Research Article

Enhancement of Solubility and Dissolution Profile of Clopidogrel by various Solid Dispersion Formulations

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ABSTRACT

The present research is aimed at enhancing solubility, and drug dissolution of clopidogrel (CPG) used as an oral antiplatelet agent by employing solid dispersion (SD) technique. Total 40 SDs formulated with drug:polymers (pluronic F127, poloxamer 407, labrafil PG, PEG 6000, and gelucire 50/13), in varying ratios (1:0.5, 1:1, 1:2, 1:3, and 1:4), of which CPG1 to CPG20 and CPG21 to CPG40 prepared by adopting solvent evaporation method fusion (melt) method, respectively. The formulation CPG40 containing pluronic F127 as polymer showed highest solubility of 6.57 ± 0.04 mg/mL, i.e., 45 folds than pure drug. Similar results reflected in the dissolution studies where CPG40 containing CPG:pluronic F127 in 1:4 ratio showed maximum % drug content, % practical yield, and drug dissolution of 99.14% in 60 minutes, when compared with other formulations and pure drug (32.76%), obtained by fusion melt method. From Fourier transform infrared spectroscopy (FTIR) studies, the optimized formulation CPG40 showed the compatibility between drugs and polymers. X-ray powder diffraction (XRD) and scanning electron microscope (SEM) studies, showed CPG40 exists in amorphous form that fetched in better drug release from the SD formulation in comparison to pure drug.

INTRODUCTION

Drug delivery by oral routes is the fundamental and simpler route of drug administration owing to smaller bulk, precise dosage, and manufacturing ease.[1] Solid dosage forms are advantageous over other oral dosage forms that produce efficient and reproducible in vivo drug plasma concentration post-administration; hence, the majority of new chemical entities (NCE) adopt solid dosage techniques that include tablets, capsules, powders, etc.

As more than 40% of NCE suffer from poor drug solubility and bioavailability, enhancement of drug solubility has always been a challenge for researchers. Drug solubility and membrane permeability are major factors that limit the drug absorption from gastro intestinal (GI) track. The first step in oral drug delivery is dissolution of drugs in intestinal fluids, which then reaches the bloodstream for circulation. Hence, drugs with poor aqueous solubility exhibit incomplete absorption and permeability through GI track, thus, reducing the drug efficiency.[2,3]

Hence, the two major challenges of pharmaceutical drug development include enhancement of solubility of sparingly water-soluble drugs and enhancing penetrations of poorly permeable drugs.[4] SD technique proved to be an effective tool for meeting these challenges. SDs are a bunch of solid-state elements comprising of two distinct components, usually hydrophilic matrix and a hydrophobic drug.

CPG is a potent oral antiplatelet agent acting by inhibiting platelet activation and aggregation often used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease. CPG is
classified as BCS class II, owing to poor water solubility and high permeability that leads to low oral bioavailability. Hence, it is essential to augment the aqueous solubility and dissolution rate of CPG to obtain faster onset of action, minimize the variability in absorption, and improve their overall oral bioavailability.[5,6]

The present study deals with SD formulation of CPG using various carriers, like pluronic F127, labrafac PG, PEG 6000, and gelucire 50/13 for enhancing dissolution and/or solubility and thereby bioavailability of the drug.

**Materials and Methods**

**Materials**

CPG gifted by Hetero Labs Limited, Hyderabad. Poloxamer 407, labrafil PG, PEG 6000, gelucire 50/13, pluronic F127, ethanol, and dichloromethane were obtained from Gattefosse, Mumbai. All the reagents used were of analytical grade.

**Methods**

**Preliminary Solubility Study of CPG**

Solubility study of CPG carried out by dissolving excess drug in 25 mL of water-soluble carrier solutions (in distilled water and phosphate buffer of pH 6.8) in varying ratios in screw-capped bottles. The contents mixed continuously for about 24 hours at room temperatures. The resultant suspension filtered, filtrate analyzed for the CPG at 240 nm, using UV method.[7]

**Preparation of CPG SD**

**Solvent evaporation method:** Twenty formulations (CPG1–CPG20) of CPG SD prepared with carriers (pluronic F127, labrafac PG, PEG 6000, and gelucire 50/13) in varying weight ratios by the solvent evaporation method.

Weighed quantity of drug and carriers in dissolved in ethyl alcohol in RB flask and evaporated at 45 °C. The obtained SDs stored in the oven under vacuum at room temperature for 48 hours for complete evaporation of solvent. The dried SDs grinded using mortar with pestle, sieved through #60, and stored in desiccator (Tables 1 and 2).[8]

**Fusion (melt) method:** Twenty formulations (CPG21–CPG40) of CPG SD prepared using carriers (pluronic F127, labrafac PG, PEG 6000, and gelucire 50/13) in varying ratios by fusion (melt) method.

Weighed quantities of carriers placed on china dish, kept on hot plate and allowed to melt with constant stirring at 50 to 60°C. Known amount of CPG incorporated into the carrier(s) by constant stirring to attain homogeneity and the mixture heated to obtain clear homogeneous melt. The China dish removed from the hot plate, the melt was transferred onto an aluminum pan and cooled to room temperature. The dried SD was pulverized and sieved through sieve number 60. The samples were stored in amber-colored bottles capped with rubber corks and kept in desiccators (Tables 3 and 4).[9]

**Pre-Compression Evaluation Parameters**

The angle of repose, Carr’s compressibility index, bulk density, tapped density, and Hausner ratio was performed on the basis of the reported method.[10]

**Evaluation of CPG SDS**

The solubility study of CPG SD performed as per published method by Higuchi and Connors in 1965.[11] The percentage practical yield,[12] % drug content,[13] and in vitro drug dissolution study[14] were evaluated as per the referred methods. The SD is further characterized for FTIR analysis,[15] X-ray diffractometer (XRD),[16,17] and SEM studies[18] for drug compatibility studies.

**In vitro Drug Dissolution of CPG SD**

The dissolution of CPG from SDs prepared was investigated in 900 mL phosphate buffer (pH 6.8) using USP type II (paddle type) dissolution test apparatus at 50 rpm. A temperature of 37 ± 5°C maintained during the course

| Table 1: Preparation of CPG SD by solvent evaporation method (CPG1–CPG10) |
|-------------------|----------------|----------|
| Solid dispersion code | Ingredients quantity (mg) | Ratio |
| CPG1 | 75 | - | 1:0.5 |
| CPG2 | 75 | - | 1:1 |
| CPG3 | 75 | - | 1:2 |
| CPG4 | 75 | - | 1:3 |
| CPG5 | 75 | - | 1:4 |
| CPG6 | 5 | - | 1:0.5 |
| CPG7 | 75 | - | 1:1 |
| CPG8 | 75 | - | 1:2 |
| CPG9 | 75 | - | 1:3 |
| CPG10 | 75 | - | 1:4 |

| Table 2: Preparation of CPG SD by solvent evaporation method (CPG11–CPG20) |
|-------------------|----------------|----------|
| Solid dispersion code | Ingredients quantity (mg) | Ratio |
| CPG11 | 75 | 35 | - | 1:0.5 |
| CPG12 | 75 | 75 | - | 1:1 |
| CPG13 | 75 | 150 | - | 1:2 |
| CPG14 | 75 | 225 | - | 1:3 |
| CPG15 | 75 | 300 | - | 1:4 |
| CPG16 | 75 | - | 35 | 1:0.5 |
| CPG17 | 75 | - | 75 | 1:1 |
| CPG18 | 75 | - | 150 | 1:2 |
| CPG19 | 75 | - | 225 | 1:3 |
| CPG20 | 75 | - | 300 | 1:4 |
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Table 3: Preparation of CPG SD by fusion (melt) method (CPG21–CPG30)

| Solid dispersion code | Ingredients quantity (mg) | Labrafac PG | Pluronic F127 | Ratio |
|-----------------------|---------------------------|-------------|---------------|-------|
| CPG21                 | 75                        | -           | -             | 1:0.5 |
| CPG22                 | 75                        | -           | -             | 1:1   |
| CPG23                 | 75                        | -           | -             | 1:2   |
| CPG24                 | 75                        | -           | -             | 1:3   |
| CPG25                 | 75                        | -           | -             | 1:4   |
| CPG26                 | 75                        | 35          | -             | 1:0.5 |
| CPG27                 | 75                        | 75          | -             | 1:1   |
| CPG28                 | 75                        | 150         | -             | 1:2   |
| CPG29                 | 75                        | 225         | -             | 1:3   |
| CPG30                 | 75                        | 300         | -             | 1:4   |

Table 4: Preparation of CPG SD by fusion (melt) method (CPG31–CPG40)

| Solid dispersion code | Ingredients quantity (mg) | Labrafac PG | Pluronic F127 | Ratio |
|-----------------------|---------------------------|-------------|---------------|-------|
| CPG31                 | 75                        | 35          | -             | 1:0.5 |
| CPG32                 | 75                        | 75          | -             | 1:1   |
| CPG33                 | 75                        | 150         | -             | 1:2   |
| CPG34                 | 75                        | 225         | -             | 1:3   |
| CPG35                 | 75                        | 300         | -             | 1:4   |
| CPG36                 | 75                        | -           | 35            | 1:0.5 |
| CPG37                 | 75                        | -           | 75            | 1:1   |
| CPG38                 | 75                        | -           | 150           | 1:2   |
| CPG39                 | 75                        | -           | 225           | 1:3   |
| CPG40                 | 75                        | -           | 300           | 1:4   |

The solubility study results indicate that the drug solubility is higher in phosphate buffer is 0.146 mg/mL compared to water (0.118 mg/mL). The solubility of CPG was highest in polymer pluronic F127 in phosphate buffer pH 6.8 (3.79 mg/mL), which was almost 26 folds compared to drug solubility in 6.8 pH phosphate buffer (Fig. 1).

Stability Study

The CPG SD was sealed in 40 cc HDPE containers under controlled conditions in the stability chamber (Thermo Lab, India) as per ICH guidelines. Samples analyzed for 1, 2, and 3 months for % drug content and drug release rates.\(^{[21]}\)

RESULTS

Pre-Compression Evaluation Parameters

The angle of repose of all CPG SDs ranged between 21.13 and 26.45. The bulk density of all CPG SDs ranged from 0.5 to 0.59 g/cc. The tapped density of CPG1 to CPG40 was within the range of 0.61 to 0.69 g/cc. The compressibility index of CPG1 to CPG40 ranged from 9 to 14%. The Hausner’s ratio values of CPG1 to CPG40 in the range of 1.1 to 1.18%. These findings designated that all the formulations had good flow properties.

Fig. 1: Solubility studies of CPG in various polymers (*±SD) n = 3
Solubility Studies of CPG SD

The results indicate that the SD formulations comprising pluronic F127 (CPG40) exhibited highest solubility in both water and buffer. CPG40 containing drug:polymer in 1:4 ratio fusion (melt) exhibited solubility of 6.57 ± 0.04 mg/mL in buffer, which is 45 folds higher than pure drug solubility (0.146 ± 0.01 mg/mL). Higher concentrations of polymer lead to increase in drug solubility (Figs 2 and 3).

% Drug Content and % Practical Yield of CPG SD

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. The % drug content values of CPG1 to CPG40 are in the range of 94.23 ± 0.34% to 99.29 ± 0.34%. The formulations CPG40 exhibited maximum value of 99.29 ± 0.34%.

The % practical yield values of CPG1 to CPG40 are in the range of 97.89 ± 0.045 to 98.53 ± 0.046. The formulations CPG40 exhibited maximum value of 98.53 ± 0.046% (Tables 5 and 6).

In vitro Dissolution Studies

The dissolution profile of SD CPG40 prepared by fusion (melt) method using 1:4 ratio of drug:polymer (CPG:pluronic F127), showed maximum drug release of 99.14% in 60 minutes, and found to be the best-optimized formulation, when compared that with other formulations and pure drug (32.76%). Increased dissolution rates of SDs is attributed to more polymer concentration used for

Table 5: % drug content and % practical yield CPG SD (CPG1–CPG20)

| F. No. | Drug content (%) | % practical yield |
|--------|------------------|-------------------|
| CPG1   | 95.23 ± 0.63     | 93.45 ± 0.031     |
| CPG2   | 97.04 ± 0.06     | 97.89 ± 0.045     |
| CPG3   | 95.56 ± 0.14     | 91.21 ± 0.018     |
| CPG4   | 98.11 ± 1.01     | 95.67 ± 0.033     |
| CPG5   | 94.23 ± 0.83     | 94.78 ± 0.012     |
| CPG6   | 95.45 ± 0.31     | 97.35 ± 0.056     |
| CPG7   | 94.78 ± 0.49     | 95.15 ± 0.027     |
| CPG8   | 97.23 ± 0.51     | 92.32 ± 0.067     |
| CPG9   | 96.13 ± 0.56     | 98.56 ± 0.017     |
| CPG10  | 95.23 ± 0.24     | 94.25 ± 0.043     |
| CPG11  | 97.97 ± 0.21     | 98.54 ± 0.013     |
| CPG12  | 95.45 ± 0.76     | 95.15 ± 0.019     |
| CPG13  | 97.45 ± 0.48     | 96.56 ± 0.028     |
| CPG14  | 96.98 ± 0.23     | 93.25 ± 0.037     |
| CPG15  | 98.45 ± 0.36     | 95.59 ± 0.026     |
| CPG16  | 96.45 ± 0.69     | 94.45 ± 0.057     |
| CPG17  | 95.34 ± 0.35     | 93.43 ± 0.078     |
| CPG18  | 97.56 ± 0.23     | 98.23 ± 0.046     |
| CPG19  | 96.29 ± 0.34     | 95.61 ± 0.089     |
| CPG20  | 97.18 ± 0.81     | 97.34 ± 0.026     |

\( (±SD) \ n = 3 \)

Table 6: % drug content and % practical yield CPG SD (CPG21–CPG40)

| F. No. | Drug content (%) | % practical yield |
|--------|------------------|-------------------|
| CPG21  | 97.55 ± 0.72     | 98.15 ± 0.026     |
| CPG22  | 98.23 ± 0.18     | 96.82 ± 0.059     |
| CPG23  | 97.23 ± 0.45     | 95.81 ± 0.017     |
| CPG24  | 97.29 ± 1.17     | 97.57 ± 0.045     |
| CPG25  | 98.78 ± 0.31     | 96.8 ± 0.037      |
| CPG26  | 95.96 ± 0.48     | 95.53 ± 0.017     |
| CPG27  | 96.18 ± 0.88     | 94.26 ± 0.053     |
| CPG28  | 98.4 ± 0.22      | 98.18 ± 0.042     |
| CPG29  | 97.27 ± 0.12     | 96.56 ± 0.075     |
| CPG30  | 96.63 ± 0.58     | 95.78 ± 0.061     |
| CPG31  | 98.17 ± 0.28     | 98.14 ± 0.026     |
| CPG32  | 97.62 ± 0.76     | 96.44 ± 0.027     |
| CPG33  | 98.45 ± 0.5      | 97.61 ± 0.039     |
| CPG34  | 97.18 ± 0.68     | 96.25 ± 0.059     |
| CPG35  | 98.45 ± 0.36     | 95.63 ± 0.018     |
| CPG36  | 97.12 ± 0.48     | 96.17 ± 0.092     |
| CPG37  | 96.57 ± 0.39     | 94.21 ± 0.067     |
| CPG38  | 98.34 ± 0.61     | 96.79 ± 0.012     |
| CPG39  | 98.89 ± 0.56     | 98.03 ± 0.063     |
| CPG40  | 99.29 ± 0.34     | 98.53 ± 0.046     |

\( (±SD) \ n = 3 \)
formulating SDs; it is clearly observed that as the polymer carrier concentration was increased in the formulation the drug release increased accordingly (Figs 4 to 7).

**FTIR Studies**

The FTIR pure CPG (Fig. 8) showed a peak at 1,753 cm\(^{-1}\) (C=O stretching), 3,012 cm\(^{-1}\) (O-H stretching of the hydrogen sulfate), 3,414 cm\(^{-1}\), and 2,343 cm\(^{-1}\) (N-H stretching), 1,066, 1,176, and 1,220 cm\(^{-1}\) (C-O stretching). The FTIR spectra of CPG optimized formulation CPG40 (Fig. 9) showed similar prominent peaks pure drug, and these results indicate the lack of any chemical interactions among CPG and used excipients in the formulation.

**X-Ray Powder Diffraction (XRD)**

The CPG SDs XRD was carried out to find out the crystalline or amorphous states of the drug. The presence of distinct peaks in the spectrum of CPG confirms its crystalline form (Fig. 10A). A change in the diffraction patterns was seen. The pure drug showed sharp peaks, whereas the co-crystals did not show sharp peaks, which suggests that there is interaction. Inter-arrangement of molecules is
indicated by different peak locations of the co-crystals with respect to the pure drug, hence, it proves the formation of a new phase. The augmentation in dissolution rate of drug from CPG40 is due to a decline in the crystallinity of the drug (Fig. 10B).

**SEM Studies**

The SEM data indicates smooth surface and irregular shape of drug crystals (Fig. 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 the complete dispersion of the drug (Fig. 12).

**Stability Studies**

Optimized formulation CPG40 was loaded for stability studies at 40 ± 2°C/75 ± 5% RH, and found stable. There was no noteworthy variation in % drug content, and in vitro drug release was observed (Table 7).

**DISCUSSION**

The CPG SDs prepared by solvent evaporation and fusion melt method. A total of 40 formulations were prepared using different hydrophilic carrier polymers, and all the formulations exhibited better drug dissolution in comparison to pure drug. The solubility of CPG was found to be highest in polymer pluronic F127 in phosphate buffer pH 6.8, which was almost 26 folds and the same reflected in the formulation CPG40, which showed the highest release of 99.54% in 60 minutes containing 1:4 ratio of CPG:pluronic F127 prepared by fusion melt method and found to be the best-optimized formulation. Solubility of CPG was also increased by 45 folds in SD formulation CPG40 when compared to pure drug. XRD and SEM studies manifest that CPG40 is in amorphous form that achieved better dissolution, when compared to the pure drug. Therefore, from the results obtained after a thorough investigation, it was assessed that SD prepared by fusion melt method showed better drug release than the solvent evaporation method and resulted in enrichment of solubility, thereby, improvement in drug release of sparingly water-soluble drug CPG.

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