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Original Article

Formulation and *In vitro* evaluation of Solid-Self- Emulsifying Drug Delivery System (SEDDS) of Glibenclamide

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ABSTRACT

Aim of present study was to develop solid self micro emulsifying drug delivery system (S-SEDDS) with Aerosil 200 for enhancement of dissolution rate of model drug Glibenclamide (GBM). SEDDS was prepared using Capmul MCM C8^{TM}, Cremophor RH 40^{TM}, and Transcutol P^{TM} as oil, surfactant and cosurfactant respectively. For formulation of stable SEDDS, micro emulsion region was identified by constructing pseudo ternary phase diagram containing different proportion of surfactant: co-surfactant (1:1, 2:1 and 3:1), oil and water. Prepared SEDDS was evaluated for turbidity measurement, globule size and zeta potential, viscosity determination and % transmittance. S-SEDDS was prepared by adsorption technique using Aerosil 200 as solid carrier. Prepared S-SEDDS was evaluated for flow properties, drug content, FTIR, SEM, DSC and in-vitro dissolution study. Results showed that prepared liquid SEDDS passed all evaluation tests. Globule size was found to be 142.8 nm with polydispersity index 0.396. S-SEDDS showed good flow property and drug content. From the experiment, it is clear thateven after conversion of the liquid SEDDS into the solid one there was no significant alteration in the properties of solid SEDDS.*in-vitro* dissolution studies showed that there was enhancement of dissolution rate of GBM as compared with that of plain drug and marketed formulation. From the results it is concluded that, Aerosil 200 can be used to develop S-SEDDS by adsorption technique to enhance dissolution rate of poorly water soluble model drug GBM

Keywords: Glibenclamide, S-SEDDS, Aerosil 200, Pseudo ternary

phase diagram

INTRODUCTION

Lipid-based formulations are well known approach to enhance water solubility and oral bioavailability particularly, the self-microemulsifying drug delivery system (SEDDS).SEDDS formulations are isotropic mixtures of an oil, a surfactant, a cosurfactant (or cosolvents), and a 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 oily 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 resulting in either brittleness or softness of the shell (2). To overcome this problem SEDDS need to convert into Solid SEDDS. Numerous reports states that, the major techniques for converting SEDDS to S-SEDDS are spray cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization. But adsorption process is simple and involves simply addition of the liquid formulation to solid carriers by mixing in a blender (2-3).

Glibenclamide (GBM) or Glyburide is5-chloro-N-[2-(4-[(cyclohexylcarbamoyl)-amino] sulfonyl} phenyl) ethyl]-2-methoxybenzamide belonging to long-acting anti hyperglycemic agents.GBM is classified as BCS class II drug, having high permeability and poor water solubility. It is a second-generation sulfonylurea used in the treatment of noninsulin-dependent diabetes. The poor water solubility of GBM is responsible for its poor dissolution rate, which ultimately leads to variable absorption of GBM. 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). Thesolubility of GBM in aqueous medium is very low. The half-life of GBM is 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 (4-5). Hence it is necessary to enhance aqueous solubility and dissolution rate of GBM.

The main objective of the study was to formulate, develop and evaluate an optimal S-SEDDS formulation containing GBM and comparison with GBM marketed formulation.

MATERIALS AND METHODS

Material

The following substances were used for the solid SEDDS preparations: Glibenclamide (GBM) was obtained as a gift sample from Wockhardt Ltd. Aurangabad, MS, India. Cremophor RH 40^{TM} and Aerosil 200^{TM} were gifted by Lupin Pharmaceuticals, Aurangabad. Capmul MCM C8^{TM} was obtained as gift sample from Abitec Corporation, USA. Transcutol P^{TM} was obtained from Colorcon Asia, Mumbai, India. All other chemicals were of AR grade.

Methods

Determination of saturation solubility of GBM in different systems

The solubility of GBM in various oil phases, surfactants, cosurfactants/cosolvents was determined by dissolving an excess amount of drug in 2 ml of each selected individual oils, surfactants and co surfactants contained in stoppered vials (5 ml capacity) separately. The liquids were mixed using a vortex mixer and the vials were then shaken using orbital shaker at 37°C±1°C for 72 h to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 15 min. The supernatants were taken out and filtered through a membrane. The concentration of GBM in various phases was determined by UV spectroscopy (Shimadzu 1800) at their respective λmax (1,5).

Formulation of liquid SEDDS of GBM

Liquid SEDDS were prepared by dispersing required quantity of GBM in appropriate quantity of co-surfactant. The mixture was homogenized and to it, accurately weighed quantity of oil: surfactant blends was added in small portion with stirring. The blends were mixed thoroughly using magnetic stirrer. The quantities of oil phase, surfactant and co-surfactant in appropriate portions were selected based on the result of solubility study and observing phase data of ternary diagram for each of the group A, B and C. The formulations were examined for signs of turbidity or phase separation prior to self emulsification, percentage transmittance, drug content and particle size studies (6-7).

Construction of pseudo ternary phase diagram for identification of microemulsion zone

Based on the observations of solubility studies, components of emulsion viz. oil phases, surfactants and co surfactants indicating 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 (Smix) were mixed with oily phase by adding small amounts with constant stirring. The proportions of oil: Smix 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 in 0.5% (w/w) increment was added taking care for 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, cosurfactant. The point indicating the clear and isotropic mixtures were considered to be within the microemulsion region (6-7).

Preparation of solid SEDDS Adsorption Method

The liquid SEDDS of GBM was adsorbed onto Aerosil200 carrier at 1:1, 2:1, 1:2 ratio by physical mixing in a small mortar and pestle. The resulting solid SEDDS was uniformly homogenized to ensure that the mixture was uniformly distributed. The damp mass was passed through sieve No.120 and was dried at ambient temperature (8-9).

Characterization of Liquid-SEDDS (8-12)

Dispersibility test

The *in-vitro* performance of SEDDS was visually assessed using the grading system used by Khoo Shui-Mei et.al. (1998) and it was found that, SEDDS rapidly formed micro emulsion within 1 min which was clear and slightly bluish (yellowish) in appearance as per grade A (8).

Droplet size analysis

Solid SEDDS were diluted to 100 ml with distilled water. The droplet size distributions and polydispersibility index of

the resultant microemulsions were determined using particle size analyzer (Malvern zetasizer 3000HS) (9-11).

Zeta potential

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SEDDS formulation was measured using a (Malvern Zetasizer 3000HS). The SEDDS were diluted with a ratio of 1:20 v/v with distilled water and mixed for 1 min using a magnetic stirrer (12).

Characterization of Solid-SEDDS (13-17)

Micromeritic properties of S-SEDDS

Prepared S-SEDDS was evaluated for micromeritic properties such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio (13).

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 ultrasonicator for 15 min and analyzed using UV spectrophotometer and absorbance was recorded (14).

Droplet size analysis

SEDDS were diluted to 100 ml with distilled water. The droplet size distributions and polydispersibility index of the resultant microemulsions were determined using particle size analyzer (Malvern zetasizer 3000HS) (15).

In Vitro Drug Release Study

Drug release studies from solid SEDDS were performed using USP XXIV, dissolution apparatus II with 900 ml of phosphate buffer pH 7.4 separately as a medium at 37 ± 0.5°C. The speed of the paddle was adjusted to 50 rpm. GBM-loaded solid SEDDS (equivalent to 5 mg of GBM) and 5 mg of powder GBM were placed in a dissolution tester (Electrolab, Mumbai). At predetermined time intervals5, 10, 20, 30, 45 and 60 min, an aliquot (5 ml) of the sample was collected, filtered and analyzed spectrophotometrically at 301 nm. The drug release of optimized S-SEDDS formulation was compared to the plain drug as well as marketed formulation of the drug in buffer pH 1.2 and phosphate buffer pH 7.4 separately.(6, 15, 17).

Differential scanning calorimetry

The physical state of GBM in solid SEDDS was characterized by differential scanning calorimetry. The sample was placed in standard Aluminium pan and dry nitrogen was used as effluent gas. The sample was scanned at the speed of 10°C/ min at a heat flow from 50°C to 250°C. DSC was performed using differential scanning calorimeter (DSC 60, Shimadzu) to study the thermal behavior of prepared optimized formulation (15).

Scanning electron microscopy

The surface morphology of solid SEDDS of GBM was determined using analytical electron microscope (JSM-6390). The sample was lightly sprinkled on double adhesive tape stuck on Aluminium stub. The stubs were then coated with platinum to a thickness of above 10°A under an Argon atmosphere using a Gold sputter module under a high vacuum evaporator and the stub containing coated sample was placed in scanning electron microscope chamber (9, 17).

Infrared spectroscopy

Solid SEDDS of GBM was mixed with small quantity of IR grade Potassium

bromide and scanned in the range of 4000-400cm^{-1} (FTIR-4100, Jasco) (9, 17).

X- ray diffraction

The physical state of drug GBM and its solid SEDDS was characterized by X ray powder scattering (XRD) measurements using X ray diffractometer (Philips). The measurements were performed at room temperature using monochromatic CuKα-radiation at 35 mA and at 40 kV over a 2Θ range of 5° to 40° with a continuous scanning speed of 10°/min. The analyzed sample was compactly packed in the cavity of an Aluminum sample holder using a glass slide (19).

RESULTS & DISCUSSION

Saturation solubility evaluation of GBM

Oils can solubilize the lipophilic drug and is the most important excipients as it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Amongst the individual oil phases the saturation solubility of GBM in Capmul MCM C8^{TM} was far superior as compared to other oils and esters (figure 2).

Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. They form a layer around the emulsion droplets and reduce the interfacial energy as well as providing a mechanical barrier to coalescence. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. Mostly, Non-ionic surfactants are used as they are known to be less toxic and less affected by pH and ionic strength compared to ionic surface-active agents. Amongst the surfactants the saturation solubility of GBM in Cremophor RH 40^{TM} was far superior to other surfactants (figure 3).

The co-surfactant along with the surfactant, lower the interfacial tension to a very small, even transient negative value. They will be beneficial to form microemulsion at a proper concentration range. However, excessive amount of co-surfactant will cause the system to become less stability for its intrinsic high aqueous solubility and lead to the droplet size increasing as a result of the expanding interfacial film. Amongst the cosurfactants/cosolvents the saturation solubility of GBM in Transcutol P^{TM} was far superior to other cosurfactants/cosolvents (figure 4).

From the above solubility study, it can be concluded that Capmul MCM C8^{TM} (oil), Cremophor RH 40^{TM} (surfactant) and Transcutol P^{TM} (cosurfactant) are suitable for the model drug GBM.

Pseudo ternary phase diagrams with varying proportion of S mix with oils

The SEDDS has an important characteristic of drug precipitation on dilution with water due to loss of solvent capacity. Selection of oil and surfactant and the mixing ratio of oil and other components play an important role in the formation of SEDDS. Therefore the phase behavior of each SEDDS needs to be carefully studied using the phase diagram constructed by using Tri-plot Microsoft® Excel spreadsheet (version 1.4) as a guide (Figure 5). The microemulsion phase was identified as the area where clear and transparent formulations were obtained on dilutions based on visual inspection of samples. Phase diagram also helped to establish the study of micro emulsifying capacity and effect of drug on phase structure. Solubility in different combination of oils/surfactants in 2:1 ratio was found to be highest in Capmul MCM C8^{TM} - Cremophor RH 40^{TM} combination followed by Transcutol

P^{TM}. It was observed that increasing the concentration of the cosurfactant such as Transcutol P^{TM} in SEDDS formulation increased the spontaneity of the self-emulsification region. Therefore, much higher concentration of cosurfactant, much higher self-emulsifying region in phase diagrams.

Characterization of Liquid SEDDS

Droplet size analysis

Droplet size distribution following self-micro emulsification is a crucial factor to evaluate a self-microemulsion 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 (16). The size of F-2was found to be below range of 200 nm which indicated that formulation F-2 was SEDDS (table 2 and figure 6).

Zeta potential

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential they will repel each other and there is dispersion stability. Zeta potential of the system was found to be -6.97, which was closer to the range -20 mV indicating the stable microemulsion (Figure 7).

Characterization of Solid SEDDS

The solid SMEDDS (S-1, S-2 and S-3) were prepared as per the procedure and free flowing powders were obtained and its various parameters were evaluated.

Micromeritic properties and drug content of S-SEDDS

From the data obtained, the optimized S-1 batch shows good micromeritic properties.

Drug content

The drug content in solid SEDDS of GBM was almost identical with those obtained in liquid SEDDS so there is no change of percentage drug content after conversion of liquid to solid SEDDS (table 4).

Drug content of the optimized SEDDS formulation batch (S-1) for ratio 1:1 was found to be highest i.e. 98.16 %. So, it was considered as optimized batch for further evaluation.

Globule Size Determination

The droplet size distributions and polydispersibility index of the resultant microemulsions were determined using particle size analyzer (Malvern zetasizer 3000HS). The mean globule size of the reconstituted microemulsion seems to be less effected by the method of conversion of liquid to solid. The mean globule size was found to be 139.3 nm and the Polydispersibility index was found to be 0.364. From this, it is clear that even after conversion of the liquid SEDDS into the solid one there was no significant alteration in the properties of solid SEDDS (Figure 8).

In vitro Drug release

The effective delivery of a drug from SEDDS is proposed to be governed primarily by small particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase. The solubilized drug may not precipitate in the lumen, and undergo rapid absorption which is independent of the lipid digestion process.

In vitro studies were performed to compare the enhancement of solubility of GBM with respect to marketed and pure drug. The formulation S-1 was released almost the 97% drug within 60 min as compared to marketed formulation and pure drug and hence it possessed maximum microemulsion efficiency and maximum release than

marketed formulation and pure drug (Figure 9 and table 5). Thus, the selected formulation S-1 indicated considerable enhancement of solubility of GBM as compared to pure drug.

Differential scanning calorimetry

Differential scanning calorigraph of pure GBM represented sharp endothermic peak at 178°C (figure 10 (A)) and S-SEDDS (figure 10(B)) represented no such peak which indicatedchange in melting behavior of drug and inhibition of crystallization thus, it can be confirmed that drug was solubilized into excipients of SEDDS.

Scanning electron microscopy

The surface morphology of pure GBM, Aerosil 200 and S-SEDDS of GBM was determined using analytical electron microscope (JSM- 6390). Pure GBM appeared under the scanning electron microscope as needle shaped crystals (figure 11 A) having rough surfaces.The SEM images of Aerosil 200 and Solid SEDDS are shown in figure 11 B and 11 C respectively. The SEM images of solid SEDDS showed well separated particles with no agglomeration. Also the rough surface of Aerosil 200 has got converted into smooth surface into solid SEDDS. The possible reason for this may be the absorption of liquid SEDDS into the solid carrier Aerosil 200.

Infrared spectroscopy

Pure GBM shows major peak at 2935, 1712, 1527.35 and 609.45cm^{-1} (figure 12A) and IR spectra of SEDDS of S-1 revealed no considerable change in major peaks when compared toIR of pure drug which proved that there was no interaction between drug and excipients (figure 12A and table 6). Figure 10 B shows the IR spectra of carrier Aerosil 200. The characteristic peak at 2360 cm^{-1} states that there is the formation of S-SEDDS of GBM (figure 12C).

X-ray diffraction

X-ray diffraction pattern of S-SEDDS of GBM verified the physical state of the drug in the solid SEDDS. Pure GBM drug represented sharp peaks which indicated it was highly crystalline in nature (figure 13A), whereas S-1 formulation was not indicating significant crystalline peaks, which confirmed the molecularly dispersed state of GBM in the formulation and effective solubilization of drug (figure 13 B).

CONCLUSION

From study it was concluded that, prepared liquid SEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. Study also concluded that, S-SEDDS of GBM prepared with Aerosil 200by adsorption technique have good flow property and drug content. S-SEDDS formed clear micro emulsion with micrometric size. Results of SEM demonstrate that spherical S-SEDDS can be obtained without agglomeration. *In-vitro* drug release of S-SEDDS was much higher than that of plain GBM and marketed formulation. Hence it was concluded that S-SEDDScan be efficiently formulated by adsorption technique using Aerosil 200 as solid carrier to enhance dissolution rate of poorly soluble drug such as GBM.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

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Table 1. Selected combination of components of SEDDS

Sr. No.	Oil (% w/w)	Surfactant (% w/w)	Cosurfactant (% w/w)
1.	30 (%w/w)	40 (%w/w)	40 (% w/w)

Table 2. Droplet size analysis of F-2

Sr. No.	Formulation code	Globule size (nm)	PDI	Zeta potential	Viscosity
1	F-2	142.8	0.396	-6.97	0.889

Table 3. Micromeritic properties and drug content of S-SEDDS (S-1)

Properties	Results
Dispersibility	Grade A
Angle of	26.56° (Good)
Bulk Density	0.166
Tapped	0.333
Hausner's	2.00
Carr's Index	50.1%

Table 4. Drug Content of S-SEDDS of GBM

Sr. No.	Ratios	Drug Content
1	1:1	98.16%.
2	2:1	97.36%
3	1:2	93.78%

Table 5. % Cumulative drug release of plain drug (PD), S-SEDDS and marketed formulation (MF)

Time (min)	PD(pH 7.4)	PD(pH 1.2)	S-SEDDS(pH 7.4)	S-SEDDS(pH 1.2)	MF(pH7.4)	MF(pH 1.2)
0	0	0	0	0	0	0
5	8.1±2.08	9±0.67	67.4±0.16	54±0.2	30.36±1.52	27.06±2.4
10	17±0.23	16.8±2.45	81.42±0.22	73.7±1.18	51.52±0.76	47.61±2.08
20	33.3±0.1	30.9±1.16	85.49±0.44	77.73±2.02	60.78±0.32	51.4±2.42
30	40.6±0.14	38.2±0.64	91.36±064	80.27±1.4	66.31±2.45	61.14±0.93
45	56.4±0.12	53.56±1.28	95.25±1.9	88.16±1.5	84.52±2.08	78.56±1.12
60	66.95±0.34	59.24±0.82	97.22±2.08	94.23±1.19	92.38±0.22	88.67±0.1

All values are expressed as mean ± SD (n=3)

Table 6. Interpretation of IR spectrum of pure GBM

Wavelength [cm-1]	Type of vibration
3300-3370 cm-1	-NH stretching
2935.13 cm-1	–CH stretching
1712.48 cm-1	C=O
1527.35cm-1	C=C
1342.21 cm-1	C-O
1157.08 cm-1	SO2
609.39 cm-1	chlorine

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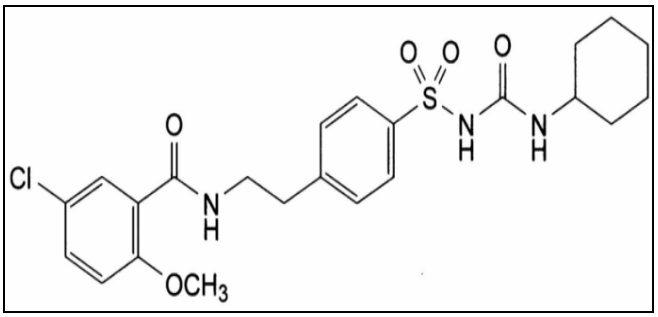

Figure.1. Chemical Structure of Glibenclamide

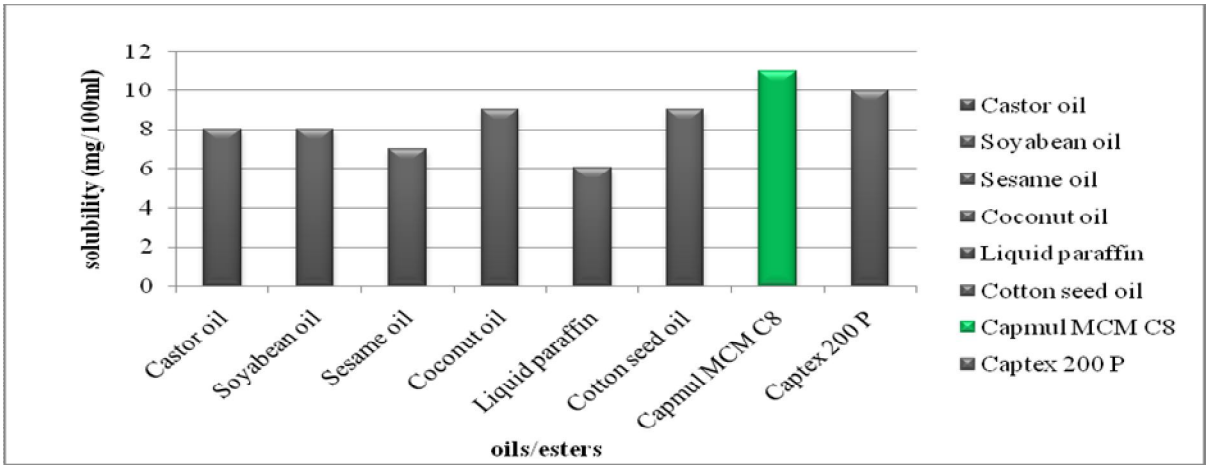

Figure.2. Saturation solubility of GBM in different excipients oils/esters

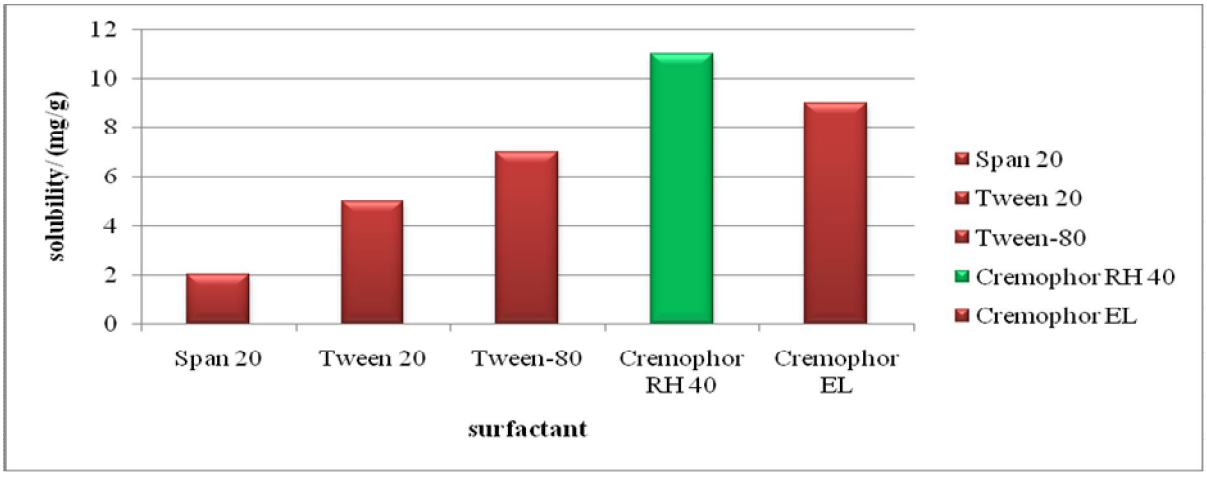

Figure.3. Solubility profile of GBM in different surfactants

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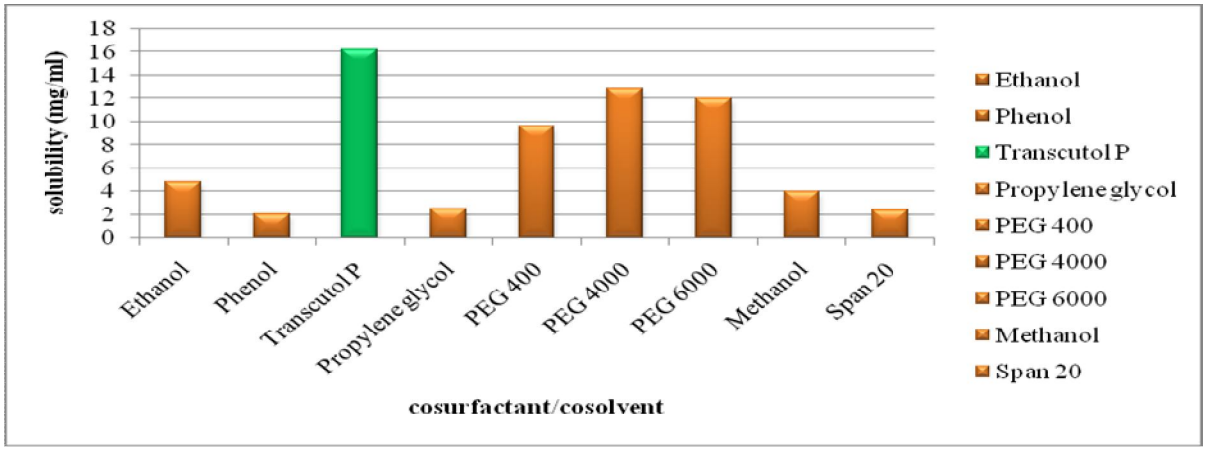

Figure.4. Solubility profile of GBM in different cosurfactants/ cosolvents

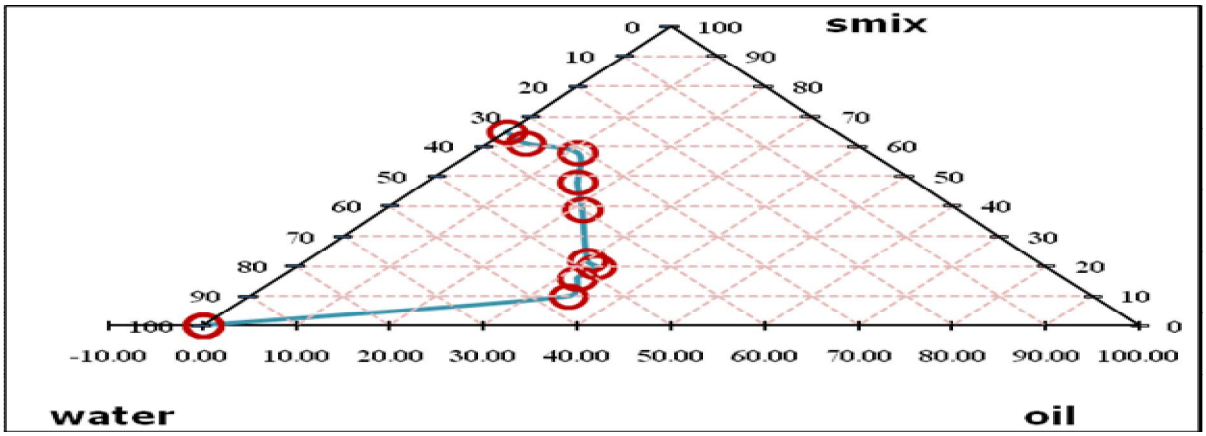

Figure.5. Ternary diagram for Capmul /Cremophor RH 40: Transcutol P (2:1): water system

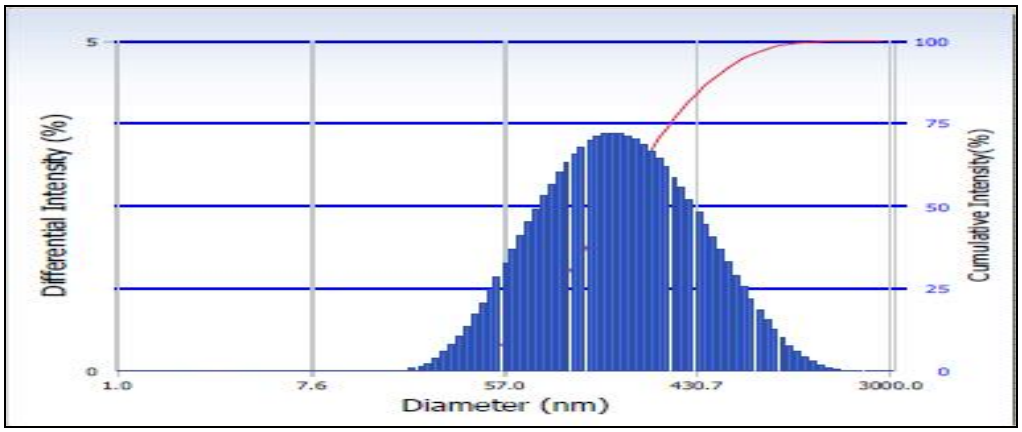

Figure.6. Droplet size analysis of F-2

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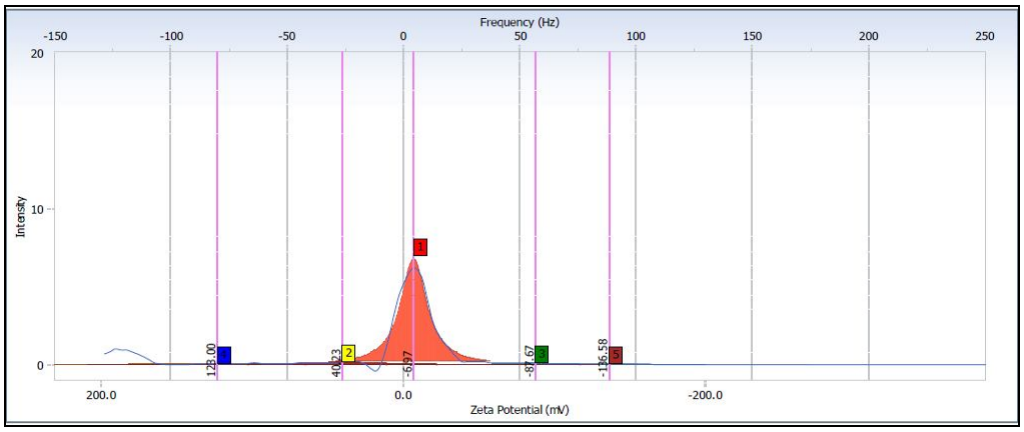

Figure.7. Zeta potential of formulation F-2

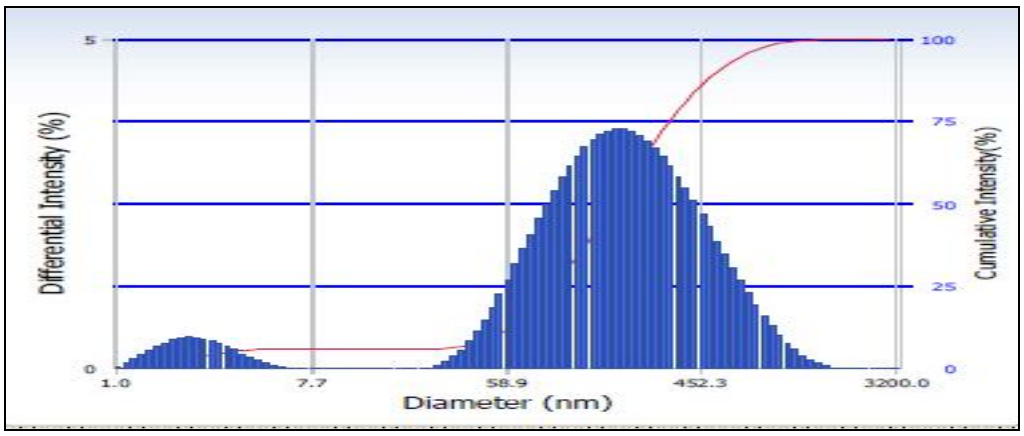

Figure.8. Droplet size of optimized Solid SEDDS batch (S-1)

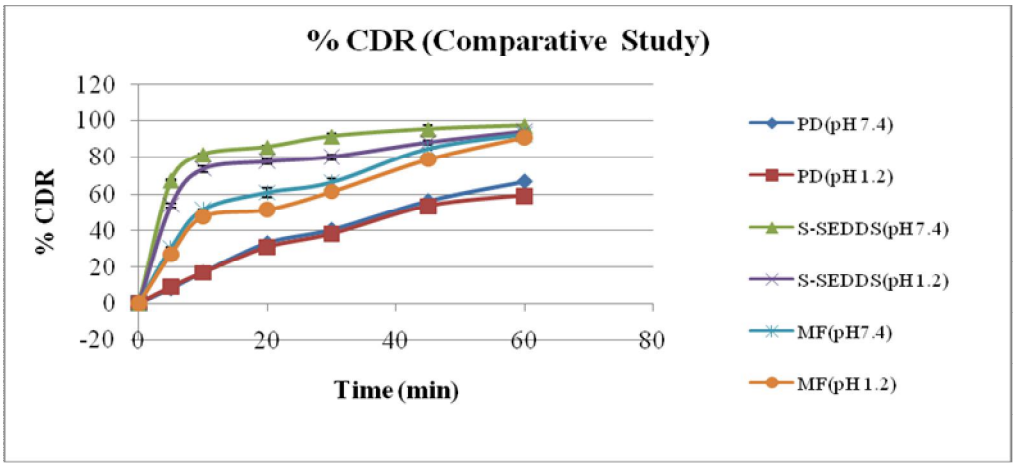

Figure.9. % Cumulative drug release of S-SEDDS and Plain GBM in pH 1.2 and 7.4 Buffer

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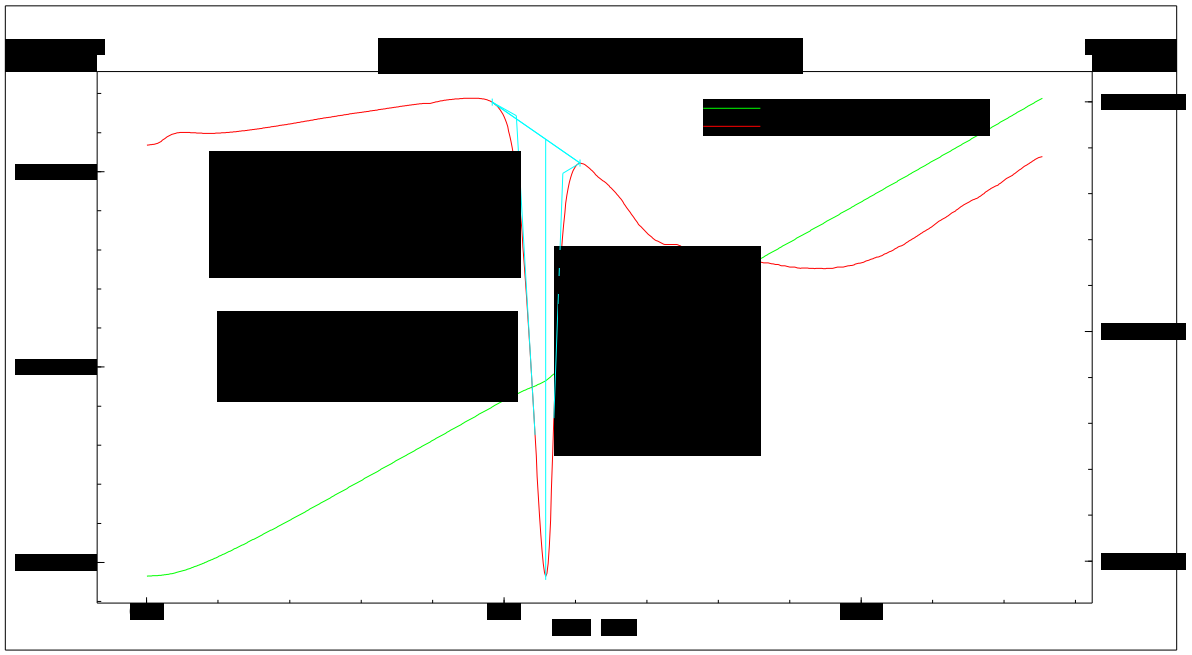

F

Figure.10(A): DSC thermogram of GBM

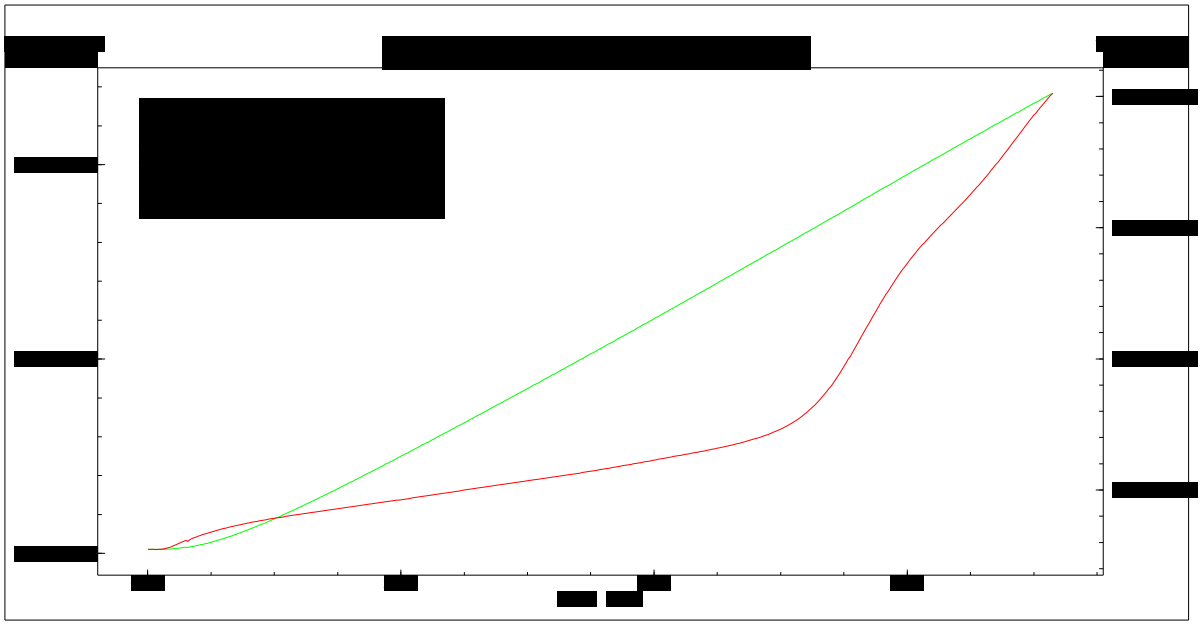

Figure.10(B): DSC thermogram of Solid SEDDS

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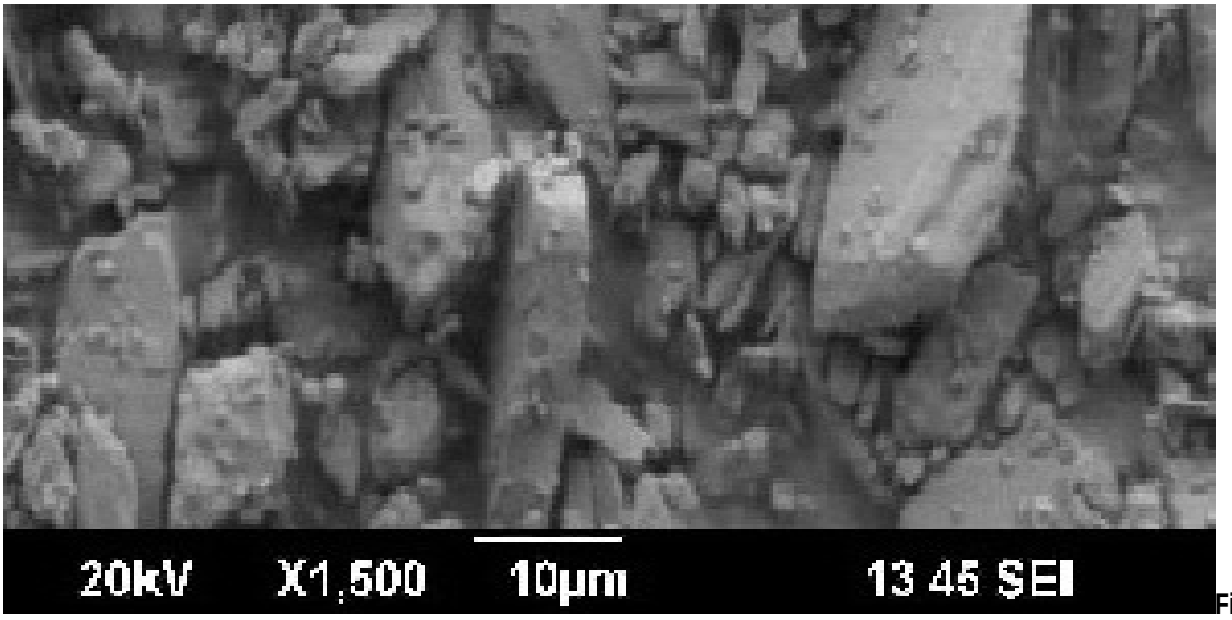

Fi

Figure.11(A): SEM Image of pure GBM

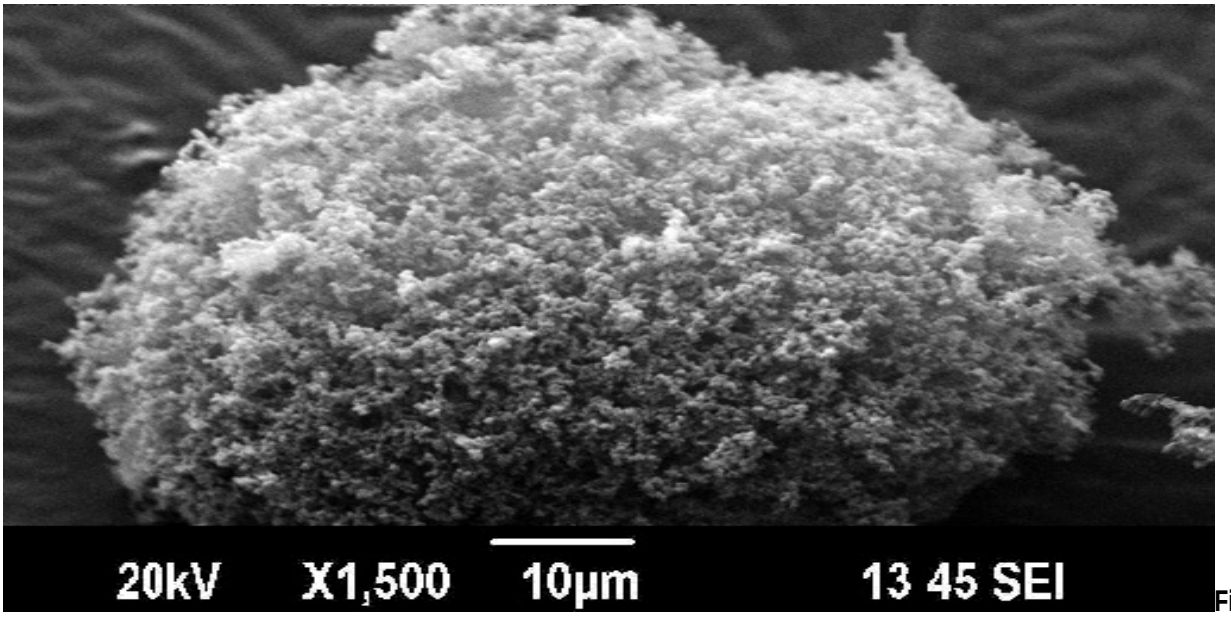

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Figure. 11(B): SEM images of Aerosil 200

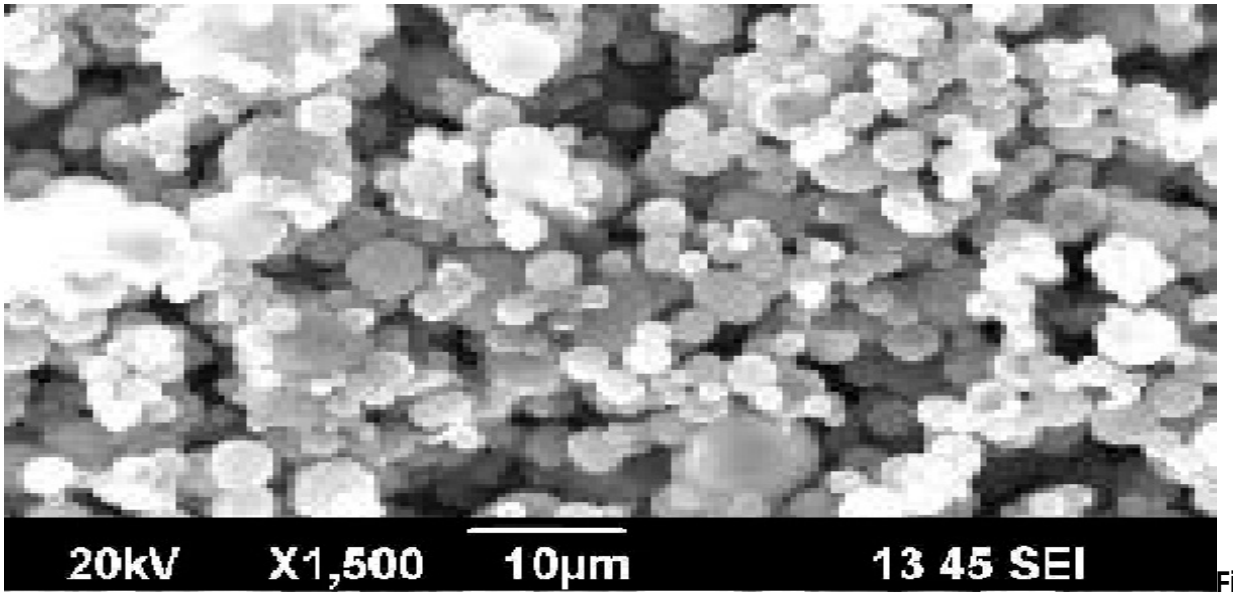

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Figure.11(C): SEM images of S-SEDDS

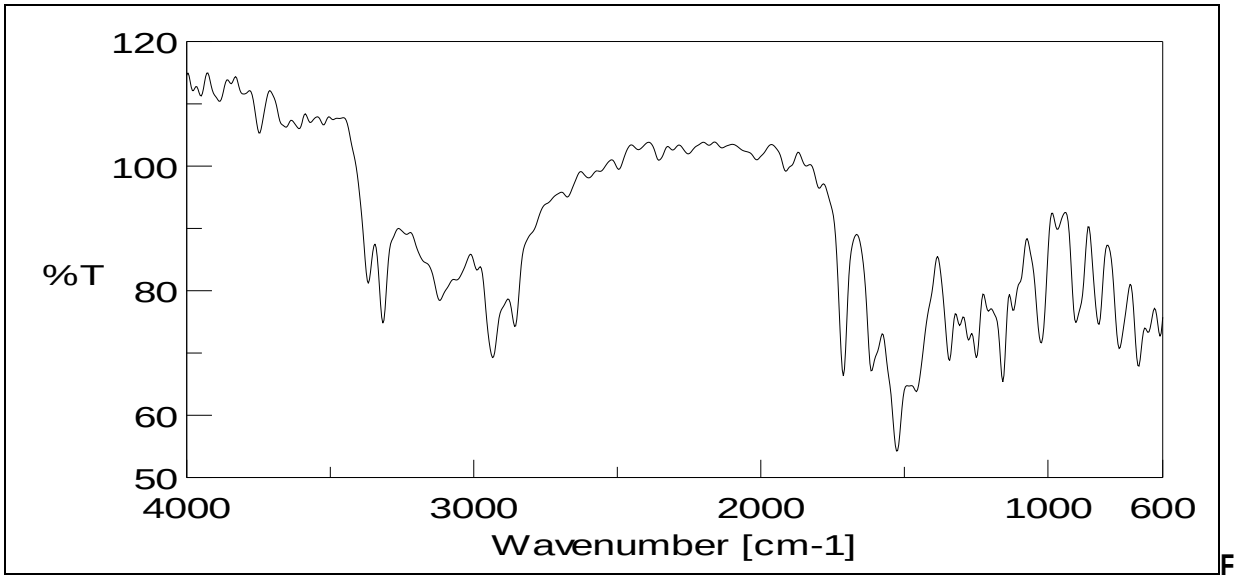

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Figure. 12(A): Infrared spectrum of GBM

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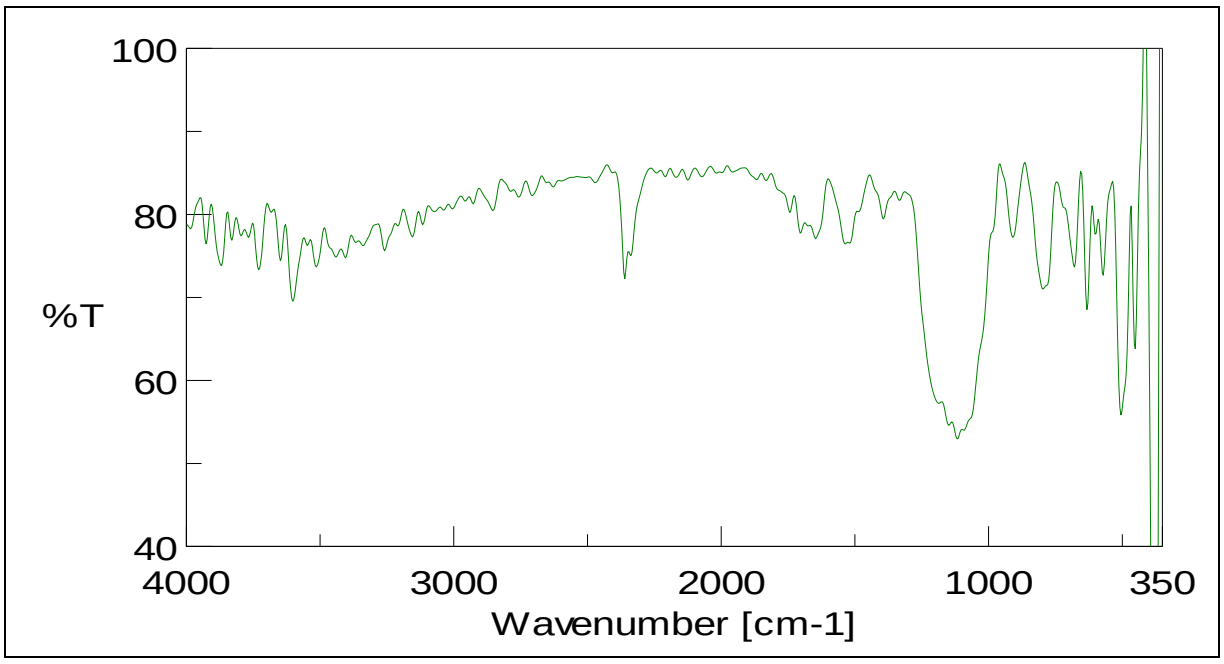

Figure. 12(B): Infrared spectrum of Aerosil 200

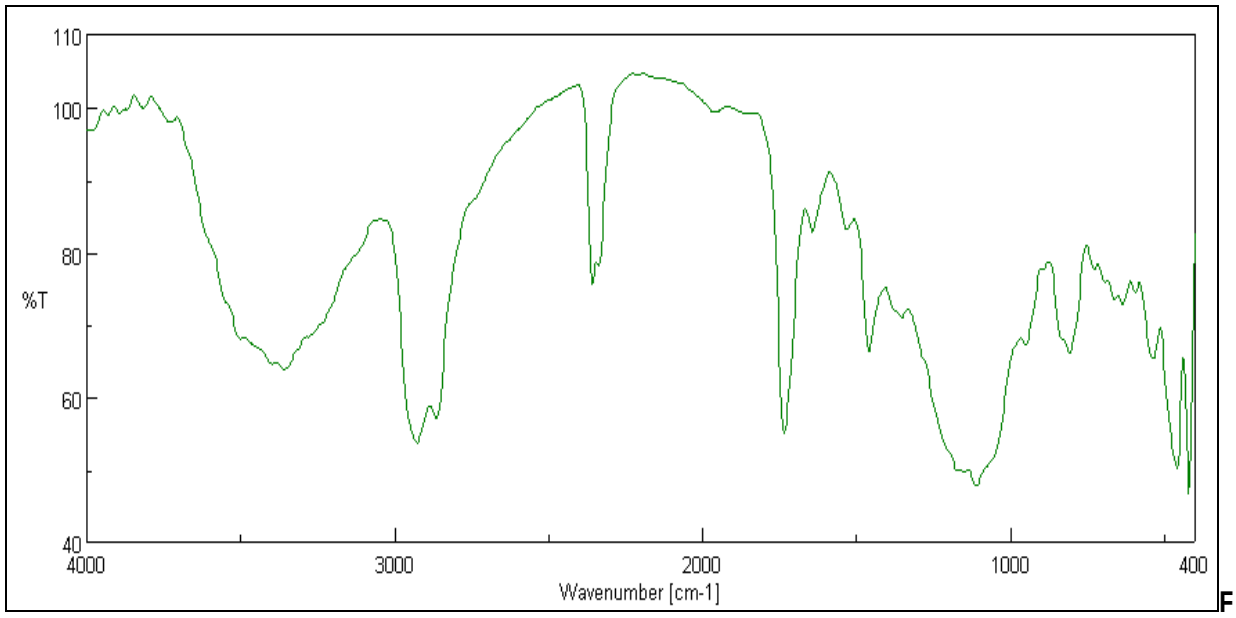

Figure. 12(C): Infrared spectrum of S-SEDDS of GBM (S-1)

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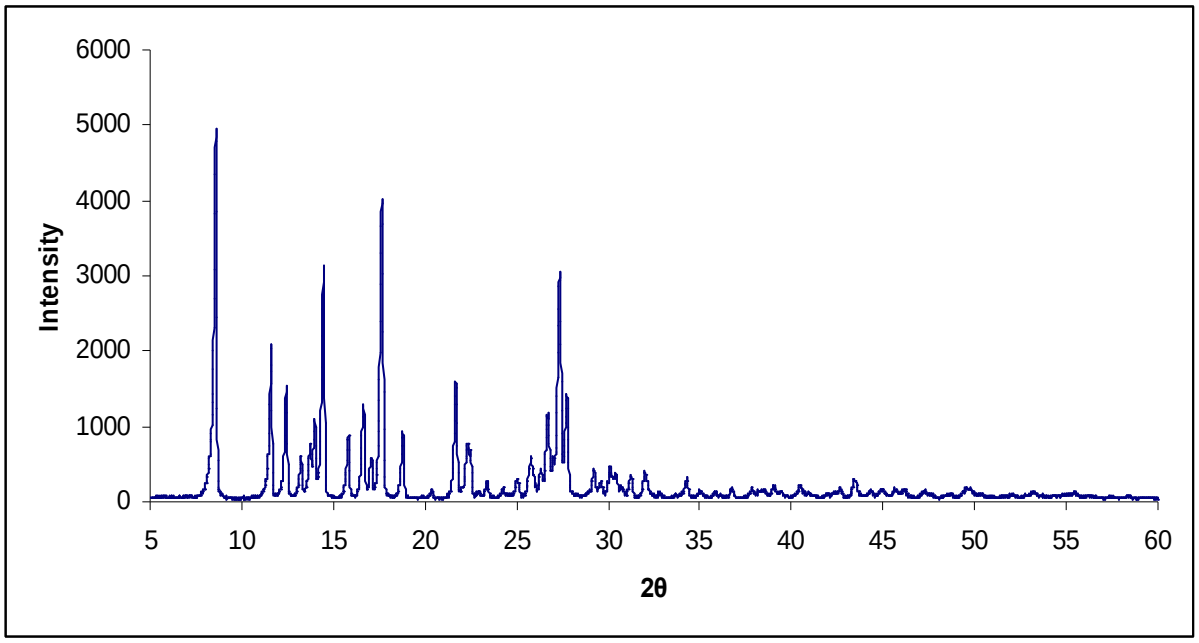

F

Figure. 13(A): X-ray diffraction pattern of pure GBM

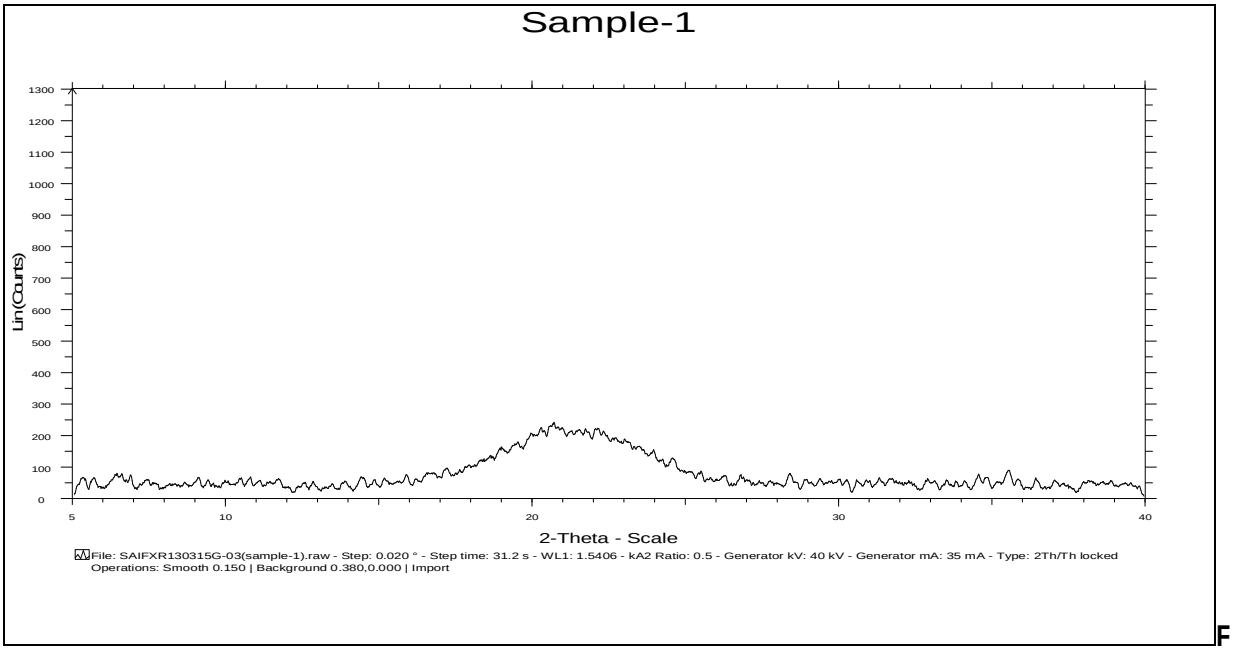

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Figure. 13(B): X-ray diffraction pattern of S-SEDDS (S-1)