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# IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF TICAGRELOR SOLID DISPERSIONS BY DIFFERENT METHODS

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## Abstract

**Introduction:** The current study is aimed at enhancing the solubility and release rates of ticagrelor (TGL), an oral antiplatelet agent by adopting solid dispersion (SD) technique.

**Material and Methods**: Forty formulations of TGL SD prepared by solvent evaporation method(TGL1-TGL20) and fusion(melt) method(TGL20-TGL40) using varying ratios of water soluble carriers(poloxamer 188, labrafil M1944, PEG 8000and gelucire 44/14).All the formulations evaluated for pre compression parameters,% practical yield,% drug content and drug dissolution. The optimized formulation further subjected to characterization by FTIR, PXRD and SEM studies.

**Results**: The solubility of ticagrelor(TGL) checked in various polymers indicate that pure drug exhibited maximum solubility in phosphate buffer(0.152 mg/ml) while drug and poloxamer 188 mixture exhibited maximum solubility of 3.8 mg/ml in phosphate buffer . The SD formulation TGL35 containing poloxamer 188 exhibited maximum solubility of 6.992±0.04 mg/ml which is 46 folds that of pure drug. Similar enhancement trends observed in % drug content, %practical yield and in-vitro dissolution rates of TGL35 (99.55% in 60 minutes) when compared to pure drug. FTIR study displayed the compatibility amongst drug and polymer used. The XRD and SEM studies showed TGL35 existed in amorphous state which fetched in better drug release rates of SD formulation in comparison to pure drug.

**Conclusion:** The results indicate that the formulation technology employed with a potential of enhancing bioavailability and solubility of ticagrelor.

**Keywords:** Ticagrelor, solid dispersion, fusion (melt) method, poloxamer 188, platelet aggregation inhibitor.

## INTRODUCTION

Drugs exhibiting low aqueous solubility have decreased absorption when given orally resulting in poor bioavailability. Drugs whose absorption is limited by dissolution can be subjected to micronization to enhance dissolution rate but this technique is sometimes limited due to poor particles wettability owing to interparticle aggregation. More such techniques that are available for bioavailability enhancement are co-solvent assisted solubilization, salt formation, inclusion complexes formation. All the methods specified have their own pros and cons. The drawbacks of these approaches have been overcome by development of solid dispersion (SD) of such drugs. Solid dispersion is defined as dispersion of one or more active hydrophobic ingredients in an inert

hydrophilic carrier at solid state [1,2].

In SD technique , a drug exist in amorphous form in the matrix thus facilitating enhanced solubility and drug release rates in comparison to crystalline forms. Drugs dispersed in polymeric carriers exhibit maximum particle size reduction and enhanced surface area which improves the dissolution rates [3, 4].

Ticagrelor (TGL), an antagonist of the P2Y12 that acts as aggregation inhibitor. It reduces major cardiovascular attacks in patients with severe coronary syndrome and exhibits potential to develop coronary artery perfusion .In the platelet inhibition and patient outcomes (PLATO) trial, TGL was superior to clopidogrel in preventing cardiovascular events, as well as death from any cause. TGL has the potential benefit of treating patients at thrombosis risk arising due to rapid off set of antiplatelet effect. However, TGL is classified as a bio-pharmaceutics classification system (BCS) class 4 drug with moderate permeability and reduced solubility (FDA, 2016). It has been reported that TGL have a low (around 35%) oral bioavailability, too. Therefore, there is a need to increase bioavailability by augmenting solubility and permeability of TGL.
The present work is aimed at developing TGL SD using two preparation methods by fusion (melt) and solvent evaporation method to increase the solubility and dissolution of TGL [5-9].

## MATERIALS AND METHODS

### Materials

TGL gifted by Hetero Labs Limited, Hyderabad. Poloxamer 188, labrafil M1944, PEG 8000 and gelucire 44/14, methanol, dichloromethane were obtained from Gattefosse, Mumbai. All other chemicals and reagents used were of analytical grade.

### Methods

#### Preliminary solubility study of TGL

Solubility of pure drug TGL tested by dissolving excess amount of drug in 25ml of carrier solutions in varying ratios in sealed bottles. The samples mixed gently at room temperature for 24h, the resultant suspension filtered and filtrate analyzed spectrophotometrically at 222 nm[10] .

#### Preparation of TGL solid dispersions solvent evaporation method

20 formulations of TGL SD (TGL1-TGL20) formulated with water soluble carriers (poloxamer 188, labrafil M1944, PEG 8000 and gelucire 44/14) in varying weight ratios by solvent evaporation technique [11].
Known amount of TGL and carriers in varying ratios were dissolved in ethyl alcohol and solvent evaporated at 45°C.the resultant SD stored in oven at room temperature for 48 h under vacuum for complete removal of solvent. The dried SDs grinded manually, sieved through # 60, stored in desiccators (Table 1 & 2).

#### Fusion (melt) method

20 formulations of TGL SD (TGL21-TGL40) were prepared using different carriers (poloxamer 188, labrafil M1944, PEG 8000 and gelucire 44/14) in varying weight ratios by fusion (melt) method [12].
Known amount of carriers were placed in a china dish, kept on hot plate and melted with continuous stirring, at a temperature of about 50-60°C. An accurately weighed amount of TGL (90mg) incorporated into the molten carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The china dish was then removed from the hot plate and melt was transferred onto an aluminum pan, allowed to cool at room temperature. The dried SD were pulverized and sieved through sieve number 60#. The samples were stored in amber colored bottles capped with rubber corks and kept in desiccators.
(Table 3 & 4)

**Table 1: Preparation of TGL SD by solvent evaporation method (TGL1-TGL20)**

| Solid Dispersion Code | Ingredients Quantity in mg | | | | | Ratio |
|---|---|---|---|---|---|---|
| | TGL | PEG 8000 | Gelucire-44/14 | Poloxamer 188 | Labrafil M1944 | |
| **TGL1** | 90 | 45 | - | - | - | 01:00.5 |
| **TGL2** | 90 | 90 | - | - | - | 1:01 |
| **TGL3** | 90 | 180 | - | - | - | 1:02 |
| **TGL4** | 90 | 270 | - | - | - | 1:03 |
| **TGL5** | 90 | 360 | - | - | - | 1:04 |
| **TGL6** | 90 | | 45 | - | - | 01:00.5 |
| **TGL7** | 90 | | 90 | - | - | 1:01 |
| **TGL8** | 90 | | 180 | - | - | 1:02 |
| **TGL9** | 90 | | 270 | - | - | 1:03 |
| **TGL10** | 90 | | 360 | - | - | 1:04 |

**Table 2: Preparation of TGL SD by solvent evaporation method (TGL11-TGL20)**

| Solid Dispersion Code | Ingredients Quantity in mg | | | | | Ratio |
|---|---|---|---|---|---|---|
| | TGL | PEG 8000 | Gelucire-44/14 | Poloxamer 188 | Labrafil M1944 | |
| **TGL11** | 90 | | - | 45 | - | 01:00.5 |
| **TGL12** | 90 | | - | 90 | - | 1:01 |
| **TGL13** | 90 | | - | 180 | - | 1:02 |
| **TGL14** | 90 | | - | 270 | - | 1:03 |
| **TGL15** | 90 | | - | 360 | - | 1:04 |
| **TGL16** | 90 | | - | - | 45 | 01:00.5 |
| **TGL17** | 90 | | - | - | 90 | 1:01 |
| **TGL18** | 90 | | - | - | 180 | 1:02 |
| **TGL19** | 90 | | - | - | 270 | 1:03 |
| **TGL20** | 90 | | - | - | 360 | 1:04 |

**Table 3: Preparation of TGL SD by fusion (melt) method(TGL21-TGL30)**

| Solid Dispersion Code | Ingredients Quantity in mg | | | | | Ratio |
|---|---|---|---|---|---|---|
| | TGL | PEG 8000 | Gelucire-44/14 | Poloxamer 188 | Labrafil M1944 | |
| **TGL21** | 90 | | - | - | - | 01:00.5 |
| **TGL22** | 90 | | - | - | - | 1:01 |
| **TGL23** | 90 | | - | - | - | 1:02 |
| **TGL24** | 90 | | - | - | - | 1:03 |
| **TGL25** | 90 | | - | - | - | 1:04 |
| **TGL26** | 90 | | 45 | - | - | 01:00.5 |
| **TGL27** | 90 | | 90 | - | - | 1:01 |
| **TGL28** | 90 | | 180 | - | - | 1:02 |
| **TGL29** | 90 | | 270 | - | - | 1:03 |
| **TGL30** | 90 | | 360 | - | - | 1:04 |

**Table 4: Preparation of SD by fusion (melt) method (TGL31-TGL40)**

| Solid Dispersion Code | Ingredients Quantity in mg | | | | | Ratio |
|---|---|---|---|---|---|---|
| | TGL | PEG 8000 | Gelucire-44/14 | Poloxamer 188 | Labrafil M1944 | |
| **TGL31** | 90 | | - | 45 | - | 01:00.5 |
| **TGL32** | 90 | | - | 90 | - | 1:01 |
| **TGL33** | 90 | | - | 180 | - | 1:02 |
| **TGL34** | 90 | | - | 270 | - | 1:03 |
| **TGL35** | 90 | | - | 360 | - | 1:04 |
| **TGL36** | 90 | | - | - | 45 | 01:00.5 |
| **TGL37** | 90 | | - | - | 90 | 1:01 |
| **TGL38** | 90 | | - | - | 180 | 1:02 |
| **TGL39** | 90 | | - | - | 270 | 1:03 |
| **TGL40** | 90 | | - | - | 360 | 1:04 |

**Pre-compression evaluation parameters**

Angle of repose, Carr's compressibility index, bulk density, tapped density and Hausner ratio was performed on the basis of reported method [13].

**Evaluation of TGL SD**

Solubility of TGL SD performed as per published method [14].The percentage practical yield [15], % drug content [16], *in vitro* drug dissolution study of [17] were evaluated as per the referred methods. The dispersions are further characterized for Fourier transform infrared spectroscopic analysis [18], X-Ray Diffractometer (XRD) [19, 20] and SEM studies [21] for drug compatibility and morphology.

**In vitro drug dissolution of TGL SD**

The dissolution of TGL SDs prepared was investigated in 900 ml phosphate buffer (pH 6.8) in USP type II (paddle type) dissolution test apparatus at 50rpm. A temperature of 37±5ºC maintained during the course of study. The SDs containing 90 mg of TGL dissolved in 5ml dissolution media followed by filtration through a filter (0.45µ) at varying time interval suitably diluted and assayed at 222 nm [22].

**Stability study TGL SD**

The TGL SD was sealed in 40CC, HDPE container under controlled conditions in stability chamber (Thermo Lab, India) at 75%±5%RH and $40^0C \pm 2^0C$. Samples analyzed for 3 consecutive months for % drug content and drug release rates [23]

## RESULTS

**Pre-compression evaluation parameters**

The angle of repose of all formulations ranged between 22.09- 28.54.The results of bulk densities formulations bearing TGL1 to TGL40 reported being in the range of 0.53g/cc to 0.61g/cc. The findings of tapped density formulations TGL1 to TGL40 reported being in the range of 0.55g/cc to 0.72g/cc. The compressibility index values of TGL1 to TGL40 ranged between 9 to 12 %. The Hausner's ratio values of TGL1 to TGL40 in the space of 1.10 to 1.17 %. These findings indicated that the all the batches of formulations exhibited good flow properties.

**TGL solubility studies**

The solubility of TGL in various carriers determined two different solvents, distilled water and phosphate buffer pH6.8.The results indicate that TGL pure drug showed more solubility in 6.8pH phosphate buffer (0.152 mg/ml) when compared to distilled water (0.127 mg/ml). The solubility of TGL and poloxamer 188 mixture in phosphate buffer pH 6.8(3.8 mg/ml) was almost 25 folds enhanced compared to TGL pure drug solubility in 6.8 pH phosphate buffer. (figure 1)

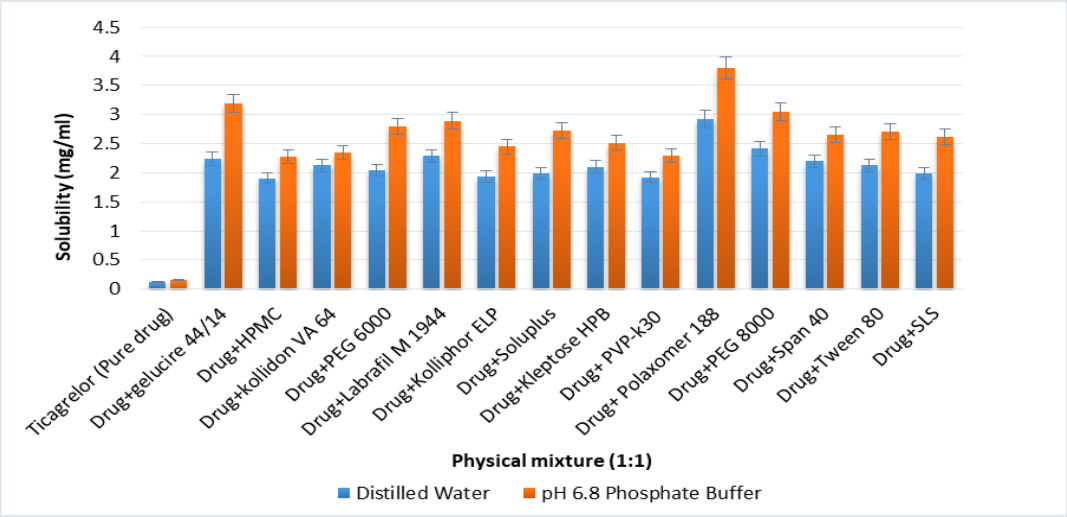



**Figure 1: Solubility studies of TGL in various polymers**

**Phase solubility studies of TGL SD**

The solubility of TGL SD was studied in two different media i.e., distilled water and phosphate buffer pH6.8. The results indicate that the formulation containing poloxamer188 showed higher solubility than other carriers. TGL35 containing drug: polymer (1:4) prepared by fusion (melt) method exhibited highest solubility in 6.8pH phosphate buffer (6.992±0.04 mg/ml) almost 46 folds increased than pure drug solubility (0.152±0.01 mg/ml)**.** Studies show that the maximum solubility is achieved when the concentration of the carrier was more in the formulation. (figure 2, 3)

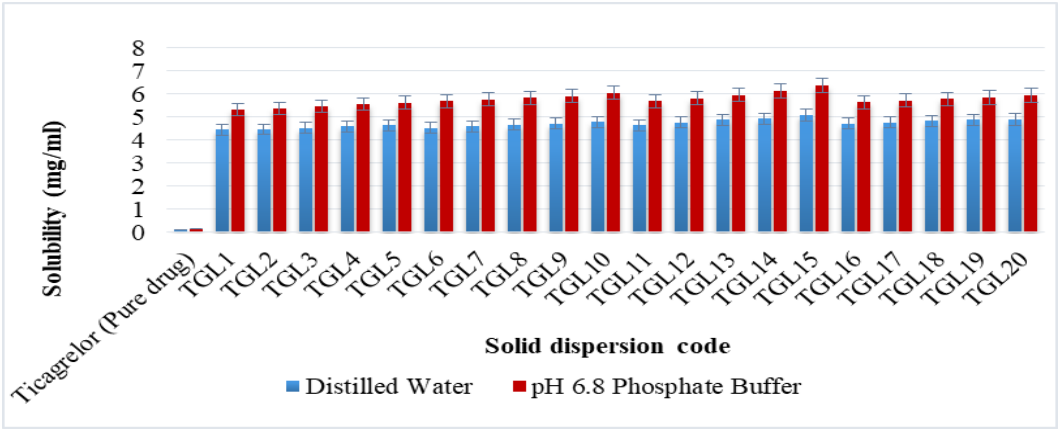
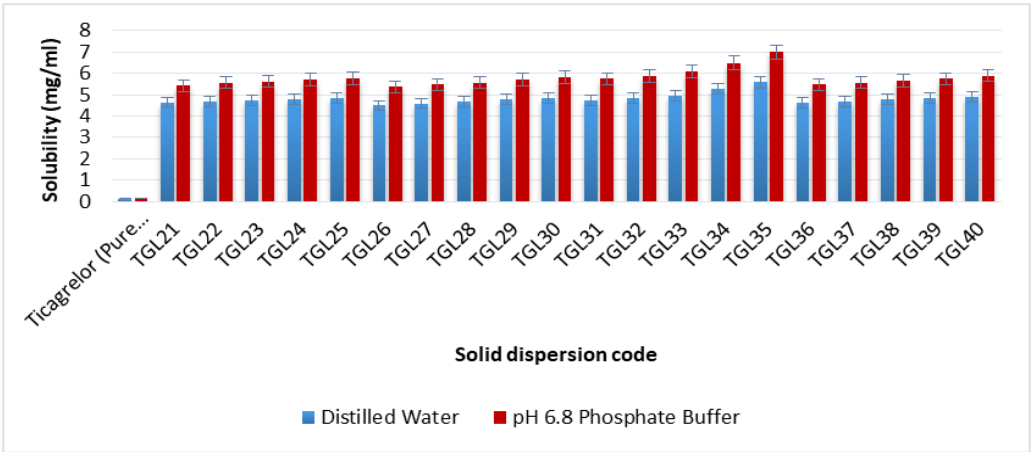



**Figure 2: Solubility studies of TGL SD (TGL1-TGL20)**




n=3 (±SD)

**Figure 3: Solubility studies of TGL SD(TGL21-TGL40)**

**% drug content and % practical yield of TGL SD**

The % drug content values of TGL1 to TGL40 are in the range of 95.38±0.45 to 99.75±0.68%. The formulations exhibited maximum solubility of 99.22±0.36% .The % practical yield values of TGL1 to TGL40 are in the range of 93.18±0.067 to 98.29±0.059%. The formulations TGL35 was found to posses maximum value of 99.07±0.018%.

The drug content and practical yield of all formulations are dependent on angle of repose which represents uniformity in flow nature of powder blend that in turn ensures uniform drug distribution (Table 5 & 6).

**Table 5: % drug content and % practical yield of TGL SD (TGL1-TGL20)**

| F. No | Drug content (%) | % Practical yield |
|---|---|---|
| **TGL1** | 96.19±0.21 | 95.29±0.043 |
| **TGL2** | 98.23±0.19 | 96.35±0.051 |
| **TGL3** | 96.89±0.65 | 96.87±0.069 |
| **TGL4** | 97.67±1.59 | 94.12±0.043 |
| **TGL5** | 96.73±0.19 | 95.61±0.022 |
| **TGL6** | 96.27±0.49 | 93.18±0.067 |
| **TGL7** | 96.12±0.78 | 94.28±0.053 |
| **TGL8** | 98.42±0.15 | 94.26±0.079 |
| **TGL9** | 98.32±0.66 | 97.68±0.073 |
| **TGL10** | 95.38±0.45 | 95.53±0.035 |
| **TGL11** | 98.76±0.13 | 97.44±0.039 |
| **TGL12** | 97.51±0.62 | 96.57±0.095 |
| **TGL13** | 98.59±0.89 | 97.67±0.084 |
| **TGL14** | 98.51±0.39 | 94.59±0.070 |
| **TGL15** | 98.96±0.78 | 98.88±0.067 |
| **TGL16** | 97.13±0.98 | 95.42±0.069 |
| **TGL17** | 96.29±0.79 | 94.45±0.018 |
| **TGL18** | 98.12±0.84 | 97.41±0.052 |
| **TGL19** | 97.62±0.82 | 96.74±0.061 |
| **TGL20** | 98.18±0.81 | 96.22±0.063 |

Above parameters are communicated as Average ± Standard Deviation; (n=3)

**Table 6 :% drug content and % practical yield of TGL SD(TGL21-TGL40)**

| F. No | Drug content (%) | % Practical yield |
|---|---|---|
| **TGL21** | 98.48±0.31 | 97.62±0.021 |
| **TGL22** | 97.89±0.82 | 97.12±0.051 |
| **TGL23** | 98.36±0.45 | 96.19±0.017 |
| **TGL24** | 98.11±1.17 | 96.23±0.045 |
| **TGL25** | 97.19±0.31 | 97.80±0.037 |
| **TGL26** | 97.14±0.48 | 96.83±0.017 |
| **TGL27** | 97.23±0.88 | 95.45±0.053 |
| **TGL28** | 98.19±0.22 | 98.62±0.042 |
| **TGL29** | 97.20±0.12 | 97.14±0.075 |
| **TGL30** | 97.33±0.58 | 96.78±0.061 |
| **TGL31** | 97.49±0.28 | 97.73±0.026 |
| **TGL32** | 98.69±0.76 | 95.27±0.027 |
| **TGL33** | 98.18±0.50 | 98.44±0.039 |
| **TGL34** | 98.75±0.68 | 98.29±0.059 |
| **TGL35** | 99.22±0.36 | 99.07±0.018 |
| **TGL36** | 98.16±0.48 | 97.56±0.092 |
| **TGL37** | 97.57±0.39 | 95.36±0.067 |
| **TGL38** | 98.17±0.61 | 97.49±0.012 |
| **TGL39** | 97.28±0.34 | 97.58±0.046 |
| **TGL40** | 98.11±0.32 | 97.45±0.089 |

Above parameters are communicated as Average ± Standard Deviation; (n=3)

**In-vitro dissolution studies of TGL SD**

Dissolution studies of all TGL solid dispersion from TGL1 to TGL40 studied to understand release properties of drug from SD formulations. The dissolution profile of formulation TGL35 prepared by fusion (melt) method using 1:4 ratio of drug: polymer (TGL: poloxamer 188) showed maximum drug release of 99.55% in 60 minutes when compared that other formulations and pure drug (36.76%). Increased dissolution rates of solid dispersions is attributed to more polymer concentration used for formulating solid dispersions, it is clearly observed that as the polymer carrier concentration was increased in the formulation the drug release increased accordingly (figure 4, 5, 6 & 7).

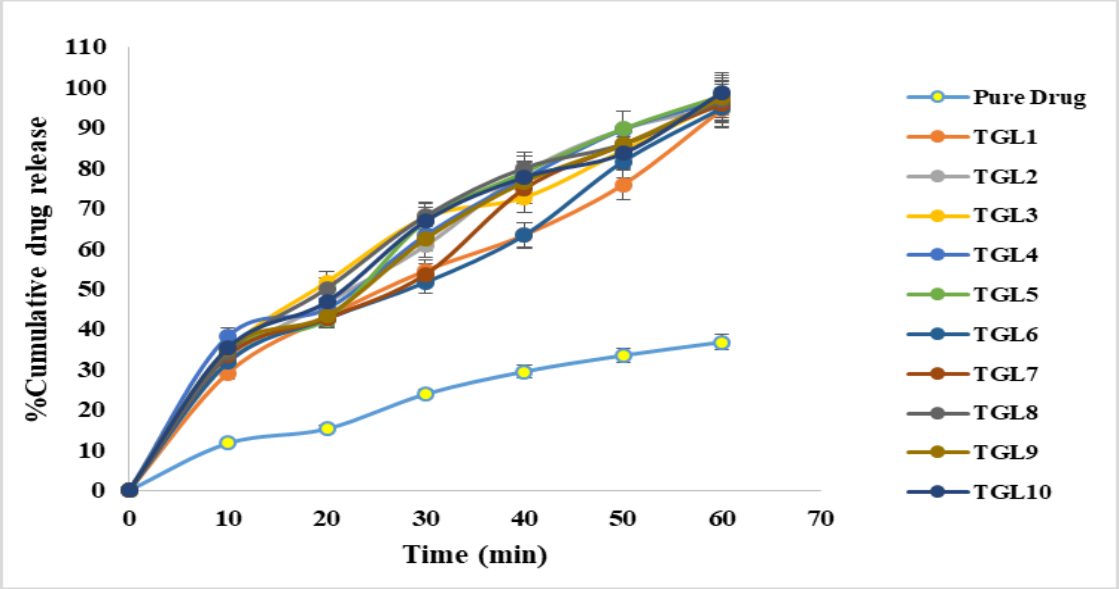



**Figure 4: Dissolution profile of TGL pure drug and TGL SD (TGL1to TGL10)**

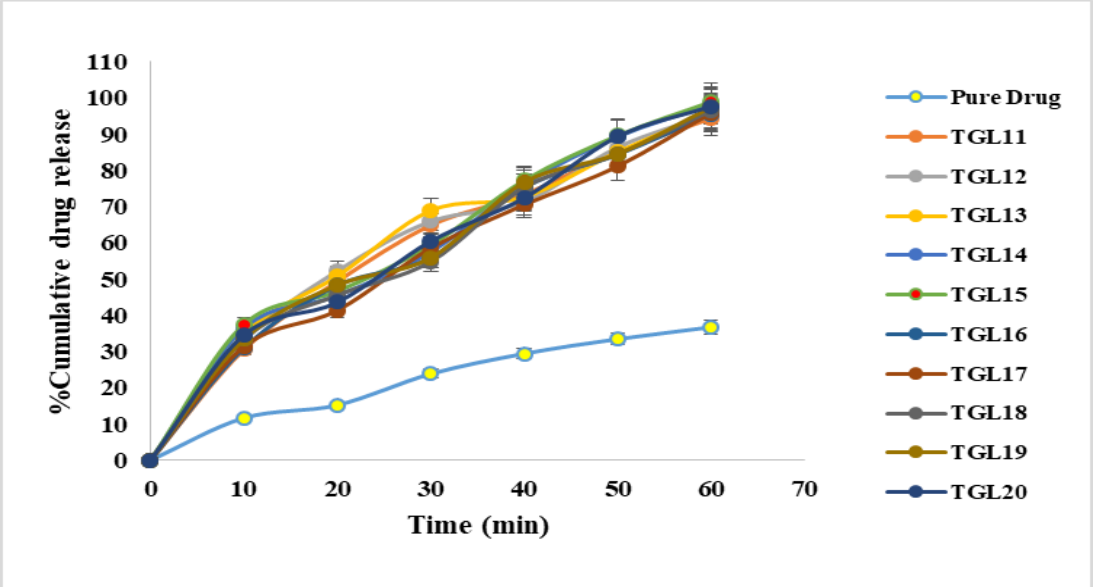



**Figure 5: Dissolution profile of TGL pure drug and TGL SD (TGL11to TGL20)**

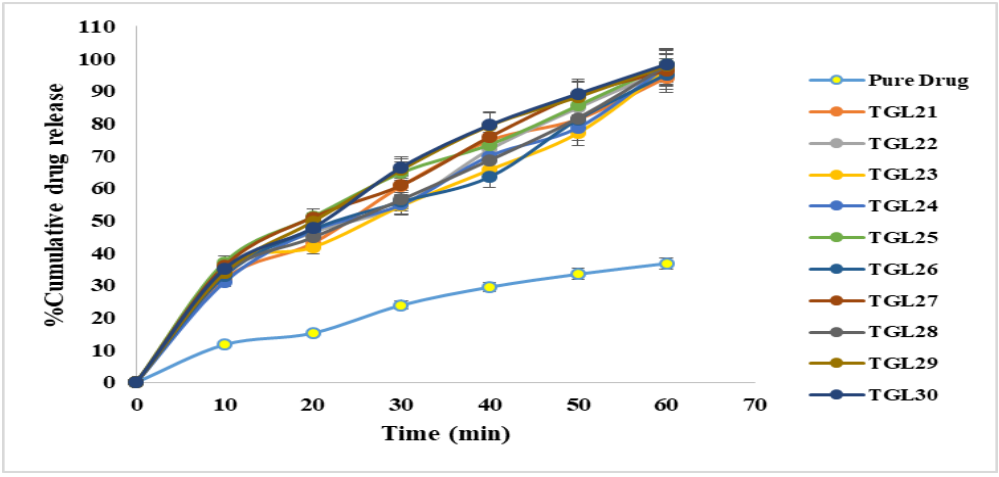



**Figure 6: Dissolution profile of TGL pure drug and TGL SD (TGL21to TGL30)**

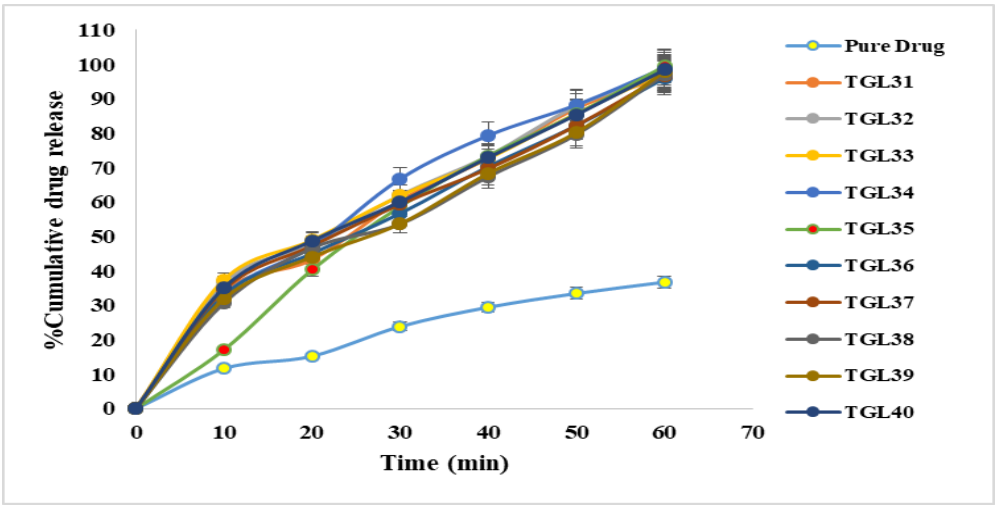



**Figure 7: Dissolution profile of TGL pure drug and TGL SD (TGL31 to TGL40)FTIR studies**

TGL pure drug displayed characteristic peaks at 3400cm$^{-1}$ due to N-H stretching because of primary and secondary amines, 2940 cm$^{-1}$due to C-H stretching for the alkenes, 1608 cm$^{-1}$ due to N-H bend presence of primary amines, 1329 cm$^{-1}$ is due to N-O symmetric stretch of nitro compounds, 1114 cm$^{-1}$ due to C-N stretch for the presence of aliphatic amines, 1051 cm$^{-1}$ due to alcohols and carboxylic acids, 991 cm$^{-1}$ due to =C–H bend due to alkenes (figure8).

The spectra of optimized TGL SD (TGL 35) displayed all characteristic peaks of pure drug at 3414 cm$^{-1}$, 2930 cm$^{-1}$, 1624 cm$^{-1}$, 1329 cm$^{-1}$, 1114 cm$^{-1}$and 995 cm$^{-1}$ indicating no significant interaction amongst drug and excipients used in formulation(figure 9).

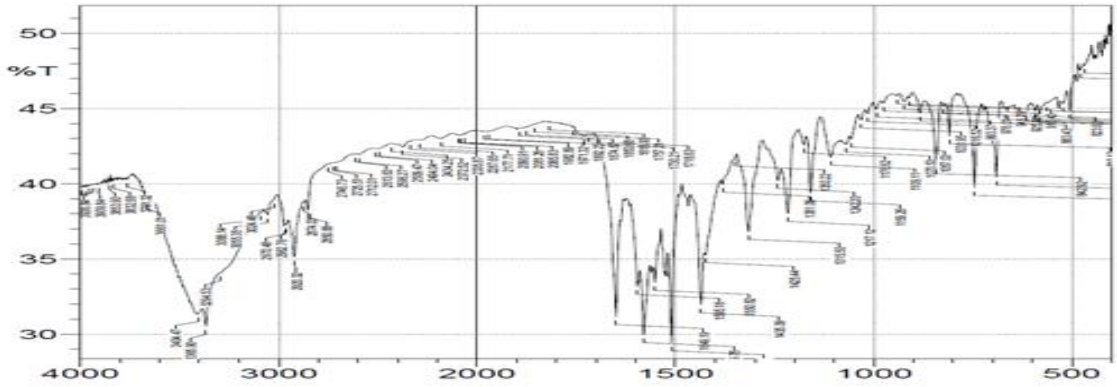



**Figure 8: FTIR TGL pure drug**

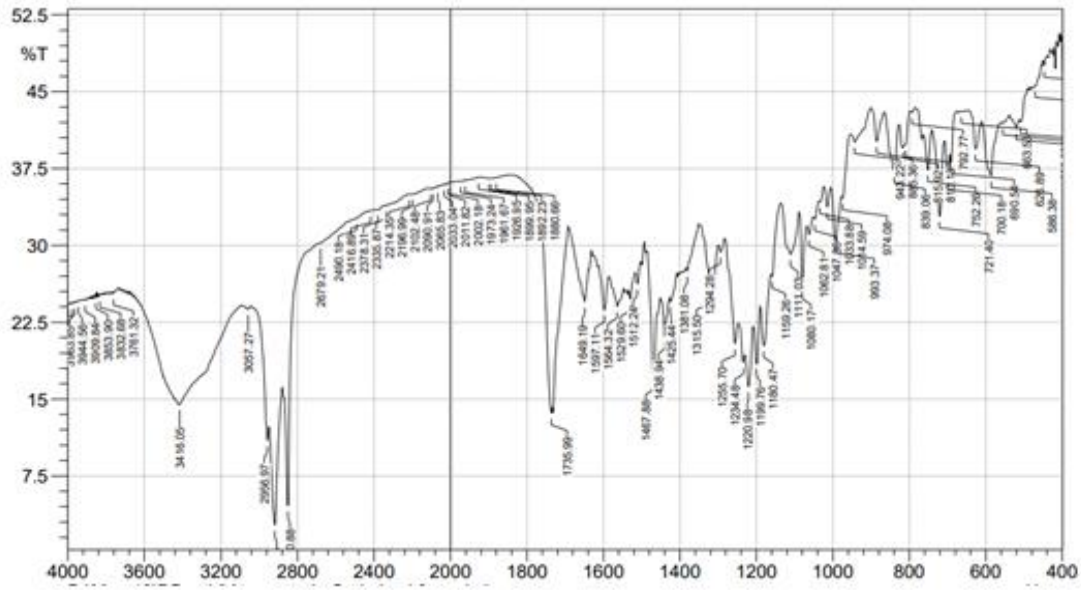



**Figure 9: FTIR spectrum of TGL SD optimized formulation TGL35**

**X-ray powder diffraction (XRD)**

The existence of many distinct peaks in XRD spectrum of pure TGL confirms it as crystalline drug (figure 10A) and the pure drug showed sharp peaks whereas the co-crystals did not show sharp peaks which suggest that there are interaction. Inter-arrangement of molecules is indicated by different peak locations of the co-crystals with respect to pure drug, hence proves formation of new phase. The increase in dissolution rate of drug from TGL35 is attributed to reduction in drug crystallinity (figure 10B).

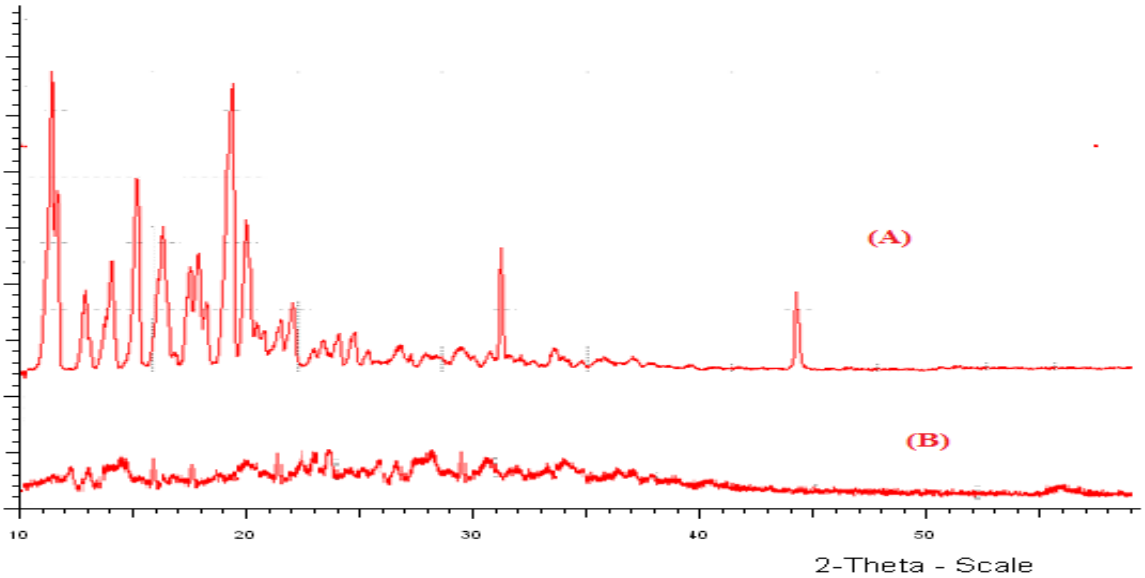



**Figure 10: XRD of TGL pure drug (A); optimized formulationTGL35 (B)**

**SEM studies**

The SEM data indicates smooth surface and irregular shape of drug crystals (figure 11).the surface of drug in SD formulation is porous and appeared a mixed mass. The drug particles seem to be completely incorporated into the formulation with the dispersion looking like a matrix. The results ensure complete dispersion of the drug.(figure 12)

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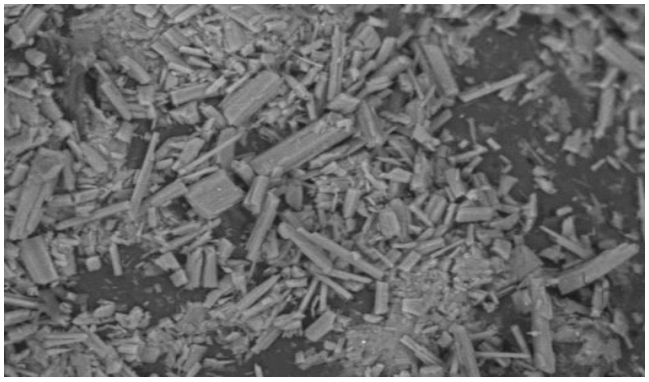

**Figure 11: SEM image of pure drug of TGL**

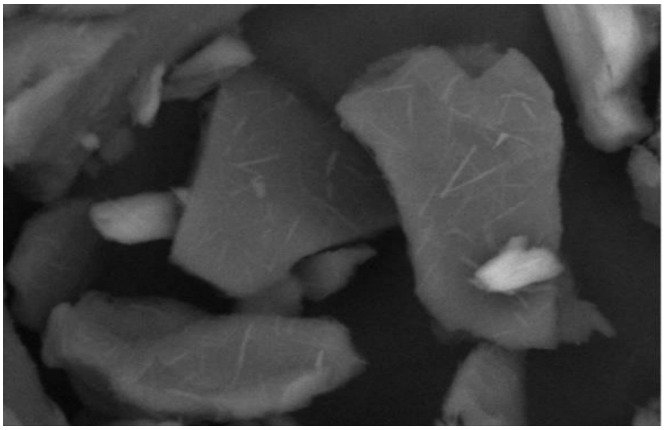

**Figure 12: SEM image of TGL SD optimized formulation TGL35**

**Stability studies**

Optimized formulation TGL35 was loaded for stability studies at 40°C±2°C/75% RH±5% and found stable. There was no noteworthy variation in % drug content and in-vitro drug release was observed.(table 7)

**Table 7: Stability study TGL SD optimized formulation TGL35**

| Retest time for optimized formulationTGL35 | %Drug content | In-vitro drug release (%) |
|---|---|---|
| **0** | 99.22±0.43 | 99.55±3.87 |
| **30** | 98.65±0.25 | 99.01±0.39 |
| **60** | 97.72±0.37 | 98.49±0.40 |
| **90** | 97.07±0.48 | 98.02±0.39 |

Above parameters are communicated as Average ± Standard Deviation; (n=3)

## CONCLUSION

Solid dispersions of TGL prepared by solvent evaporation method and fusion melt method as simple and easily reproducible methods. Total 40 formulations were prepared using different hydrophilic carrier polymers and all the formulations exhibited enhanced drug release compared to pure drug. The solubility of TGL was found to be highest in polymer poloxamer188 in phosphate buffer pH6.8 which was almost 25 folds and the same reflected in the formulation TGL35 which showed highest release of 99.55% in 60 min containing 1:4 ratio of TGL drug: poloxamer188 prepared by fusion (melt) method and found to be the best optimized formulation. Solubility of TGL was also increased by 46 folds in solid dispersion formulation TGL35 when compared to pure drug. For all the formulations evaluation was carried and found to be adequate and FTIR studies disclosed the compatibility between drug and polymers. XRD and SEM studies manifest that TGL35 was in amorphous form which achieved in better dissolution of the drug from the SD formulation when compared to the pure drug. Therefore, from the results obtained after thorough investigation it was

assessed that SDs prepared by fusion (melt) method showed better drug release and enhanced solubility thereby improvement in drug dissolution.

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