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# FORMULATION AND CHARACTERIZATION OF *Γ-ORYZANOL* LOADED SOLID SELF-NANO-EMULSIFYING DRUG DELIVERY SYSTEMS (S-SNEDDS)

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## ABSTRACT

In recent years, much attention has been paid to solid self-nanoemulsifying drug delivery systems (S-SNEDDS), which have shown reasonable successes in improving oral bioavailability of poorly soluble drugs. This drug delivery system combines the advantages of liquid SNEDDS with those of a solid dosage form and overcomes the limitations associated with liquid formulations. One optimized SNEDDS formulae F-5 were selected to be solidified by spray drying technique using Aerosil 200 as solid carrier. Characterization of GOZ Loaded S-SNEDDS by angle of repose of the one S-SNEDDS formulae F-5 were 24.12°± 1.10°, these values indicate that all formulae have good flow ability. The bulk density of the two formulae F-5 was found to be 0.47 ± 0.03 g/mL. However, tapped density was 0.57±0.02 g/mL for formula F-5. Carr's index of formulae F-5 was found to be 13.57±1.09 which give an indication about the good flowability of the one S-SNEDDS formulae. The efficiency of self-emulsification can also be estimated by measuring the emulsification time. The emulsification time was 41.57±1.12 s. for formula F-5. The small values of PDI shown by S-SNEDDS formulae F-5 (0.403±1.12) indicate homogenous droplet population and narrow globule size distribution. The thermo gram of pure GOZ exhibited a sharp endothermic peak at about 137.25°C, corresponding to its melting point. The drug loading efficiency was found to be 96.23±0.65 for formula F-5. Within the initial one hour of the *in vitro* release study, only 41.02%±1.23% of GOZ was dissolved from pure drug and marketed tablets, whereas the S-SNEDDS formulae showed improved release within the same time period. GOZ dissolved and released from S-SNEDDS reached 90.02%±1.02% for formula F-5, within one hour.

**Keywords:**Gamma Oryzanol, Solubility, Bioavailability, S-SNEDDS.

## 1. INTRODUCTION

In recent years, much attention has been paid to solid self-nanoemulsifying drug delivery systems (S-SNEDDS), which have shown reasonable successes in improving oral bioavailability of poorly soluble drugs. This drug delivery system combines the advantages of liquid SNEDDS [1] with those of a solid dosage form and overcomes the limitations associated with liquid formulations. S-SNEDDS also exhibited more commercial potential and patient acceptability. Many techniques are offered to convert conventional liquid SNEDDS to solid form such as spray drying, adsorptions to solid carriers, spray cooling, melt extrusion, melt granulation, supercritical fluid based methods and high pressure homogenization. The resulting powder may then be filled directly into hard gelatin capsules or mixed with suitable excipients before compression into tablets [2].

Rice bran (RB), a by-product of rice milling, is an important source of fat, proteins and bioactive molecules with special interest due to its antioxidant and lipid-lowering properties. These bioactive molecules include γ-oryzanol (GOZ) (a mixture of ferulic acid (FA) esters of triterpene alcohols and sterols), tocols (tocopherols and tocotrienols) and unsaturated fatty acids. RB is especially rich in the phenolic compounds GOZ and FA, which have demonstrated hypolipidemic effects [3] (reducing total plasma cholesterol and triglyceride levels, and increasing high-density lipoprotein levels) by mechanisms related to strong antioxidant activity, HMG-CoA inhibition [4] and increased cholesterol excretion.

Although RB shows a significant level of natural antioxidants and nutritional proteins, its potential use as a functional food ingredient is limited due to the low water solubility of some of its components, including GOZ [4]. These limitations have been overcome by earlier discussed technique self-nanoemulsifying drug delivery systems (S-SNEDDS).

## 2. MATERIAL AND METHODS

Gamma oryzanol (GOZ) was received as gift sample from Ricela, Ludhiana, Punjab. Gelucire 44/14, Lauroglycol FCC, Labrafac lipophile WL 1349, Capryol 90, MCT (C18), Rice brain oil, Cremophor RH40, Cremophor S9, Labrasol, Macrogol 15 Hydroxy-stearate, Transcutol HP, PEG 200, PEG 400, PEG 600, Propylene glycol were purchased from Chemdyes Pvt. Ltd., Rajkot, India. Formic acid was obtained from Qualigens, Mumbai. Dialysis Membrane-110 (Mol. weight 12,000-14,000) was obtained from HiMedia, Mumbai, India.

### 2.1. Preparation of GOZ Loaded S-SNEDDS

Based on the rank order performed for all conventional GOZ SNEDDS formulae depending on their characterization and evaluation tests, one optimized SNEDDS formulae were selected to be solidified by spray drying technique using Aerosil 200 as solid carrier. Briefly, SNEDDS formula and Aerosil 200 (1000 mg) were suspended in 200 mL ethanol with continuous stirring until forming an isotropic mixture. The mixture was then kept at room temperature and equilibrated for 24 h. The suspension was then spray dried using a Buchi mini spray dryer under the following conditions:inlet temperature, 60°C; outlet temperature, 35°C aspiration, 85%; feeding rate of the suspension, 5 mL/min and atomization air pressure, 5 kPa [5].

### 2.2. Characterization of GOZ Loaded S-SNEDDS

#### *2.2.1. Micromeritic Properties of S-SNEDDS*

*2.2.1.1. Angle of Repose (θ)*

Angle of repose is angle made by the surface of pile of powder to the horizontal surface. It is micrometric parameter related to interparticulate friction or resistance to flow. The angle of repose of powder was determined by the funnel method. The lower tip of funnel was kept at 2.5 cm from the surface of table. 10 mg of S-SNEDDS powder was poured from funnel to form a pile. Then funnel was adjusted upto height of pile and a circle was drawn around the pile. The height of tip from surface of table was measured as pile height (h) and diameter of pile (d) was measured taking average of three diameter of circumference of the circle. The height of the funnel was adjusted and the powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Tan θ=h/r, Where θ = angle of repose, h = height of the cone, r = radius of the cone base [6].

*2.2.1.2. Bulk and Tapped Density*

Bulk density or poured density is the ratio of the mass to volume of poured and an untapped powder sample considering the contribution of the interparticulate void volume. It is determined by pouring an API sample of known mass into a graduated cylinder/flask, and the volume occupied by the sample is noted for calculating ratio. The volume occupied by the sample after it is subjected to tapping over a prescribed period of time using a bulk density test apparatus is used to determine the tapped density of material [6]. A quantity of 2 g of S-SNEDDS powder previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated using following formula:

Bulk density= Weight of granules/ Volume of granules

*2.2.1.3. Tapped density*

The measuring cylinder was tapped for fixed number of taps to obtain constant volume of powder bed. The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula [6]:

Tapped density= Weight of granules/Volume of granules after 100 tapping

*2.2.1.4. Hausners ratio*

It is the proportion of tapped density to the apparent density. It proposes the stream conduct of the powder mix. Hausners ratio value is under 1.25 shows good stream and greater than 1.5 demonstrates poor stream property which was determined by utilizing following formula:

Hausnre's ratio = Tapped density/ Bulk density

### 2.2.2. Reconstitution Properties of S-SNEDDS

*2.2.2.1. Robustness to Dilution:*

This test was performed through diluting 1 mL of each formula 10, 100 and 1000 times with distilled water, 0.1 N HCl and phosphate buffer pH 6.8. The weakened frameworks were blended utilizing an attractive stirrer at 100 rpm and 37°C to mimic internal heat level to finish homogeneity. These frameworks were taken care of at an encompassing temperature for 24 h then ostensibly saw for any signs of stage detachment [7].

### 2.2.3. Assessment of efficiency of self-emulsification

The self-emulsification efficiency of SNEDDS was assessed utilizing a standard USP disintegration apparatus type II (Labtech Pvt Ltd. Mumbai). 1 mL of every equation was added to 500 mL of refined water kept up with at 37±0.5°C. Delicate fomentation was given by a standard hardened steel disintegration paddle turning at 50 rpm. The pre-arranged definitions were surveyed outwardly as indicated by the pace of emulsification and last debut of the nanoemulsion [8].

### 2.2.4. Self-Emulsification Time

In this test, a predetermined volume of each formula (1 mL) was introduced into 300 mL of distilled water maintained at 37±0.5°C in a glass beaker and the substance were blended tenderly utilizing an attractive stirrer pivoting at steady speed (100 rpm). The emulsification time (the time required for a preconcentrate to shape a homogeneous mix after debilitating) was checked by apparently seeing the disappearing of SNEDDS and the last presentation of the nanoemulsion [9].

### 2.2.5. Droplet Size Analysis and Polydispersibility Index (PDI) Determination

The drop size is a significant factor in self-emulsification execution since it decides the rate and degree of drug release as well as absorption. Before estimation, 1 mL of each SNEDDS condition was debilitated on various occasions with refined water. The globule size and polydispersibility record of the outlined nanoemulsions were directed by unique light dissipating using a photon connection spectrometer which investigates the changes in light dispersing because of Brownian movement of the particles. Light dispersing was checked at 25°C at a dissipating point of 90°C [10]. All assessments were done in three-overlay and the mean ± SD was resolved.

### 2.2.6. Scanning Electron Microscopy (SEM)

Scanning electron micrographs for GOZ, Aerosil 200 and prepared S-SNEDDS formulae were taken using Scanning electron microscope (JEOL, JSM 50A, Tokyo, Japan) operating at 20 kV to study surface topography of S-SNEDDS. The samples were fixed on SEM stub and then coated with thin layer of platinum [11].

### 2.2.7. Differential Scanning Calorimetry (DSC)

Physical state of GOZ in S-SNEDDS was characterized using differential scanning calorimeter. Thermograms of GOZ, Aerosil 200, physical mixture of both and prepared optimized S-SNEDDS formulae were obtained using differential scanning calorimeter (Shimadzu, DSC-50, Kyoto, Japan). The thermal behavior was studied by heating nearly 2 mg of samples in sealed aluminum pans under nitrogen gas flow (30 mL/min) over a temperature range of 0 to 250°C and a heating rate of 10°C/min [12].

### 2.2.8. Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR Spectra of pure OLM, Aerosil 200, physical mixture of both and prepared optimized S-SNEDDS formulae were obtained using Fourier transformed infrared spectrophotometer (Shimadzu 8400). Solid samples were mixed with small quantity of IR grade potassium bromide and compressed into discs by applying pressure. The compressed disc was placed in light path and the spectrum was obtained. Each KBr disc was scanned at 4 mm/s at a resolution of 2 cm over a wave number region of 4000-400 $cm^{-1}$ [13].

### 2.2.9. Drug Loading Efficiency

One mL of SNEDDS formulation was diluted with methanol in volumetric flask and mixed well by shaking or inverting the VF two to three times. Tests were ready in three-fold and absorbance was estimated after appropriate weakening at 327 nm utilizing UV-Vis Spectrophotometer. The measure of GOZ present in every recipe was determined from an alignment plot [13].

### 2.2.10. In Vitro Drug Release Studies

The *in vitro* drug release of GOZ from the optimized SNEDDS formulation, pure drug and marketed product was performed utilizing USP disintegration apparatus type II. The disintegration medium comprised of 900 mL of newly pre-arranged phosphate buffer pH 6.8 kept up with at 37±0.5°C and the paddle speed was set at 50 rpm. Hard gelatine cases, size "000" stacked up with pre concentrate were joined to paddles using Para film

spring to hold cases back from floating. Aliquots (5 mL) from the disintegration medium were removed at standard time stretches (5, 10, 15, 30, 45, 60, 90 and 120 min) utilizing an adjusted expendable needle. The examples were then separated through a film channel (0.45 µm, Whatmann) and medication fixation was gotten after appropriate weakening by means of UV approved technique at 327 nm using UV-Vis Spectrophotometer (SL-1800 Shimadzu, Japan) [14].

## 3. RESULTS AND DISCUSSION

Based on the rank order performed for all conventional GOZ SNEDDS formulae depending on their characterization and evaluation tests, one optimized SNEDDS formulae were selected to be converted into S-SNEDDS. From the in vitro drug release data, drug loading efficiency and particle size analysis formulae F5 were selected as optimized formulae to be solidified into S-SNEDDS.

**Table 1:Rank Order of GOZ SNEDDS Formulae**

| Formula | In Vitro Drug Release (1 h) | Drug Loading Efficiency | Particle Size | Total Rank Order | Conclusive Rank Order |
|---|---|---|---|---|---|
| F-1 | 7 | 7 | 6 | 19 | 7 |
| F-2 | 4 | 5 | 3 | 11 | 3 |
| F-3 | 5 | 5 | 3 | 14 | 5 |
| F-4 | 3 | 5 | 1 | 13 | 4 |
| F-5 | 5 | 3 | 2 | 9 | 1 |
| F-6 | 6 | 2 | 4 | 12 | 3 |
| F-7 | 1 | 4 | 8 | 13 | 4 |
| F-8 | 7 | 1 | 7 | 15 | 6 |

### 3.1. Characterization of GOZ Loaded S-SNEDDS

#### *3.1.1. Micromeritic Properties of S-SNEDDS*

The values obtained for the angle of repose of the one S-SNEDDS formulae F-5 were 24.12°±1.10°, these values indicate that all formulae have good flowability. The bulk density of the two formulae F-5 was found to be 0.47±0.03 g/mL. However, tapped density was 0.57±0.02 g/mL for formula F-5. Carr's index of formulae F-5 was found to be 13.57±1.09 which give an indication about the good flowability of the one S-SNEDDS formulae. This was further supported by the values of Hausner's ratio. The results of Hausner ratio of formulae F-5 were 1.24±0.08.

**Table 2:Micromeritic Properties of GOZ Loaded S-SNEDDS**

| Formula | F-5 |
|---|---|
| Angle of Repose | 24.12°± 1.10° |
| Bulk Density (g/mL) | 0.47 ± 0.03 |
| Tapped Density (g/mL) | 0.57 ± 0.02 |
| Carr's index (%) | 13.57 ± 1.09 |
| Hausner's ratio | 1.24 ± 0.08 |

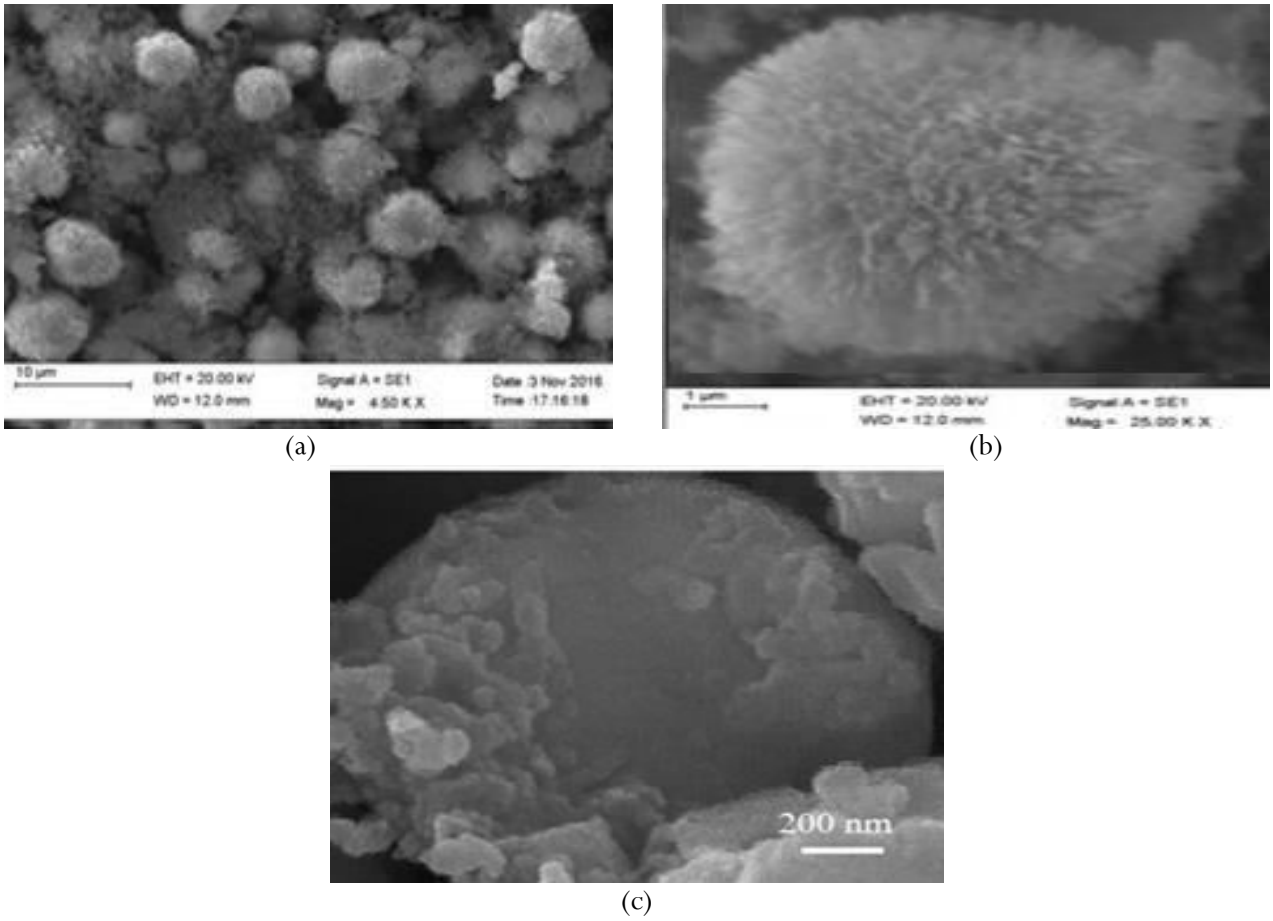
#### *3.1.2. Reconstitution Properties of S-SNEDDS*

A dilution study was done to observe the effect of dilution on S-SNEDDS, because dilution may better mimic the condition of stomach after oral administration. It was observed that the two S-SNEDDS formulae F-5 disperse quickly and completely when subjected to an aqueous environment under mild agitation. The two formulae showed spontaneous nano-emulsification and there was no sign of phase separation or phase inversion of nanoemulsion after storage of 24 h. The efficiency of self-emulsification can also be estimated by measuring the emulsification time. The emulsification time was 41.57±1.12 s. for formula F-5. The small values of PDI shown by S-SNEDDS formulae F-5 (0.403±1.12) indicate homogenous droplet population and narrow globule size distribution. It was also noticed that the emulsification times, droplet size and PDI for liquid SNEDDS and S-SNEDDS were very close to each other, indicating that the spray-drying process did not have a remarkable influence on the emulsfication performance of S-SNEDDS. These results were in complete accordance with Chun Chao et al. who prepared solid lipid-based self-emulsifying drug delivery system of agaricoglycerides and found that the spray-drying had no effect on the emulsfication performance.

#### *3.1.3. Scanning Electron Microscopy (SEM)*

The surface morphology of pure GOZ powder, hydrophilic fumed silica (Aerosil 200) and S-SNEDDS formulae of GOZ was determined using scanning electron microscope. The GOZ powder appeared with an irregular crystalline shape as irregular and plate-

shaped crystals having rough surfaces. Aerosil 200 appears to be spherical porous particles. The image of the solid SNEDDS formulae F-5 containing GOZ however, illustrate that the particles had the same outer macroscopic morphology consisting of well separated spherical particles with relatively deep dents and similar diameters. Following spray drying, the crystalline GOZ turned out to be highly amorphous in nature.




(a) (b) (c)

**Fig. 1:SEM photograph of pure (a) GOZ; (b) Aerosil 200; (c) S-SNEDDS F-5**

### *3.1.4. Differential Scanning Calorimetry (DSC)*

Thermograms of pure GOZ, Aerosil 200, physical mixture of both and prepared optimized S-SNEDDS F-5 were obtained using differential scanning calorimeter. The thermogram of pure GOZ exhibited a sharp endothermic peak at about 137.25°C, corresponding to its melting point. It is known that transforming the physical state of a drug to the amorphous or partially amorphous state leads to a high-energy state and high disorder, resulting in enhanced solubility. As a result, it was expected that the solid particles would also have enhanced solubility.

### *3.1.5. Fourier Transformed Infrared Spectroscopy (FTIR)*

FTIR spectra are mainly used to determine interaction between the drug and any of the excipients used. The presence of interaction is detected by the disappearance of the important functional group of the drug.

### *3.1.6. Drug Loading Efficiency*

The amount of GOZ present in the two optimized S-SNEDDS formulae was found to be within the USP limit. The drug loading efficiency was found to be 96.23±0.65 for formula F-5. The drug content in S-SNEDDS was almost identical with the results obtained in liquid SNEDDS, so there was no change of percentage drug content after conversion of liquid to solid SNEDDS using spray drying technique.

### *3.1.7. In-vitro Drug Release Studies*

The percentage drug release from S-SNEDDS was found to be higher than that of pure GOZ and marketed product as shown. Within the initial one hour of the *in*

*vitro* release study, only 41.02 %±1.23 % of GOZ was dissolved from pure drug and marketed tablets, whereas the S-SNEDDS formulae showed improved release within the same time period. GOZ dissolved and released from S-SNEDDS reached 90.02 % ±1.02 % for formula F-5, within one hour. The drug release study also indicates that the self-nanoemulsifying property of the formulation remains unaffected by the conversion of the liquid SNEDDS to the solid form. It was also noticed that the release of GOZ from S-SNEDDS was slightly lower than liquid SNEDDS. This might be attributed to the presence of adsorbent material which may delay the dissolution rate for a small extent.

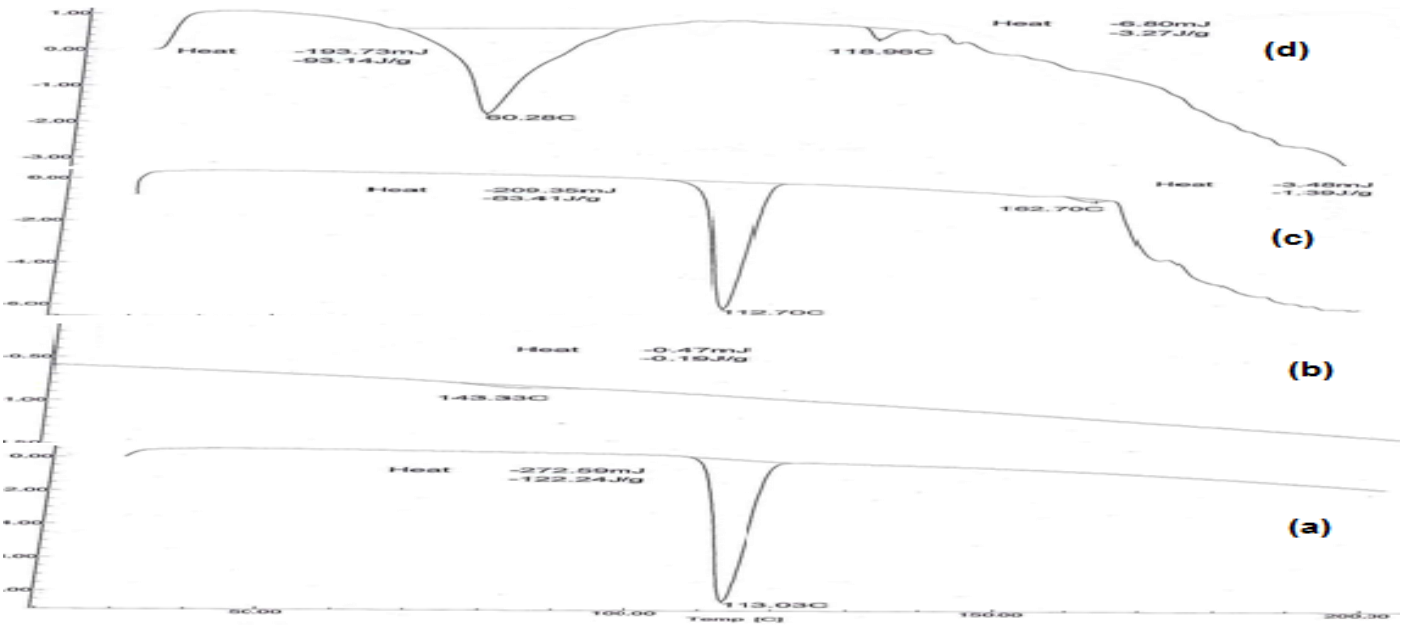
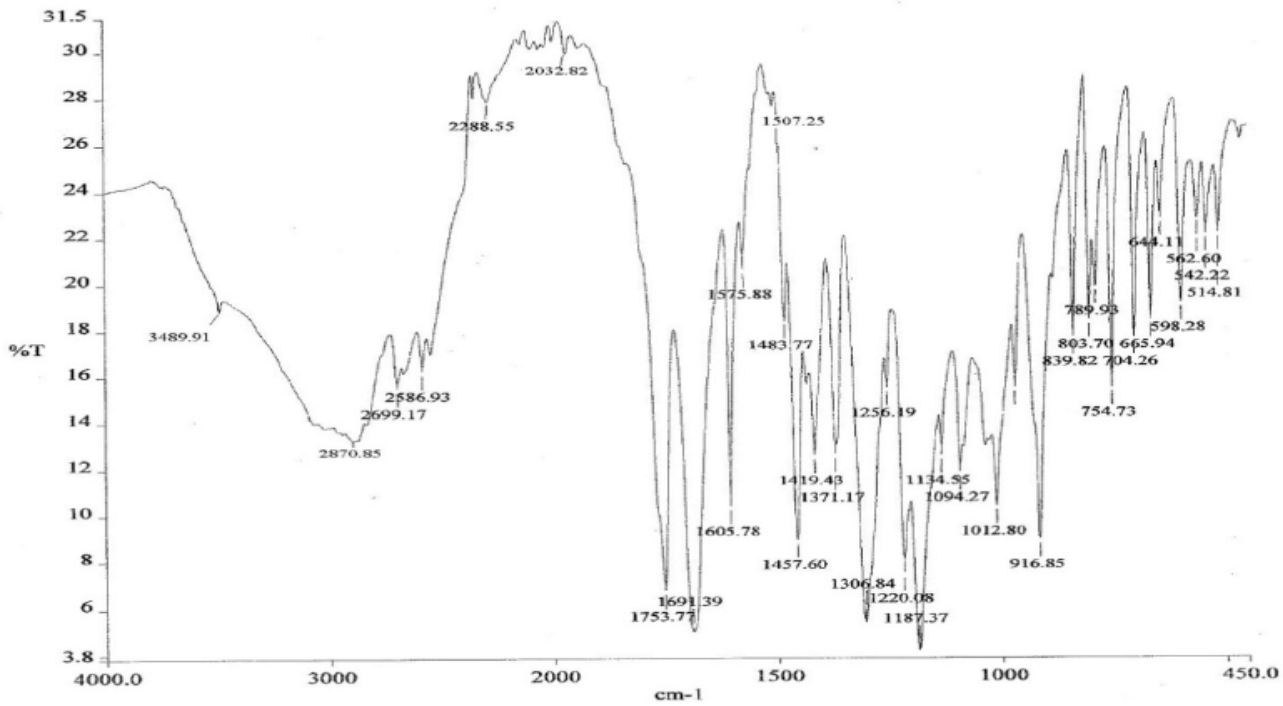
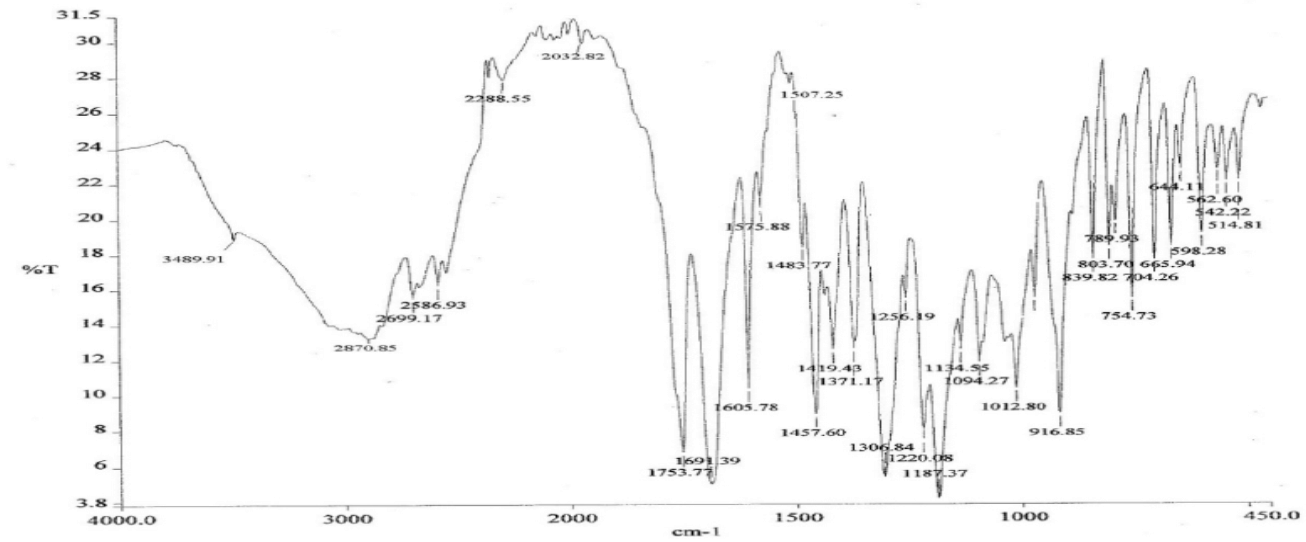


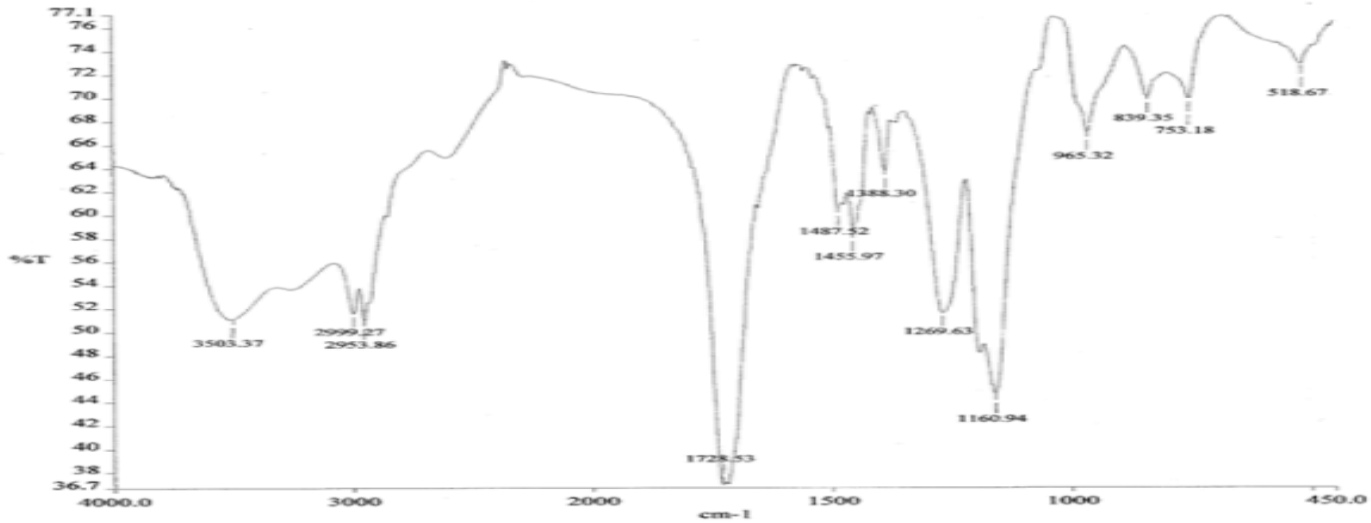

**Fig. 2:DSC thermograms of (A) pure GOZ, (B) Aerosil 200, (C) physical mixture of GOZ and Aerosil 200, (D) GOZ S-SNEDDS formula (F-5)**



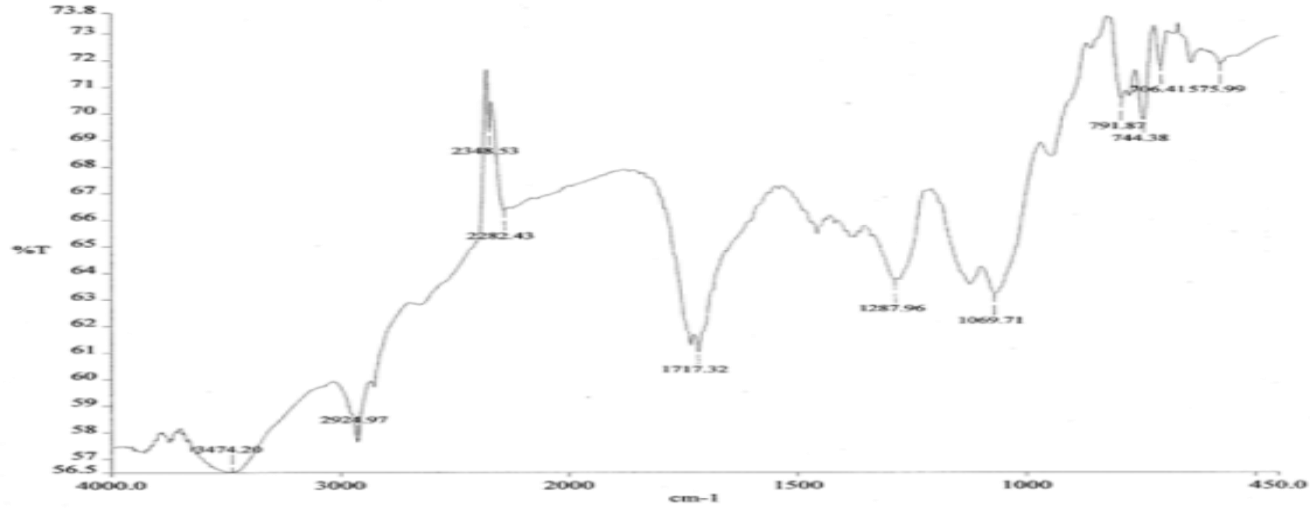

**(a)**




**(b)**




**(c)**




**(d)**

**Fig. 3:FTIR spectra of (a) Pure GOZ, (b) Aerosil 200, (c) Physical mixture of GOZand Aerosil 200, (d) GOZ S-SNEDDS formula (F-5)**

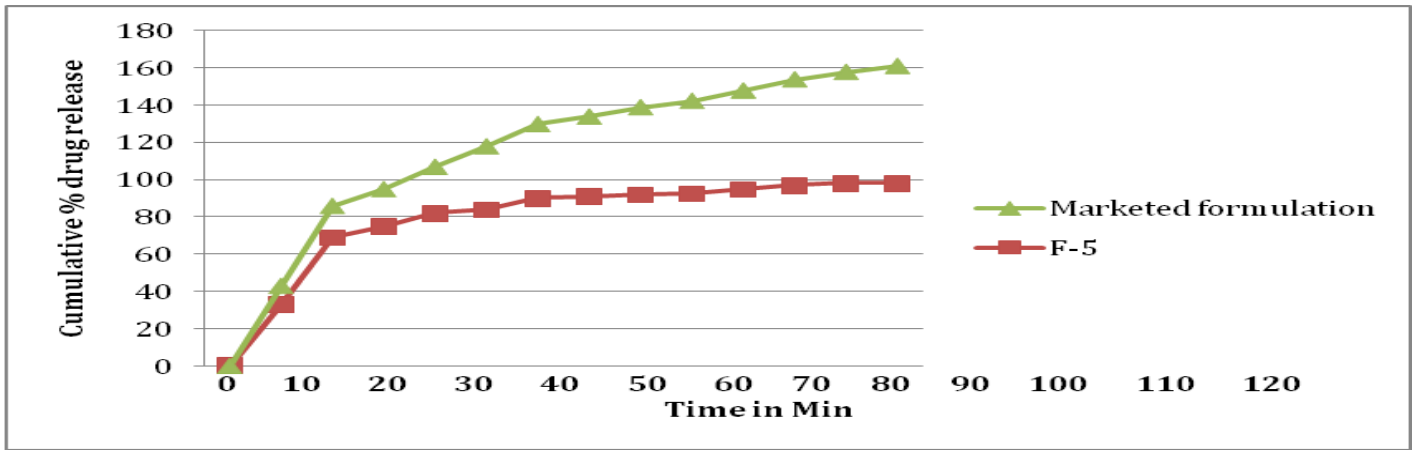



**Fig. 4: *In vitro* release profiles of GOZS-SNEDDS formulae F-5 compared with marketed product**

## 4. CONCLUSION

The S-SNEDDS could be considered and further evaluated for the oral delivery of lipophilic poor soluble drugs for which an oral route of administration is desirable. In conclusion, self-emulsifying drug delivery systems represented a promising approach for the formulation of GOZ. S-SNEDDS appeared to be an interesting approach to improving problems associated with oral delivery of GOZ. Thus, S-SNEDDS can be considered as a new and commercially feasible alternative to current marketed OLM. Finally, the oral delivery of hydrophobic drugs can be made possible by S-SNEDDS, which have been shown to substantially improve the oral bioavailability.

### *Conflict of interest*

None declared

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