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RESEARCH ARTICLE

Formulation and Evaluation of Self Emulsifying Drug Delivery System of an Anti-diabetic Drug

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ABSTRACT

Glibenclamide (GBM) belongs to BCS Class II category of poor solubility and poor bioavailability drug used for the treatment of non-insulin dependent Diabetes mellitus. Hence the oral absorption is dissolution rate limited and requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. Hence the main objective of this work was to formulate, develop and evaluate an optimal Self emulsifying drug delivery system (SEDDS) containing GBM. Solubility of Glibenclamide in oil, surfactant and co-surfactant was determined. Preliminary screening was carried out to select proper component combination. Glibenclamide SEDDS was prepared using Oleic acid (oil), Tween 80 (surfactant), PEG 400 (co-surfactant). A series of twenty one formulations were prepared. Tween 80 and PEG 400 were incorporated in the ratio1:1, 2:1 and 3:1 respectively for separate batches. Effects of lipids and surfactants on physical properties of SEDDS such as *in vitro* emulsification efficiency in terms of self-emulsification time, thermodynamic stability studies, Transmission electron microscopy (TEM), emulsion droplet size, and optical clarity were measured. Formulation F013 consisting of surfactant and co-surfactant ratio 1:2 exhibited the desired properties of ideal self-emulsifying drug delivery system ensuring the maximum dissolution property. The study revealed that higher amount of surfactants significantly increased dissolution of Glibenclamide while decreasing emulsion droplet size and emulsification time. About a four-fold increase in dissolution was achieved by SEDDS compared to pure GBM powder. Overall, the study suggests that dissolution and oral bioavailability of GBM could be improved by SEDDS technology.

KEYWORDS

SEDDS, Glibenclamide, Oleic acid, Tween 80, Polyethyleneglycol 400

INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability.

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The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms. In today's market, more than 40% of oral drug products contain poorly soluble drugs, and among the pharmacopoeia, this share is more than 30%.[1] Lipid based drug delivery systems (LBDDS) are one of the most notable findings over the past decades and the number of publications related to lipid delivery systems have been increased

exponentially.[2] Various types of lipid-based formulations exist; from simple solutions or suspensions of drug in lipid, through to emulsions and more complex self-emulsifying/ micro emulsifying/ nano emulsifying (SEDDS/ SMEDDS/ SNEDDS) systems. The use of SEDDS to improve the bioavailability of poorly water soluble drugs (PWSD) was first reported in 1982 by Pouton.[3]

In addition, these systems are more recent approach to improve the dispersibility and reduce the particle size of dispersed systems, thus potentially increasing oral absorption for poorly water soluble drugs (PWSD).[4] An example of a commercially available SMEDDS preparation is Neoral® (cyclosporine A).

Glibenclamide, 5-chloro-N-(4-[N-(cyclohexylcarbamoyl) sulfamoyl] phenethyl)-2-methoxybenzamide, it belongs to sulfonylureas class of oral antidiabetic agent and white to off-white in colour, non-hygroscopic powder. Soluble in ethanol (5 mg/mL), DMSO (Dimethyl sulfoxide) (25 mg/mL), chloroform (1:36), methanol (1:250), and DMF (Dimethyl formamide). Practically insoluble in water.[5] The current therapeutic scenario demands a strong need for a delivery strategy that can improve the therapeutic efficacy of Glibenclamide by means of increasing its solubility. The mechanism of action of Glibenclamide includes, stimulation of insulin release from the Î² cells of the pancreas by blocking the ATP-sensitive K^+ channels, resulting in depolarization and Ca^{2+} influx, reduction in hepatic glucose production and increase in peripheral insulin sensitivity.[6] The initial loading dose and maintenance dose of Glibenclamide is 1.25mg to 5mg per day and 1.25mg to 20mg per day respectively.

For the present study 5 mg was selected for the development of self-emulsifying drug delivery system of Glibenclamide. The objective of the study was to design, optimize and evaluate the SEDDS of Glibenclamide.

MATERIAL AND METHODS

Glibenclamide was gift sample from Medreich Limited, Bangalore. Oleic acid, Polyethylene glycol 400 and Polysorbate 80 (Tween 80) are purchased from Fine-Chem. Limited, Mumbai, India and all are laboratory grade chemicals.

Drug Characterization

Physical Appearance

A small quantity of Glibenclamide powder was taken in a butter paper and viewed in well-illuminated place. The color, powder and texture of the drug were observed.

Melting Point

Melting point of the drug was determined by using melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted.

Solubility Studies

The saturation solubility of Glibenclamide was evaluated in various oils, surfactants, and co-surfactants.

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 was 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.[7]

The concentration of dissolved Glibenclamide was determined by UV-VIS spectrophotometer (UV-1601, Pharmaspec, Shimadzu Ltd, Japan) at λ_{max} 226.5 nm.

Absorption Spectrum of Glibenclamide

The UV spectrophotometry method was used for the analysis of drug using UV-Visible double beam spectrophotometer 1601 (Shimadzu 1601).

FT-IR Studies

To find out any possible chemical interaction of drug with used excipients in solid and liquid form is carried out using IR spectrophotometer.

Preparation of Self Emulsifying Drug Delivery System

A series of formulations of self-emulsifying drug delivery system were prepared using the Tween 80/ PEG 400 as Surfactant /Co-surfactant (S/CoS) combination and Oleic acid as the oil (Table 1). Tween 80 and PEG 400 were weighed in the ratio1:1, 2:1 and 3:1 to the Glibenclamide. The level of Glibenclamide was kept constant (5 mg) in all the formulations. A transparent and homogenous mixture of Oleic acid and S/CoS (Tween 80/ PEG400) was formed followed by addition of the drug. Then the components were mixed by gentle stirring, heated at 40ºC on a magnetic stirrer at 1500 rpm, until Glibenclamide was perfectly dissolved. The formulations were stored at room temperature in a desiccator until further use.

In Vitro Characterization of Optimized SEDDS

Thermodynamic Stability Tests[8]

Prepared formulations were subjected to different thermodynamic stability tests (Centrifugation, Heating cooling cycle and Freeze thaw cycle). Formulations, which passed these thermodynamic stress tests, were subjected for further evaluation parameters.

Dispersibility Tests

The efficiency of dispersibility was assessed using a USP XXII dissolution apparatus II. Each formulation (0.5 ml) was added to 500 ml distilled water maintained at 37±0.5˚C, with paddle rotating at 50 rpm for gentle agitation. The *in vitro* performance of the formulations was visually assessed using the grading system.[9]

Table: 1 Formulation of Glibenclamide SEDDS

Ratio 1:1 (S/CoS)	**Formulation**	**F001**	**F002**	**F003**	**F004**	**F005**	**F006**	**F007**
	Glibenclamide (mg)	5	5	5	5	5	5	5
	Oleic acid (mg)	400	400	400	200	200	200	600
	Tween 80 (mg)	150	250	350	150	250	350	150
	PEG 400 (mg)	150	250	350	150	250	350	150
Ratio 2:1 (S/CoS)	**Formulation**	**F008**	**F009**	**F010**	**F011**	**F012**	**F013**	**F014**
	Glibenclamide (mg)	5	5	5	5	5	5	5
	Oleic acid (mg)	400	400	400	200	200	200	600
	Tween 80 (mg)	200	333	466.66	200	333	466.66	200
	PEG 400 (mg)	100	166	233.33	100	166	233	100
Ratio 3:1 (S/CoS)	**Formulation**	**F015**	**F016**	**F017**	**F018**	**F019**	**F020**	**F021**
	Glibenclamide (mg)	5	5	5	5	5	5	5
	Oleic acid (mg)	400	400	400	200	200	200	600
	Tween 80 (mg)	225	375	525	225	375	525	225
	PEG 400 (mg)	75	125	175	75	125	175	75

The formulations that passed the thermodynamic stability and dispersibility tests in Grade A and B were selected for further studies.

Assessment of Emulsification Time

The emulsification time of SEDDS formulations was determined in a USP dissolution tester (Electrolab, India). The SEDDS formulation containing 2.5 mg of Glibenclamide was added drop-wise to 500 ml of distilled water maintained at 37 ± 0.5°C. Gentle agitation was provided by a paddle rotating at 50 rpm and emulsification time was recorded manually.[10]

Spectroscopic Characterization of Optical Clarity

Each formulation containing 2.5 mg Glibenclamide was diluted with 500 ml of distilled water. The absorbance values of each emulsion at 0, 10, 20, and 30 min post-dilutions were measured by a UV spectrophotometer (UV -1610, Shimadzu, Japan) at 226.5 nm.[11]

Drug Content

Glibenclamide quantity equivalent to 100 mg from individual SEDDS formulation is dissolved in 0.2M NaOH. The percent drug content of GBM in SEDDS was estimated by using UV spectrophotometer and absorbance was recorded.[12]

Droplet Size Analysis

The droplet size distributions and polydispersibility index of the resultant microemulsions (SEDDS) were determined using particle size analyzer (Malvern Zetasizer 3000HS).[13]

Zeta potential Determination

Aliquots (1ml) of the samples serially diluted 1000 folds with purified water were employed to determine zeta potential. Zeta potential was determined by Malvern Zetasizer. Each study was carried out in triplicate to ensure reproducibility.[14]

Transmission Electron Microscopy

Addition of distilled water to prepared SEDDS and shaking the mixture manually for 5 minutes. A drop of the resultant microemulsion was placed onto a carbon–coated copper grid, forming a thin liquid film. The films on the grid were negatively stained by adding immediately a drop of 2% (w/w) ammonium molybdate in 2% (w/v) ammonium acetate buffer (pH6.8), removing the excess staining solution with a filter paper, and followed by a thorough air-drying. The stained films were then viewed on a transmission electron microscopy (TEM, FEI-Philips Tecnai 12) and photomicrograph was taken (Figure 1)

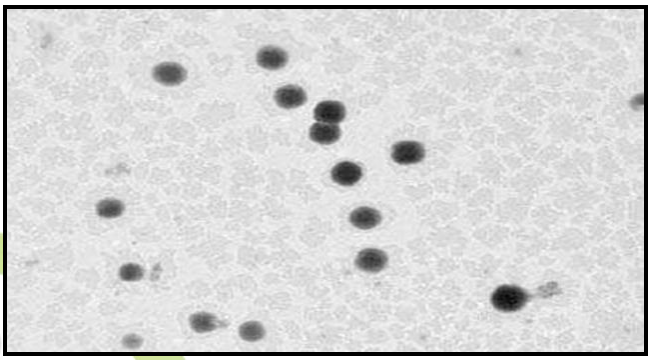

Figure: 1 Transmission Electron Microscopy (TEM) of SEDDS of Glibenclamide

In-Vitro Dissolution Studies

Dissolution Release Specification

In vitro dissolution studies for Glibenclamide SEDDS and plain Glibenclamide were studied using United States Pharmacopeia (USP) XXIII apparatus II (Paddle Type) at 37±0.5°C with a rotating speed of 50 rpm using buffer pH 7.4 as the dissolution media. For dissolution purposes, SEDDS formulations equivalent to 2.5 mg of Glibenclamide were filled in hard gelatin capsules (size # 3). The amount of Glibenclamide released in the dissolution medium was determined by UV-VIS spectrophotometer (UV - 1610, Shimadzu, Japan) at λ max 226.5 nm.[15]

Stability Study

Optimized SEDDS formulations were subjected to a stability study at accelerated conditions of 40°C/75% relative humidity for over a period of three months. Samples were withdrawn at regular intervals and were considered for visual analysis. The change in the color, clarity and any kind of precipitation was observed visually.

RESULTS AND DISCUSSION

Spectral analysis and all the physicochemical properties of pure drug and the SEDDS form were found to be normal.

FT-IR Studies

IR spectrum of pure drug and pure drug with used excipients is given in (Figure 2 and 3) and showed that, there are NO possible interactions between drug and excipients used.

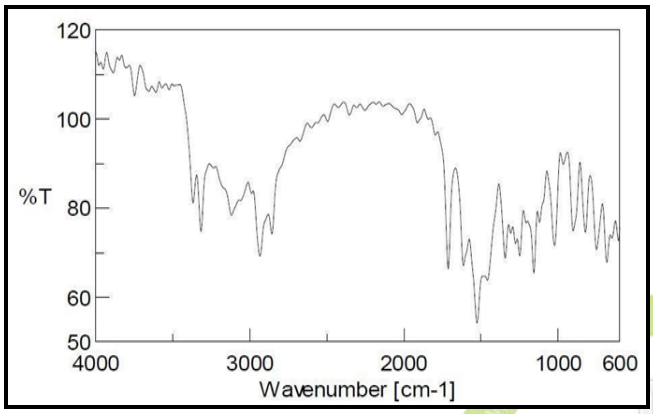

Figure: 2 FT-IR Spectrum of Pure Glibenclamide

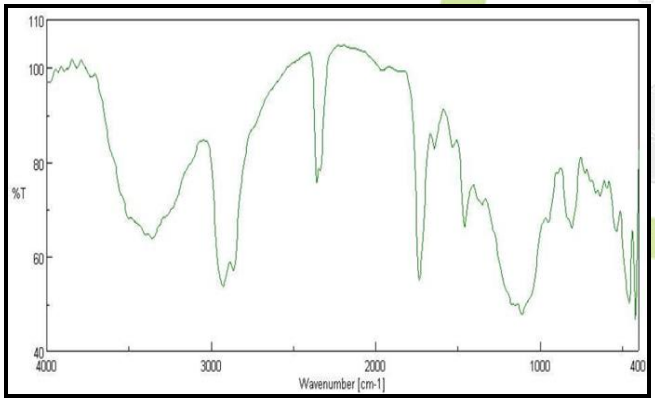

Figure 3: FTIR Spectrum of SEDDS of Glibenclamide (F013)

Thermodynamic Stability Studies

Formulations selected were subjected to thermodynamic stability in order to eliminate metastable formulations in minimum possible time. The results of formulations which passed thermodynamic test are presented in (Table 2) along with their concentrations.

Dispersibility Tests

Dispersibility tests were carried to find the formation of emulsions from the prepared SEDDS after oral administration. The results of dispersibility tests are given in the (Table 2). Formulations F008-F014 in which Surfactant/Co-surfactant ratio is 2:1 (Smix 2:1) found to pass dispersiblity test with grade A and B but mostly found to be failed for other thermodynamic stability tests. Formulations in which Surfactant/Co-surfactant ratio is 3:1 (Smix 3:1) found to comply with thermodynamic stability studies and dispersiblity tests. On the basis of thermodynamic stability studies and dispersibility tests, seven formulations were selected for further characterization. (Table 3)

Assessment of Self Emulsification Time

The results of self-emulsification and precipitation studies are given in (Table 4). It was seen that an increase in the proportion of oil (Oleic acid) and surfactant (Tween 80) 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.

Spectroscopic Characterization of Optical Clarity

Optical clarity may be checked visually. But in order to measure it quantitatively, a UV-visible spectrophotometer was used. 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.[11] All formulated batches were transparent (Table 5). The values remained unchanged even after 30 min of dilution which may be considered as a primary indication about the fact that the optimized SEDDS batches were stable (Table 5).

Drug Content

Drug content in various SEDDS formulations are given in (Table 6). The content of drug in various SEDDS formulation varies from 95.21% to 99.91%. However, it was showed that as the surfactant increased in composition and oil decreased in composition of SEDDS formulation, drug content was proportionally increased.

Table: 2 Thermodynamic Stability Test and Dispersion Test

Ratio	Formulations	Oil	Smix	Centrifuge	H/C Cycle	Freeze Thaw	Disperse Grade	Inference
1:1	F001	400	300	Pass	Pass	Pass	A	Pass
	F002	400	500	Pass	Fail	Fail	A	Fail
	F003	400	700	Pass	Fail	Fail	B	Fail
	F004	200	300	Pass	Pass	Pass	A	Pass
	F005	200	500	Pass	Fail	Fail	C	Fail
	F006	200	700	Pass	Fail	Fail	C	Fail
	F007	600	300	Fail	Fail	Fail	C	Fail
2:1	F008	400	300	Pass	Fail	Fail	B	Fail
	F009	400	500	Pass	Fail	Fail	A	Fail
	F010	400	700	Fail	Fail	Fail	A	Fail
	F011	200	300	Pass	Fail	Fail	A	Fail
	F012	200	500	Fail	Fail	Fail	B	Fail
	F013	200	700	Pass	Pass	Pass	A	Pass
	F014	600	300	Pass	Pass	Pass	A	Pass
3:1	F015	400	300	Pass	Fail	Fail	B	Fail
	F016	400	500	Pass	Fail	Fail	B	Fail
	F017	400	700	Pass	Pass	Pass	A	Pass
	F018	200	300	Pass	Fail	Fail	A	Fail
	F019	200	500	Pass	Pass	Pass	A	Pass
	F020	200	700	Pass	Fail	Fail	B	Fail
	F021	600	300	Pass	Pass	Pass	A	Pass

Table: 3 Optimised Formulations from Thermodynamic Stability Studies

Formulation Code	Smix ratio	Drug (mg)	Oil (mg)	Surfactant 150(mg)	Cosurfactant (mg)
F001	1:1	5	400	150	150
F004			200	150	150
F013	2:1		200	466.66	233
F014	3:1		600	200	100
F017			400	525	175
F019			200	375	125
F021			600	225	75

Table: 4 Self-emulsification Times

Formulation code		F001	F004	F013	F014	F017	F019	F021
0.1N HCl	Emulsification Time (s)	23	28	26	45	25	29	67
	Tendency for Emulsification	Good	Good	Good	Good	Good	Good	Good
Phosphate Buffer pH (7.4)	Emulsification Time (s)	20	31	22	50	26	34	61
	Tendency for Emulsification	Good	Good	Good	Good	Good	Good	Good

Table: 5 Spectroscopic Characterization of Optical Clarity

Sl. No.	Formulations	Absorbance
1	F001	0.458
2	F004	0.422
3	F013	0.319
4	F014	0.524
5	F017	0.521
6	F019	0.481
7	F021	0.652

Table: 6 Estimation of Drug Content

Sl. No.	Formulations	Drug content (%)
1	F001	96.38
2	F004	98.36
3	F013	97.18
4	F014	99.73
5	F017	98.54
6	F019	99.91
7	F021	95.21

Droplet Size Analysis

The average size of droplets formed after emulsification was measured by using Malvern Zetasizer at room temperature which was found to be 461.7 nm with poly dispersity index of 0.9 showing that the particles generated were monodisperse.[16] Gursory and Benita also reported that an increased amount of surfactant concentration can lead to droplets with smaller mean droplet size.[17] The smallest droplet was found when 200 mg OA and 700 mg of S/CoS were used (F013) (Figure 4).

Zeta Potential Determination

Zeta potential is the potential difference between the surface of tightly bound layer (shear plane and electroneutral region of the solution). Zeta potential of optimized Glibenclamide SEDDS (F013) was found to be -26.8 mV, which indicates that emulsion was stable (Figure 5).

Transmission Electron Microscopy

Sample for transmission electron microscopy were prepared and by using a transmission electron microscope (TEM, FEI-Philips Tecnai 12) the photomicrograph was taken (Figure 1).

***In-Vitro* Dissolution Studies**

Drug release from all SEDDS formulations was found to be significantly higher as compared with that of plain Glibenclamide as showed in Figure 6. All Glibenclamide SEDDS formulations were found to have drug release above 60% within 15 min as showed in (Table 7). It was showed that increase in surfactant concentration and decrease in oil concentration in formulation increase in drug release.

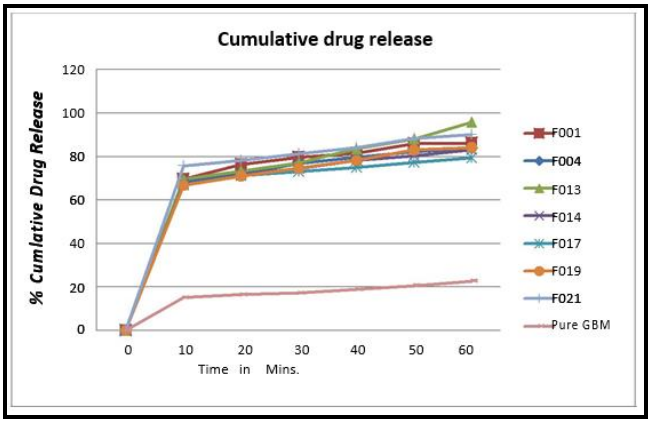

Figure: 6 Cumulative Drug Release Profiles of Pure Glibenclamide and SEDDS Formulations

Stability Screening

Developed formulations were subjected to accelerated stability testing (40°C/75% relative humidity) to evaluate their stability and the integrity of the final dosage form as well. Physical characteristics were re-evaluated after one month and three months from formulation-time. After the first month, three out of seven formulations became cloudy which were considered as unstable, where two of them showed precipitation (Table 8). After the third month, all the three cloudy preparations showed precipitation. So, the rest of the four formulations were found to be stable based on color, clarity and precipitation.

DISCUSSION

Glibenclamide also known as glyburide is an anti-diabetic drug belongs to the class of medications known as Sulfonylureas. The drug is marketed generally in the dose of 1.25, 2.5 and 5 mg. It is also sold in combination with metformin. Glibenclamide is used in the treatment of type 2 diabetes. No formulations have been brought into market as Self emulsifying drug delivery system. Therefore the present study was planned to develop a Self-emulsifying drug delivery system of Glibenclamide intended to provide a better bioavailability of the drug.

Table: 7 Cumulative Drug Release of Plain Drug (pd) and Glibenclamide SEDDS

Sl. No.	Time (mins)	In vitro drug release data							
		Plain GBM	F001	F004	F013	F014	F017	F019	F021
0	0	0	0	0	0	0	0	0	0
1	10	15.21	69.63	68.78	69.61	67.58	66.98	66.81	75.80
2	20	16.54	76.37	72.08	73.32	71.80	71.31	71.14	78.26
3	30	17.28	79.69	76.75	77.04	74.61	73.17	74.63	81.39
4	40	18.95	81.61	79.60	83.54	78.33	74.97	78.25	84.14
5	50	20.62	86.09	82.35	88.18	80.50	77.28	83.06	88.31
6	60	22.81	86.29	83.82	95.88	83.21	79.51	84.14	90.20

Table: 8 Results of the Stability Study of the SEDDS Batches

Formula-tion	After preparation			After 1 month			After 3 months		
	Color	Clarity	Precipitation	Color	Clarity	Precipitation	Color	Clarity	Precipitation
F001	Light Yellow	Clear	No	Light Yellow	Cloudy	Yes	Light Yellow	Cloudy	Yes
F004	Light Yellow	Clear	No		Clear	No	Yellow	Clear	No
F013	Yellow	Clear	No	Light Yellow	Clear	NO	Yellow	Clear	NO
F014	Light Yellow	Clear	No	Light Yellow	Cloudy	NO	Light Yellow	Cloudy	Yes
F017	Light Yellow	Clear	No	Light Yellow	Clear	No	Yellow	Clear	NO
F019	Light Yellow	Clear	No	Light Yellow	Clear	No	Light Yellow	Clear	No
F021	Yellow	Clear	No	Yellow	Cloudy	Yes	Yellow	Cloudy	Yes

A total of twenty-one formulations (F001 to F021) of SEDDS of Glibenclamide were prepared by using different concentrations of surfactant: co-surfactant (S/CoS), i.e., Tween 80 and Polyethylene glycol 400 (PEG 400) along with an oil, i.e., Oleic acid. The different ratios used were 1:1, 2:1 and 3:1. Twenty one formulations were developed in such a way that each batch consisted of seven formulations under each ratio [F001-F007 (1:1), F008-F014 (2:1) and F015-F021 (3:1)].

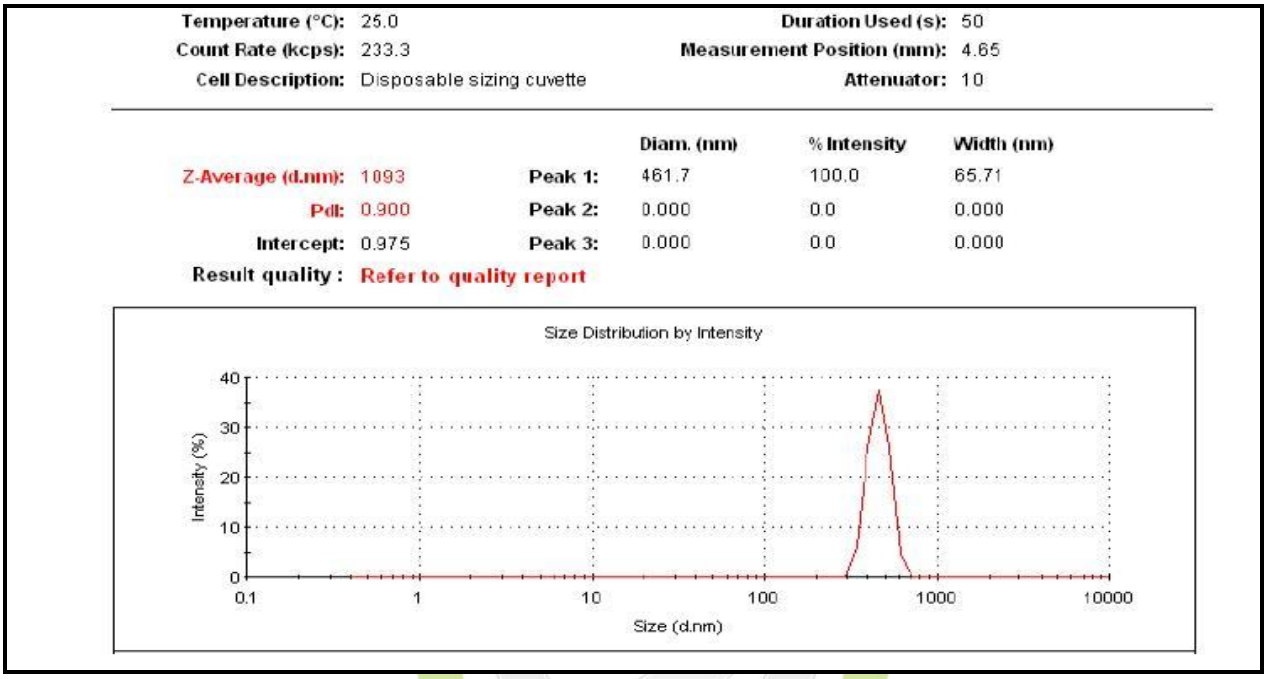

Figure 4 Droplet Size Analysis of Optimised Self-emulsifying Drug Delivery System of Glibenclamide

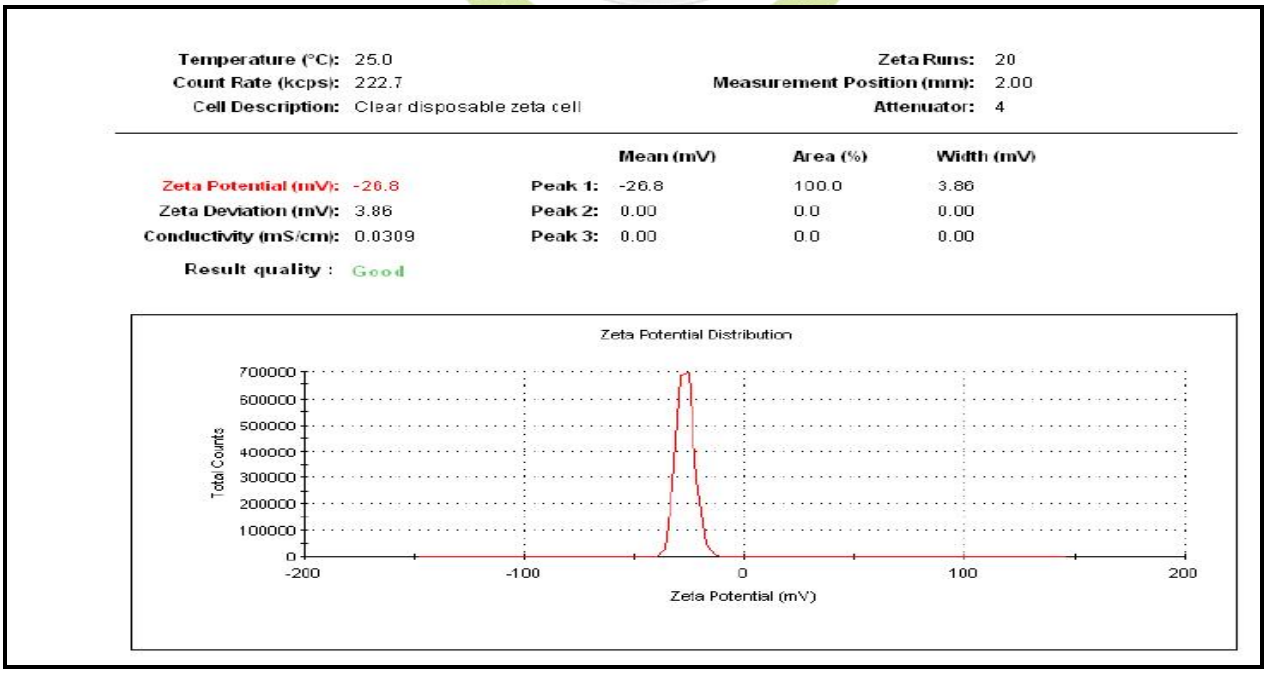

Figure: 5 Zeta Potential Analysis of Optimised Self-emulsifying Drug Delivery System of Glibenclamide

All the formulations were subjected to initial *in vitro* characterization studies. Most of the formulations were found to fail for thermodynamic stability studies and dispersion studies. Among twenty one formulations, seven formulations were shortlisted from the three batches since other formulations were a failure initially exhibiting pH separation and instability to temperature variations. Therefore it could be concluded that these formulations wouldn't give desirable properties of an ideal SEDDS. Furthermore, there is no assurance that these formulations would be stable within the hard gelatin capsule shell.

Thus, Formulations F001 and F004 of ratio 1:1, formulation F013 and F014 of ratio 2:1 and formulations F017, F019 and F021 of ratio 3:1 were found to comply with the desired results for a self-emulsifying drug delivery system. Of these, the formulation with Surfactant: Cosurfactant ratio 3:1 showed better results compared to other ratios.

The seven formulations were then subjected for further evaluation parameters such as self-emulsification time, optical clarity evaluation, drug content, droplet size and zeta potential analysis, TEM studies, *in vitro* evaluation studies and stability studies.

In F001 formulation, 1:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 23 and 20 seconds respectively in acidic and basic pH. Drug content estimation showed 96.38 % of drug content in the formulation. *In vitro* dissolution studies showed a release of 86.29% at the end of 60th minute.

In F004 formulation, 1:1 S/CoS ratio was used. Thermodynamic stability studies showed good results. Self-emulsification time was found to be 28 seconds and 31 seconds in acidic and basic pH respectively which was slightly more than the previous formulation F001. *In vitro* dissolution studies showed a release of 83.82% at the end of 60th minute.

In F013 formulation, 2:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 26 and 22 seconds respectively in acidic and basic pH. Drug content estimation showed 97.18 % of drug content in the formulation. *In vitro* dissolution studies showed a release of 95.88% at the end of 60th minute.

In F014 formulation, 2:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 45 and 50 seconds respectively in acidic and basic pH. Drug content estimation showed 99.73% of drug content in the formulation. *In vitro* dissolution studies showed a release of 83.21% at the end of 60th minute.

In F017 formulation, 3:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 25 and 26 seconds respectively in acidic and basic pH. Drug content estimation showed 98.54% of drug content in the formulation. *In vitro* dissolution studies showed a release of 79.51% at the end of 60th minute.

In F019 formulation, 3:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 29 and 34 seconds respectively in acidic and basic pH. Drug content estimation showed 99.91% of drug content in the formulation which was comparatively highest among all the formulations. *In vitro* dissolution studies showed a release of 84.14% at the end of 60th minute.

In F021 formulation, 3:1 S/CoS ratio was used. The formulation was found to pass for thermodynamic stability studies. The self-emulsification time was found to be 67 and 61 seconds respectively in acidic and basic pH. Drug content estimation showed 95.21% of drug content in the formulation. *In vitro* dissolution studies showed a release of 90.20% at the end of 60th minute.

All the seven formulations were compared with release profile of pure Glibenclamide and it was observed that all the seven SEDDS formulations exhibit three to four fold increases in the drug release. The formulations were then kept for stability studies at 40°C/75% for over a period of three months. Samples were withdrawn at regular intervals and were considered for visual analysis. Formulations F004, F013, F017, and F019 found to pass for stability studies after 3 months at 40°C/75% relative humidity.

Hence, based on all the evaluation parameters, F013 formulation was found to have desired properties of self-emulsifying drug delivery system. The formulation was further subjected to particle size analysis, zeta potential analysis and Transmission electron microscopy. The particle size analysis showed 461 nm globule size and zeta potential of -20.8 mV. Based on the stability studies at 40°C/75% relative humidity, the formulation was found to have no color change and it was found to be clear without any precipitation. Therefore the formulation F013 was found to be stable even after 3 months. The results concluded that formulation F013 could be considered as the optimized formulation.

CONCLUSION

In the present work, Glibenclamide, an anti-diabetic drug was incorporated and formulated in the form of Self emulsifying drug delivery system. Glibenclamide is a second-generation sulfonylurea used in the treatment of noninsulin-dependent diabetes. Glibenclamide is classified as BCS class II drug, having high permeability and poor water solubility. The poor water solubility of the drug is responsible for its poor dissolution rate, which ultimately leads to variable absorption. Furthermore, there are reports which have documented that Glibenclamide 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 the drug is dependent on its dissolution rate.[73]

Hence, the main objective of the study was to formulate, develop and evaluate an optimal SEDDS formulation containing Glibenclamide and comparison with pure drug. Among the various formulations, F013 formulation containing 2:1 S/CoS ratio was found to pass for evaluation parameters giving desired results and dissolution showing 95.88% release of drug in phosphate buffer solution 7.4. Hence, Self-emulsifying drug delivery system of Glibenclamide was successfully developed using Tween 80 as surfactant, PEG 400 as cosurfactant and Oleic acid as oil. Based on the evaluation parameters and dissolution profile it could be concluded that formulation F013 was the optimized formulation and this formulation could be pipelined for production and used as best alternative to the marketed formulations. Further the potential of these formulations for bioavailability enhancement and possible gastric irritation due to the use of large amount of surfactants needs to be further evaluated by *in-vivo* studies.

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