Development and Characterization of Solid Self-emulsifying Drug Delivery System Containing Nateglinide

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Abstract

Introduction: To develop self-emulsifying drug delivery system (SEDDS) of nateglinide to convert it into solid SEDDS (S-SEDDS) aerosil-200 as adsorbent. Materials and Methods: Nateglinide solid self-micro emulsifying drug delivery system (S-SMEDDS) formulation was prepared by adsorption to solid carrier technique, where the liquid SMEDDS are allowed to adsorb onto the surface of free flowing aerosil-200. Solubility study, ternary phase diagram, robustness to dilution, viscosity determination, cloud point measurement, thermodynamic stability study, and globule size analysis were adopted to optimize liquid SEDDS. S-SEDDS were evaluated for various studies including in vivo study. The optimized liquid SEDDS formulation consisted of nateglinide, capyrol-90, tween 80, Transcutol P. Results: The results of this study suggest the potential use of developed S-SEDDS formulation for the delivery of poorly water-soluble drug nateglinide. Conclusion: The developed S-SMEDDS is a promising strategy for solubility enhancement of poorly water-soluble drug nateglinide.

Key words: Adsorbent, nateglinide, self-emulsifying drug delivery system, solubility

INTRODUCTION

Oral intake has been the most sought-after route of drug delivery by the patients for the treatment of most diseases. However, the pharmaceutical industry discovers 40-70% of active new chemical entities of which 40-70% has been estimated to be poorly water-soluble or lipophilic compounds to allow consistent oral absorption of a magnitude sufficient to ensure therapeutic efficacy.[1] Poorly water-soluble compounds have solubility and dissolution related bioavailability problems.[2] The absorption of such compounds is typically dissolution rate limited. According to Biopharmaceutical Classification System (BCS), such compounds are classified as Class II or IV compounds. Class II compounds rate and extent of absorption are highly dependent on the performance of the formulated product.[3-6] Self-emulsifying drug delivery systems (SEDDS) are relatively newer lipid-based technique with immense promise to improve the rate and extent of absorption of poorly water-soluble drugs.[7-9] SEDDS are anhydrous homogeneous liquid mixtures, composed of surfactant, lipids, drug, and/or co-solvents, which spontaneously form transparent and stable microemulsion on aqueous dilution with gentle agitation.[10,11] These formulae owe their self-emulsifying properties to the low free energy requirement for microemulsion formation.[12] The spontaneous microemulsion formation allows the drug to be in dissolved form and it provides a large surface area from small globule size for absorption and drug release.[13] Some marketed examples from this category are Aptivus (tipranavir) Sandimmune Neoral (cyclosporine A), Kaletra (lopinavir and ritonavir), Fortovase (saquinavir), and Norvir (ritonavir).[14] However, SEDDS in the form of liquids or encapsulated in soft gelatin capsules have some demerits, especially in the manufacturing process, leading to lower portability and high production costs[15] and it may be inconvenient to use, and incompatibility problems with the excipient-capsule are usual.[16] It is therefore of considerable interest to produce a solid dosage form by incorporating liquid SEDDS into an inert solid carrier. This approach

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Received: 18-10-2016
Revised: 19-11-2016
Accepted: 28-11-2016
thus overcomes the disadvantages of liquid SEDDS as it provides a more stable and robust dosage form with lower manufacturing costs.\textsuperscript{[17]} In recent years low-density porous carriers with large surface area composed of magnesium aluminum metasilicate (Neusilin\textsuperscript{®}) or silicon dioxide (Syloid\textsuperscript{®}) are used to improve dissolution and bioavailability of poorly soluble drugs such as candesartan cilexetil, ezetimibe, fenofibrate, danazol, dexibuprofen nitrendipine, and quercetin.\textsuperscript{[8,18,19]} Nateglinide, BCS Class II drug a metaglinide derivative prescribed in diabetes mellitus Type II. It blocks K + ATP channel which help to control glycemic conditions in Type II diabetes. It has low aqueous solubility (0.00848 mg/mL) and oral bioavailability is 72%.

When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients probably because of impaired gastric motility and/or gastric emptying. Thus, increasing aqueous solubility and dissolution of nateglinide is of therapeutic meaning and foremost aim.\textsuperscript{[20,21]}

To improve the rate and extent of absorption of such BCS Class II compound solid lipid nanoparticles,\textsuperscript{[22]} nanocrystal,\textsuperscript{[23]} nanosuspensions,\textsuperscript{[24]} solid dispersions,\textsuperscript{[25]} emulsions, microemulsions,\textsuperscript{[26]} nanoemulsions,\textsuperscript{[27]} self-emulsifying system,\textsuperscript{[28]} and liposomes\textsuperscript{[29]} has been reported.

SEDDS formulation of nateglinide will primarily increase its solubility and dissolution rate. Further to convert this liquid SEDDS into solid formulation by adsorbing onto adsorbent. Formulations were evaluated for various physicochemical parameters including in vitro and in vivo studies.

Hence, there is a need for enhancement of the dissolution rate and solubility of nateglinide irrespective of pH for its improved absorption rate and therapeutic efficacy.\textsuperscript{[30]}

SEDDS gives uniform and higher drug dissolution irrespective of pH. Nateglinide when formulated as SEDDS, dissolution performance improved. To prevent any possible hypoglycemic shock-like condition due to fast dissolving SEDDS formulation, dose of drug need to be decreased.

The rationale of this study was to prepare SEDDS as an alternative approach for the delivery of BCS Class II drug, i.e., hydrophobic drug.

**Solubility of nateglinide**

The solubility of nateglinide in various oils, surfactants, and cosurfactants was determined by shake flask method.\textsuperscript{[31]} In 2 mL of each selected oils, surfactant and cosurfactant an excess amount of nateglinide were added in sealed vials. The sealed vials were subjected to homogenizer were homogenized for 10 min and then kept in orbital shaker for 48 h to attain equilibrium. For 15 min, the equilibrated sample was centrifuged at 3,000 rpm and the resulting supernatant was diluted with 10 mL of methanol.

The concentration of nateglinide was subsequently quantified using ultraviolet (UV)-visible spectrophotometer at $\lambda_{\text{max}}$ 210 nm, and further calibration curve was constructed which yielded a linear correlation ($r^2 = 0.9967$).

**Screening of components**

For selection of optimum oil: Smix (surfactant; cosurfactant mixture) ratio emulsification studies were carried out. Based on their emulsification efficacy, water uptake capacity and percent transmittance, where 300 mg of surfactant added to 300 mg optimized oily phase and mixed thoroughly. After mixing, it was kept undisturbed for 2 h and percent transmittance was recorded using UV-visible spectrophotometer at 640 nm using distilled water as blank. Whereas selection of cosurfactant depends on microemulsion formation with surfactant, where 150 mg of surfactant was mixed with 150 mg of cosurfactant in a ratio of 1:1, 2:1, 3:1 and 300 mg of optimized oily phase was added to the above mixture and heated up to 45°C-50°C on a water bath and 50 mg from the resultant mixture was further diluted to 50 mL with distilled water. Thus, the resulting emulsion kept undisturbed for 2 h and percent transmittance was recorded using UV-visible spectrophotometer at 640 nm using distilled water as blank.

**Construction of pseudoternary phase diagram for SEDDS formulation**

Pseudoternary phase diagram was constructed using CHEMEX school software to determine self-emulsifying region. Surfactant (tween 80) and cosurfactant (Transcutol P) were mixed (Smix) in different volume ratios (1:1, 2:1, 3:1). By screening the results obtained from surfactants, cosurfactants and oil and their solubility data self-emulsifying region was selected.\textsuperscript{[32]} For each phase diagram different ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) were selected for oil (capyrol-90) and specific surfactant/cosurfactant (Smix). To develop pseudoternary phase diagram titration method was developed, slow titration with aqueous phase was performed. The data obtained from phase diagram gives an appropriate amount of oil, surfactant, and cosurfactant for SEDDS formulation.\textsuperscript{[33]}

**MATERIALS AND METHODS**

Nateglinide was a gift sample from Glenmark Pharmaceuticals Pvt. Ltd., Pune, India. Tween 80 was purchased from LobaChemie Pvt-Ltd., India. Capryol-90 was purchased from Gattefosse, Mumbai, India. Other chemicals used were of analytical grade.
Preparation of SEDDS formulations

SEDDS formulation on the basis of microemulsification region was prepared using oil, surfactant, and cosurfactant in pseudoternary phase diagram. Nateglinide was dissolved in oil in an isothermal water bath to facilitate solubilization; Surfactant and cosurfactant were added to the above mixture. The resultant mixture was vortexed until a clear solution was obtained and stored in sealed vial at room temperature for further use. Six formulations (F1-F6) each containing 60 mg of Nateglinide with different concentrations of oils, surfactant and cosurfactant were prepared.[34]

Evaluation of SEDDS formulations

Robustness to dilution

The pH and dilution of the vehicle have sizable impact on phase separation of emulsifying system. In view to evaluate, nateglinide loaded SMEEDS were diluted (50, 100, 250 times) with various diluents including water, phosphate buffer solution pH 6.8 and phosphate buffer solution pH 7.4. The resulting emulsions were stored for 12 h at room temperature and demonstrated for any signs of phase separation or drug precipitation.[35]

Thermodynamic stability studies

Nateglinide loaded SEDDS were diluted with purified water and centrifuged at 3500 rpm for 30 min and then checked for instability such as phase separation, creaming or cracking. Freeze-thaw cycle was carried out at −21°C and +25°C, which involved three cycles with storage at each temperature for not <48 h.

Heating cooling cycle involve six cycles at temperature 4°C and 45°C with storage at each temperature for NLT 48 h. Formulations that passed these thermodynamic stress tests were selected for further studies.[36]

Globule size determination

Globule size determination by dynamic light scattering with Zeta sizer HSA 3000 (Malvern Instruments Ltd, UK) were selected SEDDS were subjected to sonication was analyzed.[37]

Zeta potential determination

Zeta potential measurement of the selected SEDDS formulations (F1-F6) was subjected to sonication diluted with excess (100 times) double distilled water and then analyzed using Zetasizer (Malvern Instrument Ltd., UK). The instruments operating principle is based on the Doppler shift caused by the movement of globules across interference fringes which are produced by the intersection of two laser beams.[38]

Cloud point determination

Cloud point, a temperature at which there is sudden appearance of cloudiness. The liquid SEDDS formulation was diluted with distilled water in a ratio 1:250. The diluted samples were placed in water bath and its temperature was gradually increased.

Viscosity determination

The viscosity of the liquid SEDDS was determined using Brookfield viscometer, at a speed of 15 rpm for 10 min for each formulation (F1-F6).

Precipitation analysis

For precipitation analysis studies SEDDS formulation was diluted with 0.1 N HCl up to 250 times and then the diluted microemulsion was observed at 1 h intervals up to 6 h for any sign of drug precipitation and phase separation.

Preparation of solid SEDDS (S-SEDDS)

SSEDDS was prepared using aerosil-200 in 1:0.5 ratios from selected liquid SEDDS. Liquid SMEEDS was introduced to 250 mL of purified water to form homogenous emulsion at 100 rpm for 10 min. To this formed emulsion, 5 g of aerosil-200 was added and stirred with magnetic stirrer for 10 min at 100 rpm, further the resultant suspension was spray dried by Jay LSD-48 Mini Spray dryer (Jay Instrument & System Pvt. Ltd., Mumbai), at 2.5 mL/min feeding rate; 105°C inlet temperature; 70°C outlet temperature; 85% aspiration; 500 NL/h drying air flow.

Solid state characterization of S-SEDDS

Micromeritics properties

The micromeritics properties were determined by evaluating bulk and tapped density angle of repose, Hausner’s ratio and compressibility index of S-SEDDS.

Scanning electron microscopy (SEM)

SEM was used to study surface topography at WD - 1010.3, HV - 20.00 KV, Magnification - 8000x, detector-PDF, Pressure-95 pascal, HFW - 32 µm for nateglinide and S-SEDDS.

Differential scanning calorimetry (DSC)

Using DSC thermograms were obtained for characterization of nateglinide and S-SEDDS.
**X-ray diffraction study (XRD)**

An XRD study was carried out using XRD to verify the physical state of pure nateglinide and S-SEDDS for changes in crystallinity.

**In vitro dissolution studies**

In vitro dissolution studies of S-SEDDS were performed using USP dissolution Apparatus I with basket at 75 rpm maintained at 37 ± 0.5°C in 900 mL dissolution medium. To imitate the physiological conditions, three different pH were employed, i.e., phosphate buffer of pH 1.2 phosphate buffer of pH 6.8 and pH 7.2.

For dissolution studies S-SEDDS equivalent to 60 mg of nateglinide was used, a sample of 5 mL was withdrawn at predetermined time interval of 5, 10, 15, 30, 60 and 120 min and filtered through Whatmann filter paper. To maintain sink conditions, an equal amount of fresh respective media was added.

**Accelerated stability studies**

Stability studies for S-SEDDS were carried out according to ICH at different temperatures. The samples were maintained at 25°C ± 2°C/60% ± 5% relative humidity (RH) and at 40°C ± 2°C/75% RH ± 5%. Samples were withdrawn at predetermined time interval as 0, 7, 15, 30, 60, and 90 days. S-SEDDS equivalent to 60 mg of nateglinide was dissolved in methanol and further diluted and using UV-visible spectrophotometer; the drug content was estimated at $\lambda_{max}$ 210 nm using methanol as blank.

**RESULTS AND DISCUSSION**

**Solubility studies**

Solubility study for Nateglinide was carried out with various oil, surfactant and cosurfactant. Highest solubility was observed in capyrol-90 (83.69 ± 1.06) whereas in other oils it showed lower solubility, i.e., labrafil M-2130 (64.06 ± 2.11) and Gelcire 44/14 (69.05 ± 1.36). In case of surfactant, high solubility was observed in tween 80 (121.83 ± 3.03) and in cosurfactant high solubility observed in Transcutol P (183.69 ± 3.3). So depending on solubility data capyrol-90 was screened as oil phase [Figure 1].

**Screening of components**

The components were screened on the basis of their percent transmittance of surfactant and cosurfactant. As various surfactant and cosurfactant were screened, surfactant tween 80 with capyrol-90 showed the highest transmittance (72.46%) whereas labrafil M-2130 and tween 80 showed 55.67% transmittance and gelucire 44/14 showed 58.36% transmittance. In case of cosurfactant Transcutol P with capyrol-90 and tween 80 showed the highest transmittance (100.151%) whereas Labrafil M-2130, tween 80 and Transcutol P showed 68.92% transmittance and gelucire 44/14, tween 80 and Transcutol P showed 75.66% transmittance. As tween 80 and Transcutol showed higher percent transmittance, so was selected for development of formulation.

**Construction of ternary phase diagrams**

Pseudo-ternary phase diagram determines self-emulsifying region. The pseudo-ternary phase diagram is shown in Figure 2 with varied surfactant and co-surfactant ratios. The ratio of surfactant to cosurfactant was chosen to be 1:1 and 2:1 (v/v). The shaded region designates stable microemulsifying region, which was observed in 1:1 ratio. At an appropriate concentration range, cosurfactants are useful to form a microemulsion. An excess amount of the co-surfactant will affect the stability of the system, i.e., affect intrinsic solubility and results in increased droplet size. Hence 1:1 ratio was selected a superlative ratio for surfactant to co-surfactant [Figure 2]. The prepared six SMEEDS formulation was compared for their self-emulsifying performance.

**Formulation of self-micro emulsifying drug delivery system (SMEDDS)**

Series of SEDDS were prepared by vortex method using various concentrations of oil, surfactant and co-surfactant each containing 60 mg of nateglinide.

**Physicochemical characterization of SMEDDS**

**Drug content**

Drug content of liquid and S-SEDDS was found to be between 92% and 99.17% which indicates better loading capacity.
Thermodynamic stability studies

Thermodynamic stability studies evaluate the ability of SEDDS formulation to withstand stress condition, where the SEDDS formulation to freeze-thaw cycle, centrifugation, and heating-cooling cycle.

Cloud point determination

The studies were carried out at higher temperature to observe the formulation for cloudiness and phase separation that occurs due to dehydration of its ingredients. Hence, to avoid this phenomenon cloud point of the SEDDS should be above 37°C. The cloud point of selected formulation was above 60°C.\[39\]

Precipitation analysis

Six formulations (F1-F6) were diluted with 0.1 NHCl up to 250 times, where the diluted solutions were observed for signs of precipitation. There were no signs of precipitation for 2 hrs, but F1 and F2 formulation were precipitated after 6 h.

Globule size

The globule size of SSEDDS was found to be 243.9 nm respectively for F6 formulation [Figure 3]. The results from Zeta sizer indicated varied range sizes from 141.5 to 243.9 nm [Table 1]. The formulation which was observed with lowest globule size was F1-F4 formulation.

Zeta potential

Zeta potential predicts emulsions stability. The range of zeta potential found to be between −9.35 mV and −24.87 mV [Figure 4].

Viscosity determination of self-emulsifying drug delivery system

During viscosity determination, it was observed that as the concentration of surfactant and co-surfactant was increased, a significant increase in viscosity of formulation was observed. The viscosity range of formulation was found to be between 13 and 24 cp.

Physicochemical characterization of solid SMEDDS

Micromeritics properties

The formulations were observed for their micromeritics properties, where the angle of repose for SF1-SF4 was <30, indicating excellent flow properties. The formulation SF4 Carr’s index was 13.2 ± 0.12, exhibits good flow and Hausner’s ratio of SF4 was 1.15 ± 0.04 displays good flow property [Table 2].

Table 1: Physiochemical characterization of liquid SEDDS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug content (mg)</th>
<th>Droplet size (nm)</th>
<th>Zeta potential (mV)</th>
<th>Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>90.8±0.12</td>
<td>141.5</td>
<td>−9.35</td>
<td>13.56±0.12</td>
</tr>
<tr>
<td>F2</td>
<td>92.35±0.82</td>
<td>165.3</td>
<td>−10.3</td>
<td>15.33±0.16</td>
</tr>
<tr>
<td>F3</td>
<td>96.16±0.02</td>
<td>180.6</td>
<td>−11.5</td>
<td>17.84±0.44</td>
</tr>
<tr>
<td>F4</td>
<td>97.76±0.21</td>
<td>204</td>
<td>−12.7</td>
<td>18.27±0.21</td>
</tr>
<tr>
<td>F5</td>
<td>99.43±0.33</td>
<td>227.6</td>
<td>−14.5</td>
<td>20.47±0.24</td>
</tr>
<tr>
<td>F6</td>
<td>99.52±0.24</td>
<td>243.9</td>
<td>−24.87</td>
<td>23.69±0.16</td>
</tr>
</tbody>
</table>

SEDDS: Self-emulsifying drug delivery system
Drug content

The drug content of prepared liquid and SSEDDS formulation was found to be between 92 and 99.17%.

Solid state characterization of S-SEDDS

Fourier transform infrared (FTIR) studies

FTIR spectra of nateglinide [Figure 5a] showed peaks at 1701/cm (carboxyl, carbonyl and amino group), and at 1724/cm (C=O and C-C stretching) in ester and aliphatic chain. Prominent peaks at 1296/cm (C-O stretching), 1446/cm (C-O-H stretching) and at 1642/cm (C=O stretching) in acidic groups and peaks at 1215/cm (carboxylic and keto group). Broad peaks between 2950/cm and 2850/cm (aromatic C=C stretching) Peaks appearing at 2931/cm (aromatic C-H stretching and in CH3) and at 1408/cm (CH2 stretch, aliphatic). The intense peak between 3296/cm and 3311/cm (N-H stretch, amino group). The majority of above peaks are weakened, sifted or slightly appeared in S-SEDDS as shown in Figure 5b and 5c.

DSC analysis

The sharp endothermic peak from DSC thermogram at 142.02°C for pure nateglinide, corresponds its melting point [Figure 6]. In case of aerosil-200 thermogram, no edothermic peaks were observed. However, in SEDDS thermogram amorphous state of nateglinide was confirmed due to the absence of endothermic peaks which was shown in physical mixture.

Table 2: Micrometric properties of S-SEDDS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Carr’s index (%)</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF1</td>
<td>28.7±0.01</td>
<td>0.58±0.01</td>
<td>0.68±0.01</td>
<td>22.3±0.02</td>
<td>1.32±0.02</td>
</tr>
<tr>
<td>SF2</td>
<td>27.3±0.02</td>
<td>0.57±0.02</td>
<td>0.75±0.02</td>
<td>18.2±0.12</td>
<td>1.27±0.04</td>
</tr>
<tr>
<td>SF3</td>
<td>24.6±0.01</td>
<td>0.54±0.02</td>
<td>0.69±0.01</td>
<td>17.2±0.05</td>
<td>1.16±0.03</td>
</tr>
<tr>
<td>SF4</td>
<td>22.4±0.03</td>
<td>0.56±0.02</td>
<td>0.72±0.02</td>
<td>13.2±0.12</td>
<td>1.15±0.04</td>
</tr>
</tbody>
</table>

S-SEDDS: Solid self-emulsifying drug delivery system
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Figure 5: (a) Fourier transform infrared (FTIR) spectrum of powder nateglinide, (b) FTIR spectrum of aerosil-200, (c) FTIR spectrum of optimized formulation (F4)

Figure 6: Differential scanning calorimetry (DSC) thermogram of (a) plain nateglinide, (b) DSC thermogram of pure nateglinide and physical mixture
XRD analysis

XRD analysis verifies physical state of drug in SSEDDS. In figure the absence of sharp peak illustrate highly crystalline nature of nateglinde [Figure 7a] and aerosil-200 [Figure 7b] sharp diffraction pattern indicate its amorphous nature. However, the physical mixture of nateglinide and aerosil-200 (1:0.5) showed sharp peak, which indicate % crystallinity of these formulations reduced and % amorphous increased which specifies that solubility of nateglinide is enhanced in formulation [Figure 7c].

SEM

SEM images indicate crystalline nature of pure nateglinide powder [Figure 8a], whereas S-SEDDS did not show crystalline nature of drug, [Figure 8b] which states liquid SEDDS is absorbed inside the pores of aerosol - 200.

In vitro dissolution studies

The dissolution profile of nateglinide from SSEDDS, optimized formulation (F4) in 1.2 pH buffer [Figure 9a] and 6.8 pH buffer [Figure 9b] was compared with pure drug (PD) powder and marketed formulation (MF). The release of drug was checked in phosphate buffer pH 1.2 where the drug release shown by MF was 10%, PD 5%, optimized formulation (F4) 40% in 10 min and in 120 min MF was 45%, PD 15%, optimized formulation (F4) 97%. Furthermore, dissolution profile in phosphate buffer pH 6.8 where MF showed 15% drug release, PD powder 10% and the optimized formulation (F4) 45% in 10 min and in 120 min MF showed 70%, PD powder 42%, and optimized formulation (F4) showed 98% drug release. However within 5 min SEDDS containing aerosil-200 as carrier showed 20% drug release, due to quick emulsification properties as the drug stays in solubilized form upon dilution. This shows that the total nateglinide in S-SEDDS could dissolve, and consequently, be absorbed more rapidly and completely than the PD in the stomach or intestine. Thus, SEDDS was useful for improving the dissolution rate of the poorly water-soluble nateglinide.

Accelerated stability studies

Stability studies

The results obtained from stability studies was found to be satisfactory after a period of 3-month at different temperatures 25°C ± 2°C and 40°C ± 1°C. The appearance and flowing property of SEDDS was maintained. The accelerated stability data did not show any significant change in appearance and visual grade of the optimized product [Table 3].

CONCLUSION

Self-emulsifying drug delivery system overcomes formulation difficulties and also improves oral bioavailability. In this study, SEDDS formulation of poorly water-soluble drug, nateglinide using capyrol-90 as oil, tween 80 and Transcutol P as surfactant and co-surfactant respectively was successfully developed. The conversion to solid form by aerosil-200 served to overcome the traditional drawbacks of liquid SEDDS. SEM analysis demonstrated spherical shape of the system. Compatibility between drug and excipients was indicated Fourier transformed infrared spectra. In vitro dissolution studies specified drug release where optimized formulation (F4) showed better release than MF, PD powder. Furthermore, the stability
studies indicated consistent drug content, visual grade and appearance.

**REFERENCES**


Source of Support: Nil. Conflict of Interest: None declared.