above suspension and stirred continuously at 40^0C until clear homogeneous suspension was formed. The resulting suspension was spray dried using peristaltic pump (0.7 mm nozzle diameter) under following operating conditions: Feed flow rate (2 ml/min), Inlet temperature (60^0C), Outlet temperature (50^0C), Air pressure (6.5 kg/cm^2), Aspirator (35 Nm^3/hr) and Vacuum (101 mm of Wc) The solid SEDDS powder was collected and stored in a desiccator at room temperature until its use [14].

Evaluation of Solid SEDDS

Percentage Practical Yield

The percentage yield of spray dried powder was calculated using following formula:

$$\% \text{ Practical yield} = \frac{\text{Wt. of Spray dried formulation obtained}}{\text{Wt. of (liquid SEDDS + Aerosil 200)}} \times 100$$

FT-IR Study

The Fourier Transform Infrared (FTIR) spectroscopy was used to record the FT-IR spectrum of S-SEDDS with diffuse reflectance principle using KBr pellet technique. The spectra were scanned over a frequency range of 4000-400cm^{-1} with a good resolution [15, 16].

Dispersion Time

The dispersion time of formulations was determined according to USP Type II dissolution apparatus. Approximately 1 gm of formulations was added directly to dispersion vessel containing 250 ml phosphate buffer (pH 7.4). The dispersion time was assessed visually and noted [2].

Percentage Drug Content

The percent drug content of GBM in SEDDS was estimated by dissolving appropriate quantity of individual SEDDS equivalent to 100 mg in 0.2 M NaOH. The samples were mixed thoroughly to dissolve the drug in 0.2 M NaOH. The sample was sonicated using bath sonicator for 15 min and analyzed using UV spectrophotometer and absorbance was recorded [10, 17].

Evaluation of Optimized Formulation

Solid State Characterization by DSC

Differential scanning calorimetry (DSC, Mettler Star SW 9.01) analysis gives an idea about the interaction of various materials at different temperature. It also allows us to study the possible degradation of the material. Sample approximately 1-4 mg was placed in aluminum pan sealed with an aluminium cover. An empty sealed pan in the same way was used as reference. Thermo grams were measured by heating the sample from 35 to 300^{0}C at the rate of 10^{0}C /min, under a nitrogen flow of 10 ml/min [13].

Globule Size and Zeta Potential

Mean particle size and size distribution of S-SEDDS was determined by dynamic light scattering technique using Malvern Hydro 2000 SM particle size analyzer.

Charge on drug loaded droplet surface was determined using Zeta sizer 300 (Malvern Instruments, Malvern, UK). Analysis time was kept for 60s and average charge and mobility of optimized batch of S-SEDDS was determined. The potential was measured after dilution of samples with distilled water at room temperature.

X-Ray Diffractometry Study

The diffraction pattern of solid SEDDS were recorded using an X-ray diffractometer in order to determine the nature of the drug in the formulation

RESULTS AND DISCUSSION

Solubility Study

The solubility of glibenclamide in various oils, surfactants and co-surfactants are tabulated in Table 1. Linseed oil, Tween 80 and PEG 200 were selected as oil phase, surfactant and co surfactant respectively though the solubility of glibenclamide was not highest but the system was stable and not showed phase separation after storage.

Pseudo Ternary Phase Diagram

The pseudo ternary phase diagrams were constructed to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant and co-surfactant. The series of mixtures were prepared and their self-emulsifying properties were observed visually. The surfactant and co-surfactant in the ratios of 1:1, 2:1 and 3:1 were evaluated. The emulsification area obtained with the surfactant to co-surfactant ratio of 2:1 was quite larger as compared to other ratios (Fig. 1). Hence, it was used in the formulation development.

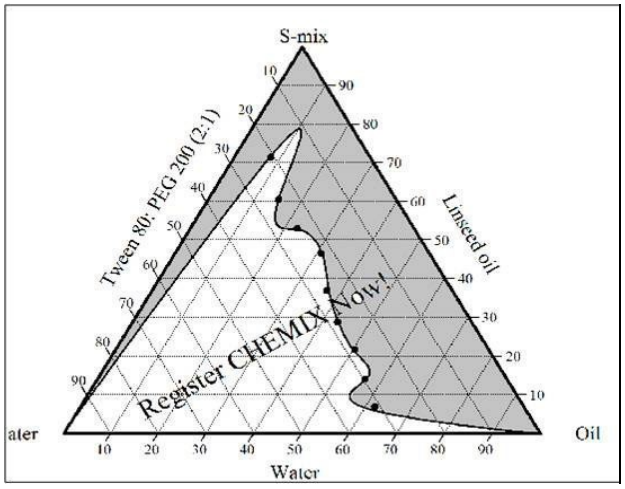

Figure 1: Pseudoternary phase diagram of selected oil, surfactant and co-surfactant (2:1)

Percent Transmittance

The percent transmittances in various SEDDS formulations are presented in Table 2. The percent transmittance in various SEDDS formulation varies from 88.95 to 96.76%. However, it was showed that as the surfactant increased in composition and oil decreased in composition of SEDDS formulation, percent transmittance was proportionally increased.

Emulsification Time

The emulsification time (Table 2) of various SEDDS formulation varies from 31.25 to 70.57 sec. It was observed that the emulsification time was decreased when the concentration of surfactant increased with decreased concentration of oil. The high concentration of surfactant and co-surfactant at the interface induces spontaneous formation of emulsion. The percentage drug content found in the internal phase of the emulsion is high because of the solubilization of glibenclamide by surfactant and co-surfactant mixture.

In-Vitro Drug Release

Drug release from the all SEDDS formulation was found higher as compared to pure glibenclamide and its marketed formulation (Fig. 2). The SEDDS formulation released drug above 90% as showed in Table 3. The study also includes determination of % dissolution efficiency (%DE) of drug, marketed and developed formulation. The % DE for drug was 11.27%, while for marketed and developed formulation was 30.05 and 57.76% respectively. It could be suggested that the SEDDS 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 SEDDS 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.

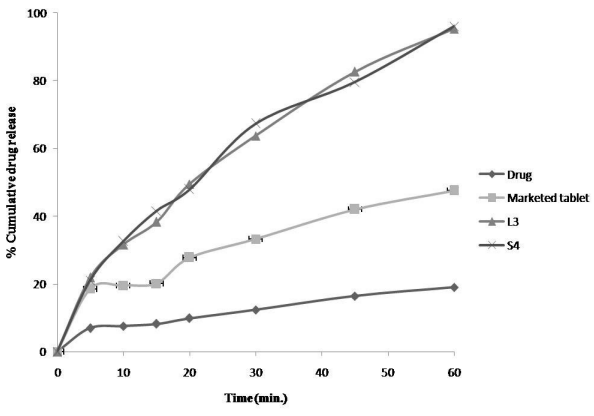

Figure 2: Percent cumulative drug release

Table 1: Solubility of glibenclamide in various oils, surfactant and co-surfactants

Sr. No.	Oil	Solubility (mg/ml) (mean± SD)	Surfactant	Solubility (mg/ml) (mean± SD)	Co-surfactant	Solubility (mg/ml) (mean± SD)
1	Arachis oil	9.00± 0.24	Tween 80	22.09± 0.21	Glycerol	4.16± 0.15
2	Oleic acid	0.26± 0.11	Tween 20	11.70± 0.07	PEG 200	6.79± 0.05
3	Labrafil M2125 CS	144± 0.05	Span 20	5.98± 0.11	PEG 400	5.42± 0.19
4	Linseed oil	2.73± 0.02	Labrasol	134.11± 0.24	Propylene glycol	13.91± 0.04
5	Ethyl oleate	5.22± 0.16	Cremophor	216.67± 0.08		

n=3

Table 2: Percent transmittance, emulsification time and drug content of SEDDS batches

Batch	Transmittance (%)(mean± SD)	Emulsification time (sec) (mean± SD)	Drug content (%) (mean± SD)
L1	91.48± 0.17	58.14± 0.98	96.27± 0.12
L2	94.27± 0.34	70.57± 1.84	98.61± 0.37
L3	96.79± 0.34	31.25± 1.04	98.91± 0.20
L4	88.95± 0.82	49.76± 1.27	97.82± 0.23
L5	93.58± 0.51	45.78± 2.15	96.34± 0.31
L6	95.68± 0.87	49.26± 1.95	97.32± 0.22

n=3

Table 3: Percent cumulative drug release from liquid SEDDS

Time (min.)	Cumulative Drug Release (%) (mean± SD)					
	L1	**L2**	**L3**	**L4**	**L5**	**L6**
5	21.37± 0.34	20.25± 1.02	21.88± 0.05	21.06± 0.12	20.55± 0.005	20.96± 0.004
10	27.33± 0.05	29.16±0.02	31.53± 1.03	30.71± 0.05	28.86± 1.003	26.10± 1.034
15	33.26± 0.18	32.86± 0.14	38.32± 0.95	35.95± 1.02	32.86± 0.042	34.98± 0.061
20	45.69± 1.14	41.61±1.053	49.48± 0.19	42.48± 0.6	43.75± 0.05	45.59± 0.007
30	58.67± 0.95	57.60± 1.20	63.73± 0.03	58.29± 0.01	54.15± 1.00	54.68± 1.004
45	77.10± 1.01	74.18± 1.03	82.62± 1.04	75.59± 0.21	77.24± 0.46	80.12± 0.037
60	91.74± 0.03	90.53± 1.07	95.28± 0.72	88.27± 0.04	92.70± 1.02	93.37± 0.006

L stands for liquid self emulsifying formulation, n=3

Table 5: Cumulative drug release of S-SEDDS

Time	Cumulative Drug Release (%) (mean± SD)						
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**Pure drug**
5	19.63± 0.40	19.73± 0.12	20.55± 1.2	21.06± 0.52	20.45± 0.41	20.96± 0.54	6.95±0.63
10	26.70± 1.02	28.13± 0.49	31.72± 0.24	32.55± 0.24	28.86± 0.24	26.10± 1.42	7.54±1.00
15	33.03± 0.63	36.12± 0.14	39.74± 0.41	41.50± 0.31	32.76± 0.31	34.98± 0.02	8.23±0.42
20	42.90± 1.00	41.93± 0.58	51.53± 1.03	47.88± 0.13	43.75± 0.42	43.75± 0.28	9.86±0.20
30	53.39± 0.74	53.02± 1.00	63.04± 0.49	67.32± 0.52	54.15± 1.03	54.66± 1.52	12.32±1.04
45	78.21± 0.39	71.60± 0.37	74.46± 0.87	79.61± 1.14	74.47± 1.17	75.19± 0.75	16.44±1.21
60	92.15± 1.01	86.18± 0.91	89.58± 1.23	96.02± 0.57	92.66± 0.28	92.68± 0.63	18.97±0.42

S stands for solid self emulsifying formulation, n=3

Table 6: Statistical analysis of drug release (Pure drug and from formulation)

	ANOVA				
	df	**SS**	**MS**	**F**	**Significance F**
Regression	1	125.5698758	125.5698758	123.8736237	0.000102096
Residual	5	5.068467043	1.013693409		
Total	6	130.6383429			

Droplet Size and Zeta Potential

Droplet size distribution following self-micro emulsification is a crucial factor to evaluate a self micro-emulsion system. Droplet size of GBM emulsion decreased with reducing the oil content in SEDDS. The smaller the droplet size, the larger the interfacial surface area will be provided for drug absorption. The size of F-3 was found to be below range of 200 nm indicating the micro-emulsifying system (Fig. 3). The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. Zeta potential of the system was found to be -8.69, indicating the droplets are apart from each other showing the stability.

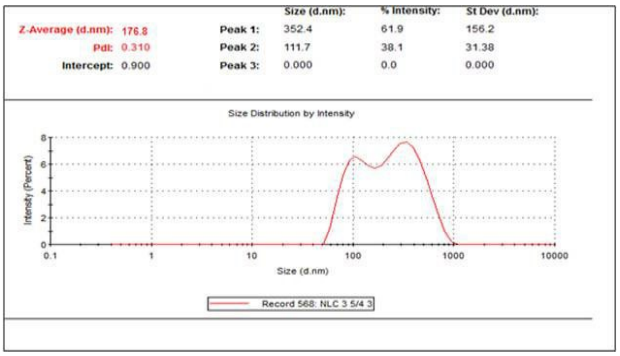

Figure 3: Globule size of formulation F-3

Process Yield and Flow Properties of Dried Powder

It was observed that the batches containing a higher amount of Aerosil 200 which was used as a carrier (hydrophilic fumed silica with specific surface area of 200 m^2/gm) had higher process yield. This study was initiated with the optimization of the concentration of Aerosil 200 and it was kept constant in all batches.It was observed that the flow properties of spray dried formulations were in acceptable range whereas, pure drug showed poor flow. It confirms that the spray drying technique improves flow properties too.

Dispersion Time

Measurement of dispersion time determines the ability of the formulation to disperse in the gastrointestinal tract. This parameter is an indicator of wetting of the material by the dissolution medium spontaneously. The results indicated that increase in amount of surfactant decreases the dispersion time. Surfactant modifies the surface properties of the material and helps the content to make intimate contact with medium. The dispersion time for all formulation ranges from 39 to 77 seconds which satisfy the requirement. The percentage drug content of S-SEDDS were in range of 89.76-97.67% (Table 4).

Table 4: Dispersion time and drug content of S-SEDDS

Batch	Dispersion time (sec) (mean± SD)	Drug content (%) (mean± SD)
S1	76.91± 0.716	91.76± 0.47
S2	49.57± 0.173	91.38± 0.45
S3	42.27± 0.249	89.76± 0.41
S4	39.27± 0.28	97.67± 0.20
S5	67.38± 1.195	92.81± 0.38
S6	45.59± 1.37	92.29± 0.26

In-Vitro Drug Release

The results of i*n-vitro* drug release study (Table 5) indicated that increase in amount of surfactant directly related to drug release whereas amount of adsorbent is inversely proportional to % CDR. Maximum drug release was shown by S4 batch which may be due to optimum amount of oil required for self-emulsification. Also the higher concentration of oil and surfactant form droplets of smaller size so that maximum surface area is available to get in contact with dissolution medium. The % cumulative release of glibenclamide was in the range of 19.63 to 96.02% at the end of 60 min. When the dissolution of pure drug and optimized formulation was compared for the period of 60 minutes it was observed that the drug release from formulation was more than that of pure drug. When the drug release data was compared using one-way ANOVA (Table 6); it was observed that F_{exp} (123.87) exceeds the F_{tab} (0.00010) which indicated that there was a significant difference in drug release between pure and formulation sample.

FT-IR

The FTIR spectrums of physical mixture showed the presence of peaks for C=O, S=O, N-H, C=C and C-C functional groups at respective wave numbers. The peaks are neither added, disappeared nor shifted indicating compatibility of all formulation composition with each other which is a prerequisite for development of stable formulation. Also the FT-IR spectrum of spray dried formulation seems to be the summation of spectrums of glibenclamide and all other excipients used confirming the non interference of the ingredients with each other at their used concentration (Fig. 4).

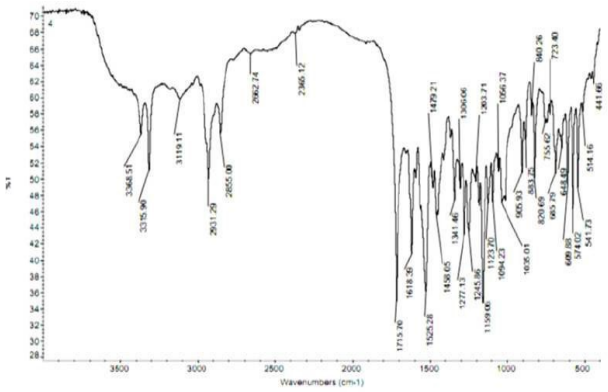

Figure 4: FT-IR spectrum S-SEDDS formulation

Differential Scanning Calorimetry (DSC) Study

The DSC thermogram is showing the melting point of drug at 177^{0}C and of the optimized formulation appeared at 54.88^{0}C. This indicated that drug was present in dissolved state in formulation composition system (Fig. 5).

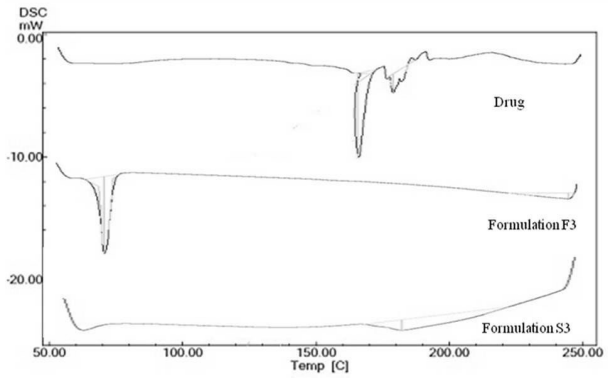

Figure 5: Comparison of DSC thermograms (Drug, liquid and solid formulations)

X-Ray Diffractometry Study

The X-ray diffraction pattern indicated that the drug was present in amorphous form and this could be one of the probable mechanisms for increased dissolution as compared to pure drug (Fig. 6).

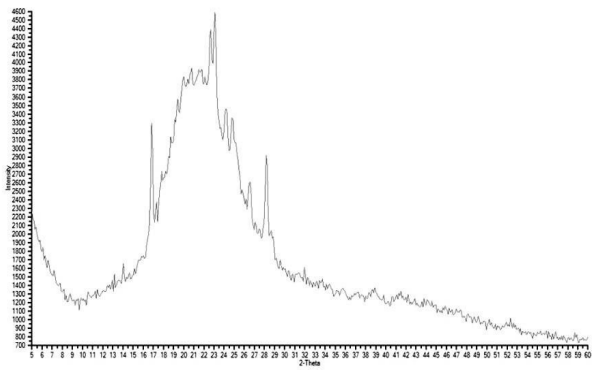

Figure 6: XRD spectrum of S-SEDDS formulation

Evaluation of Optimized Formulation

The optimized formulation was evaluated for globule size and zeta potential. The globule size was found 185 nm indicating self-micro emulsifying system characteristics. The zeta potential of L-SEDDS and S-SEDDS were found to be in -8.69 and -8.94 respectively. These parameters revealed that the formulation may forms very small droplets when in contact with the GIT fluid. The charged droplet indicated sufficient stability.

CONCLUSION

From the study it can be concluded that prepared liquid SEDDS was stable with good self-emulsification efficiency and having globule size in nanometer range. Results of DSC demonstrated that the drug was present in dissolved state in formulation. *In-vitro* drug release of SEDDS was significantly higher than that of pure drug and marketed formulation when analyzed statistically by ANOVA. The results prompted that application of self-emulsifying delivery system approach can be useful for development of stable formulation of glibenclamide with increased solubility and increased bioavailability.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

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