Preparation, Characterization and *In vitro* Evaluation of Solid Dispersion Formulation of Clopidogrel Using Hydrophilic Polymers

A.S.M. Monjur Al Hossain[1‡], Fahima Jannat Koly[2‡], Sajib Chandra Roy[2], Uttom Kumar[1], MD Hasanuzzaman[3] and Dipa Islam[4]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka Dhaka-1000, Bangladesh
[2]Department of Pharmacy, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh
[3]Institute of Glass and Ceramic Research and Testing, Bangladesh Council of Scientific and Industrial Research Dhaka-1205, Bangladesh
[4]Biomedical and Toxicological Research Institute, Bangladesh Council of Scientific and Industrial Research Dhaka-1205, Bangladesh

(Received: April 03, 2024; Accepted: October 10, 2024; Published (web): December 23, 2024)

ABSTRACT : Clopidogrel bisulfate is a BCS class II drug with low water solubility leading to problematic dissolution behavior for oral drug delivery. The solid dispersion method was used to investigate the improvement of the dissolution profile of clopidogrel. Solid dispersions of clopidogrel were formulated using two polymers, PEG 6000 and poloxamer 188, at varying ratios through physical mixing and solvent evaporation techniques. A low-cost UV-Vis spectroscopic analytical method was developed at a λ_{max} of 219 nm and validated following ICH guidelines. The dissolution of clopidogrel from solid dispersion improved significantly compared to pure drug, fitting most of the kinetics into the Korsmeyer-Peppas model. Comparisons showed that the binary solid dispersion formulation with clopidogrel: poloxmaer 188 at a ratio of 1:5 made via solvent evaporation method had the highest drug dissolution of 90.38% after 60 minutes, whereas the dissolution of pure clopidogrel was only about 66.67% in HCl media at pH 2. Characterization of prepared solid dispersions using FTIR, DSC, TGA and SEM confirmed the conversion of clopidogrel from crystalline to amorphous form.

Key words: Solid dispersion, clopidogrel bisulfate, validation, UV-spectroscopy, BCS class-II, physical characterization

INTRODUCTION

Cardiovascular events stand as the number one reason for mortality worldwide.[1] Pathophysiology of a class of patients involved in cardiovascular complications relies on the aggregation of elevated platelet levels and consequently formation of a thrombus. Therefore, to reduce the high rates of morbidity and mortality of such cardiovascular patients, safe and effective antiplatelet therapy is crucial.[2] There are many drugs available in the market to treat such cardiovascular events, but among them, clopidogrel stands out in terms of antiplatelet therapy. Clopidogrel bisulfate (CLOP) also known as methyl(2*S*)-2-(2-chlorophenyl)-2-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5-yl)acetate; sulfuric acid is a Biopharmaceutical Classification System (BCS) class II drug, which means, it has sufficient lipid solubility but inefficient aqueous solubility. CLOP is an irreversible P2Y12 receptor antagonist which selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, subsequently inhibiting ADP-mediated activation of glycoprotein GP IIb/IIIa complex, acting as an antiplatelet drug which is reliably used in reducing arteriosclerotic-related cardiovascular events.[3] CLOP, being a second-generation thienopyridine, is administered as an inactive pro-drug, which after oral

Correspondence to: A.S.M. Monjur Al Hossain
E-mail: monjur.shiplu@du.ac.bd
Mobile: 01756306309
‡Equal contribution

Dhaka Univ. J. Pharm. Sci. **23**(2): 123-134, 2024 (December)
DOI: https://doi.org/10.3329/dujps.v23i2.78570

administration, undergoes enzymatic activation by multiple cytochrome P450 (CYP) enzymes.

The oral route of drug delivery is considered the most convenient and acceptable route of drug administration.[4] Although most formulation scientists aim to utilize this preferred route for drug delivery, the challenges of converting poorly water-soluble, lipophilic drugs, responsible for low bioavailability due to decreased aqueous solubility in the gastrointestinal tract creates a backlog in choosing this route of delivery.[5] Solid dispersion (SD) technology is an approach to enhance the solubility or dissolution of poorly aqueous soluble drugs, especially BCS class II drugs that help to increase drug bioavailability and ultimately increase the pharmacological response of such drugs.[6] The term, 'solid dispersion' involves a combination of solid products, which are commonly a hydrophobic active ingredient or drug and a hydrophilic carrier system.[7] The carrier system is mainly held responsible for drug release in the form of fine colloidal particles from the matrix, by dissolving itself in aqueous media resulting in increased drug dissolution or aqueous solubility.[8] SD can be prepared by several methods such as physical mixing, solvent evaporation, melt-fusions, kneading methods, melt extrusions etc. These preparation methods help in enhancing solubility by reducing particle size, improving wettability, increasing particle porosity and converting crystalline drugs to amorphous form.[9] A number of hydrophilic carriers are reported in the literature, being used to enhance the dissolution of poorly soluble drugs. The most commonly used carriers are polyethylene glycols (PEGs), hydroxypropyl methylcellulose (HPMC), cyclodextrins, polymethyl methacrylates (PMMA), polyvinylpyrrolidones (PVP), poloxamer, gelucire, soluplus etc.

A number of SD formulations for CLOP have been reported in the literature. There were reports of clopidogrel solid dispersions with pluronic F127, poloxamer 407, labrafil PG, PEG 6000 and gelucire 50/13.[9] One study compared clopidogrel napadisilate-loaded solid dispersion (SD) with solid self-microemulsifying drug delivery system (solid SMEDDS). The SD system consisted of HPMC as a polymer and cremophor RH60 as a surfactant. In that study, SD showed excellent stability and bioavailability compared to solid SMEDDS and was recommended as an alternative to the clopidogrel-based oral formulation.[10] Another study used dextrose and cornstarch as carriers for CLOP SD leading to enhanced dissolution rate.[11] While one similar study evaluated the effect of PEG 4000, PEG 6000 and poloxamer 188 as carriers for CLOP SD formulations alongside neusilin as an adsorbent using solvent evaporation (SE) and hot-melt methods, the study concluded with CLOP and PEG 4000 with neusilin at a ratio of 1:2:1 using SE technique as the best formulation having 85.69% drug release in 30 min.[12] These studies indicate that clopidogrel solid dispersion formulations can become a cheaper and more bioavailable option for the broad market and hence, further validation of the methods was necessary. Thus, further investigations were planned using PEG 6000 and poloxamer 188 to evaluate their dissolution-enhancing potential as carriers with CLOP without any adsorbent or any disintegrant using more economical methods, that is, physical mixing and solvent evaporation to understand the dissolution behavior of CLOP SD preparations.

Therefore, the present study aims to enhance the oral bioavailability of CLOP using the SD method with two commercially available polymers PEG 6000 and poloxamer 188 and contribute to the launch of a CLOP solid dispersion formulation in the market providing low-cost and more effective medications to people.

MATERIALS AND METHODS

Chemicals and reagents. Clopidogrel bisulfate standard was obtained as a generous gift from Incepta Pharmaceuticals Ltd (Dhaka, Bangladesh). PEG 6000, poloxamer 188, methanol, ethanol and HCl were purchased from local sources of Sigma-Aldrich, India. All solvents were of high purity and analytical grade to avoid contamination.

Validation of UV-Vis spectrophotometric method. Validation of the analytical method was performed according to International Conference on Harmonization (ICH) guidelines. According to ICH, linearity range, limit of detection (LOD), limit of quantification (LOQ), specificity, accuracy, precision, robustness, ruggedness and an assay of the developed method were determined.[13]

Preparation of standard stock solution. Stock solution of clopidogrel bisulfate (CLOP) was prepared by taking 10 mg CLOP in a 100 volumetric flask and adding methanol up to the mark, sonicated to dissolve completely making a uniform solution. This was used to dilute further with methanol to prepare the concentrations ranging from 1-50 µg/ml for calibration curve preparation and validation of the method.

Formulation of clopidogrel bisulfate solid dispersion.

Physical mixing method (PM). Solid dispersion of CLOP was prepared as a binary formulation using the polymer, PEG 6000 and surfactant, poloxamer 188, separately. In the PM method, the measured amount of CLOP and PEG 6000 was taken according to the defined ratio in a mortar and pestle and pulverized for 15 minutes to obtain a uniform mixture of CLOP and PEG 6000.[9] The physical mixture was then sieved (mesh size 40) and transferred into vials and labeled according to its defined ratio. The vials were then stored in a desiccator to prevent moisture absorption. Similarly, physical mixing of CLOP and poloxamer 188 (POL) was obtained, sieved and then transferred into vials and labeled accordingly.

Solvent evaporation method (SE). In the SE method, the required amount of CLOP and PEG 6000 were taken according to compositions and dissolved completely using an adequate volume of methanol with continuous stirring. The solution was then heated using a hot plate stirrer at 55º C for about 15-20 minutes until the solvent evaporated. The formulation was further put inside a desiccator over silica making a vacuum chamber using a vacuum motor pump to dry the formulation completely. After complete drying, the formulation was scrapped off from the container, sieved and transferred to vials with labeling and stored in a desiccator for further use.[14]

Drug entrapment efficiency studies (DEE). The drug entrapment efficiency (DEE) was calculated using the following equation measuring absorbances[15] in triplicates at 219 nm:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} x100\%$$

***In vitro* release study.** The solubility of clopidogrel bisulfate in water (pH 7.4) is low whereas, in 0.1N HCl media, it is freely soluble (694.5 mg/ml). [16-17] Hence, 0.1N HCl (pH 2) was chosen for the *in vitro* dissolution studies for maintaining the sink conditions. The dissolution of pure clopidogrel bisulfate (pure CLOP) and prepared SD formulations were performed in triplicates taking identical amounts of each sample in an independent study to confirm reproducibility. The data from dissolution studies of the formulations were compared with pure CLOP to evaluate *in vitro* release behavior in 0.1N HCl media (pH 2) at a temperature of 37 ± 0.5ºC.[18] An USP dissolution apparatus type II (rotating paddle type) was used at 50 rpm with glass vessels containing 900 ml media volume. The dissolution study was conducted for an hour with sampling at every 10 minutes to evaluate the release profile expressed as cumulative percent release vs time (min) graphs.

Characterization of prepared solid dispersions. FTIR spectrophotometry (Perkin Elmer, UK) was performed by scanning from 4000 cm^{-1} to 400 cm^{-1} wave number with a resolution of 1 cm^{-1} to attain the desired spectrums. Scanning electron microscopy (SEM) (JSM-7610) was conducted using a 15 kv acceleration voltage. The samples were prepared by mounting them on an aluminium stub using carbon tape. The platinum coating was used to make the samples electrically conducting. The DSC

and TGA of pure CLOP, polymers and selected formulations were performed using NETZSCH (Germany). Simultaneous thermal analysis (STA) instrument was employed to perform both DSC and TGA simultaneously. About 5-15 mg sample was used and scanned at 10 K/min using nitrogen purge from 30°C to 250°C.[19]

Analysis of drug kinetics. Linear regression was used to delineate the drug release kinetics of the solid dispersion formulations using the models: zero-order kinetics (cumulative % release vs time), first-order kinetics (log cumulative % release vs time), Higuchi's model (cumulative % release vs square root of time), Hixon-Crowell's model (cube root of % drug remaining vs time) and Korsmeyer-Peppas model (log cumulative % release vs log time).

RESULTS AND DISCUSSION

Validation of analytical method. The ICH guidelines were strictly followed for method validation.[20]

Linearity. The range was determined to be 8 µg/ml- 50 µg/ml (Table 1) with a correlation coefficient, i.e. R^2 of 0.99 for linearity which is under the acceptable limits.[20]

Sensitivity. The LOD (limit of detection) and LOQ (limit of quantification) values were 2.672 µg/ml and 8.0978 µg/ml, respectively (Table 1).

Table 1. Calibration curve points including range, LOD and LOQ of the proposed method for the estimation of clopidogrel bisulfate (CLOP).

SI. No.	Parameters	Values
1.	Absorption maxima	219 nm
2.	Beer's law limit/ range	8-50 µg/ml
3.	Regression equation	y = 0.0343x + 0.3214
4.	Slope, m	0.03
5.	Y-Intercept	0.32
6.	Correlation coefficient	0.99
7.	Standard error of intercept	0.01
8.	Standard deviation of intercept	0.03
9.	Limit of detection (LOD)	2.67 µg/ml
10.	Limit of quantification (LOQ)	8.10 µg/ml

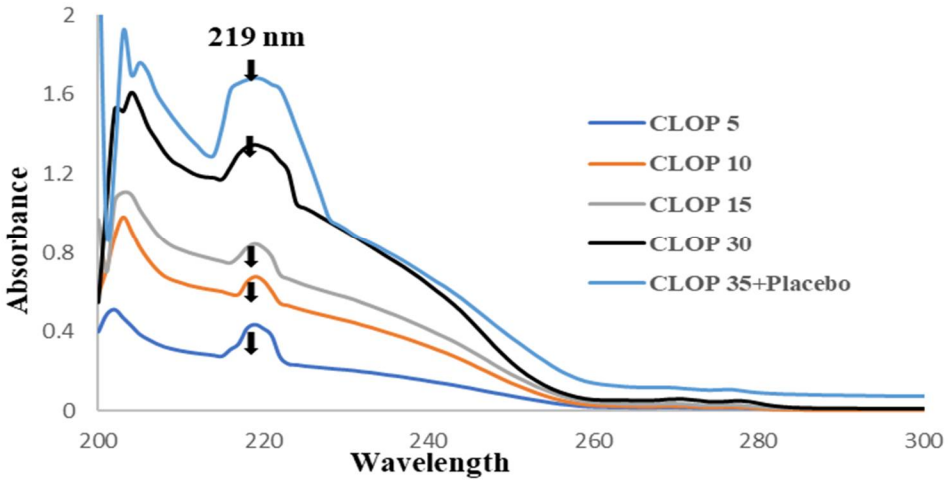

Figure 1. Determination of λ_{max} and specificity of CLOP.

Specificity. The overlay graphs of different concentrations of CLOP formed the same peaks, indicating the specificity of the method. Again, as no interfering peaks arose in the graph of CLOP mixed with excipients, this means that the method has no interference from the excipients used in the formulation rendering the UV method to be specific for the purpose (Figure 1).

Accuracy. The % RSD for the accuracy of the method was 1.323, which was under the limit of 2% and thus acceptable.[21]

Precision. Precision was calculated for both repeatability and inter-day precision and obtained acceptable % RSD values of 0.152 and 0.834, respectively. The acceptable % RSD value for method validation according to ICH guidelines is equal to or below 2.[21]

Robustness and Ruggedness. All the % RSD values for robustness and ruggedness testing were under the acceptable limit of less than 2% by changing between two temperatures and interchanging analysts.[22] As the method passed the robustness and ruggedness tests, it infers the method's capacity to withstand minor changes in method conditions.

Assay. CLOP tablets (75 mg) commercialized by a local pharmaceutical manufacturer were collected and assayed. The recovery was found to be 99.64% with an % RSD of 0.225. This confirms the suitability of the developed UV method for the quantitation of CLOP as a pure drug and in drug product as well.

Formulation design. Binary formulations of CLOP were prepared using pure CLOP and one of two excipients PEG 6000 or poloxamer 188. The formulations were designed to keep the market oral dose of CLOP intact (75 mg) and mix with several ratios of the excipients to evaluate the effect of increasing polymer on CLOP dissolution profile (Table 2).[23, 24]

Table 2. Different binary compositions of CLOP solid dispersions.

Method	Pure drug	Polymer	Drug: Polymer	Code
Physical Mixture	75 mg	PEG 6000	1:1	PG1
			1:2	PG2
			1:5	PG3
	75 mg	Poloxamer 188	1:1	PX1
			1:2	PX2
			1:5	PX3
Solvent Evaporation	75 mg	PEG 6000	1:1	SG1
			1:2	SG2
			1:5	SG3
	75 mg	Poloxamer188	1:1	SX1
			1:2	SX2
			1:5	SX3

Evaluation of prepared clopidogrel bisulfate (CLOP) solid dispersions (SD).

Drug entrapment efficiency. The drug entrapment efficiency was between the ranges of 82.53% to 98.58%. The drug entrapment efficiency increased with the increase in polymeric ratio.[25] The highest drug entrapment efficiency was gained from solvent evaporation method. Solid dispersion with poloxamer 188 made via solvent evaporation method had the highest drug entrapment efficiency at an extent of 98.58% (SX3).

***In vitro* dissolution studies.** The dissolution of pure CLOP was compared with the dissolution profiles of solid dispersion formulations in 0.1N HCl media at pH 2.0. The dissolution of the prepared solid dispersions increased significantly compared to pure CLOP (Figure 2). The highest dissolution was observed for SX3 (SE CLOP: POL 188 1:5) at 90.38% after 60 minutes whereas, the dissolution of pure CLOP was only 66.67% (Figure 3). The dissolution was increased at an extent 23.71% in solid dispersion formulations prepared using

poloxamer 188 at the drug: polymer ratio of 1:5 by the solvent evaporation method. The second highest dissolution rate was obtained for PX3 (PM CLOP: POL 188 1:5) at 82.66% where the same drug to poloxamer ratio (1:5) was used made prepared by physical mixing method. Though polymer plays a vital role in enhancing the dissolution profile of clopidogrel, it seems that the solvent evaporation method adds some extra benefits over physical mixing in enhancing the dissolution profile by solid dispersion technique.

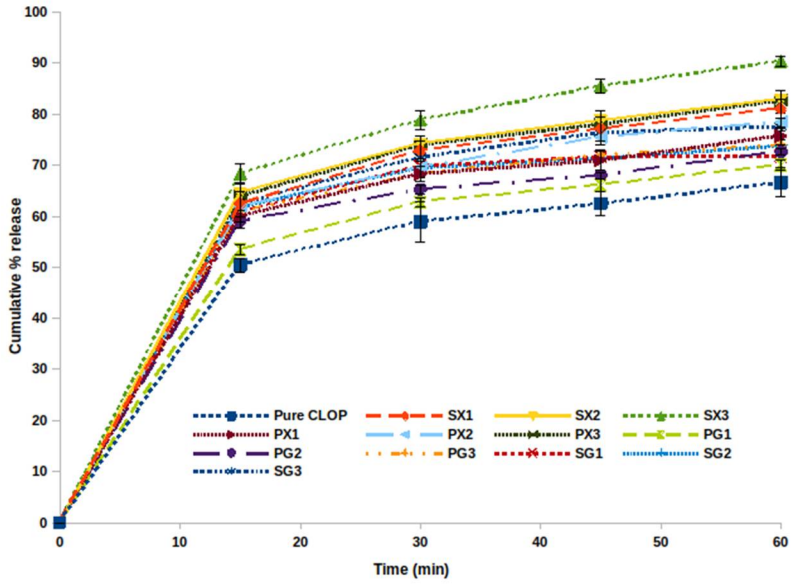

Figure 2. Cumulative percent release vs time graph for pure CLOP, and PM and SE solid dispersion formulations of CLOP: POL 188 and CLOP: PEG 6000 at ratios of 1:1, 1:2 and 1:5 (n=3).

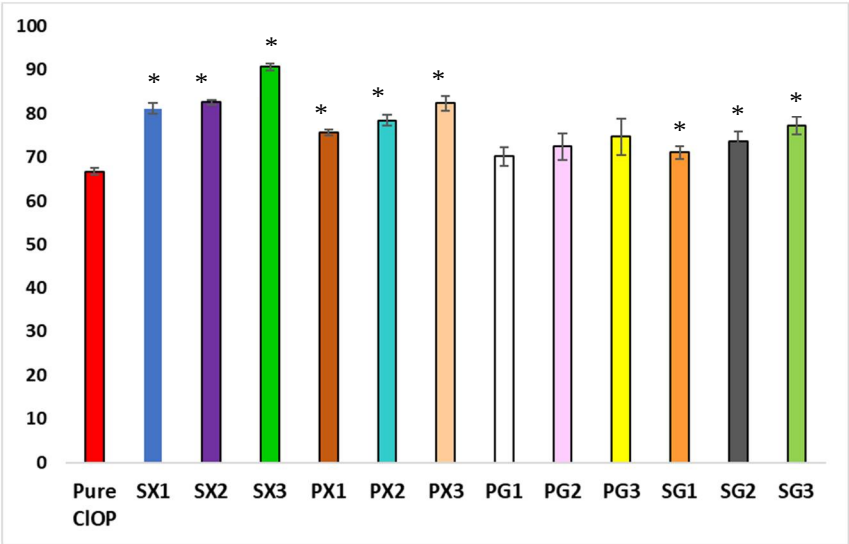

Figure 3. Cumulative percentage of drug release after 60 minutes for pure CLOP, and SE and PM formulations of CLOP: POL 188 and CLOP: PEG 6000 at ratios of 1:1, 1:2 and 1:5 (n=3, t-test, *p < 0.05).

Two-tailed unpaired t-tests were performed using GraphPad Prism t-test calculator comparing the dissolution of the formulations with the dissolution of pure CLOP in HCl media at 30 mins and 60 mins

respectively. The statistical significance in terms of p value at 60 mins has been demonstrated in figure 3. It is evident from figure 3 that all the formulations except for the physical mixtures of clopidogrel bisulfate with PEG 6000 (PG1, PG2, PG3) had significant dissolution rates at 60 mins compared to its pure form where p values were less than 0.05. Similarly, dissolutions of pure CLOP with the formulations were compared at 30 mins to observe its statistical significance using p values. It was observed that all the formulations except for PG1 and PG2 had a significant rise in dissolution at 30 mins compared to pure CLOP with p values less than 0.05 in two-tailed unpaired t-test.

Difference factor (f1) and similarity factor (f2) were calculated between pure CLOP and the highest dissolution formulation SX3 to statistically compare if the formulation SX3 was truly more efficient than pure CLOP alone. The difference factor (f1) came out to be 35.31 and the similarity factor (f2) resulted in 36.06. It is stated that the accepted range for equivalence in terms of difference factor (f1) is 0-15 and of similarity factor f2 is 50-100.[26] As both the difference factor f1 (35.51) and similarity factor f2 (36.06) don't comply with the given range of equivalence, we can claim statistically that the difference of dissolution between pure CLOP and solid dispersion formulation of CLOP with poloxamer 188 (SX3) is statistically significant and that the dissolution increases significantly for SX3 compared to pure CLOP.

The dissolution of CLOP solid dispersions with poloxamer increased with the increase in polymeric ratio prepared by both physical mixing and solvent evaporation methods. Though lower in extent compared to poloxamer, an increase in dissolution was also observed in formulations prepared with PEG 6000 using physical mixing (PM) and solvent evaporation (SE) methods (Figure 3). In the case of PEG 6000, the dissolution of formulations prepared by solvent evaporation technique was higher compared to that with formulations made by physical mixing, as the case also observed for solid dispersions with poloxamer. However, in both cases, the dissolution gradually increased with increasing the polymer content. The use of a hydrophilic carrier resulted in better water absorption compared to pure CLOP API where no carrier was used. Hydrophilic carriers, like poloxamer 188 and PEG 6000, increase drug-water interaction resulting in better solubility and increased dissolution rate. All data suggested that the solid dispersions of CLOP using PEG 6000 and poloxamer 188 are suitable for enhancing the dissolution profile of the drug and thus capable of incorporating into CLOP immediate-release formulations.

Characterization of prepared solid dispersions.

FTIR spectroscopy. The FTIR graph of the binary SDs of clopidogrel with poloxamer 188 prepared by both physical mixing and solvent evaporation methods showed congruent characteristic peaks both in the regions of pure CLOP and polymer (Figure 4a). Sharp peaks were observed at 2883.94 cm^{-1}, 1751.9 cm^{-1}, 1339.17 cm^{-1} and 1100.38 cm^{-1} for pure CLOP, poloxamer 188 and all PM and SE binary solid dispersions (Figure 4a). Similarly, sharp peaks at 2883.94 cm^{-1}, 1465.94 cm^{-1}, 1342.12 cm^{-1}, 1103.33 cm^{-1} and 840.957 cm^{-1} were observed for pure CLOP, PEG 6000 and all PM and SE formulations of clopidogrel bisulfate and PEG 6000 binary SDs (Figure 4b). No additional peaks beyond the peaks of pure CLOP and polymers (poloxamer 188 and PEG 6000) were observed in the formulations which determines that no chemical interaction or degradation happened between the API and polymers.[27] The characteristic peaks of pure CLOP observed were at 3122.73 cm^{-1} (aromatic C-H vibrations due to chlorophenyl ring), a very high-intensity peak at 1751.9 cm^{-1} (C=O stretching vibrations due to ester functional group), 1439.41 cm^{-1} (due to N-H deformations), 1185.88 cm^{-1} (due to C-H in plane motion), 1153.45 cm^{-1} (due to the rocking of CH_3 bond).[19] Peaks observed from prepared SDs indicate that a strong physical interaction was present between CLOP and the polymers used. A strong physical interaction between the API and polymers in prepared SDs observed from small shifts in peaks

indicate intermolecular interactions which ultimately reduce the level of crystallinity of pure CLOP, improving the dissolution of the BCS class II drug. This assures that the polymers used will play a very essential role in stabilizing the prepared amorphous form of clopidogrel bisulfate in the SD matrix.

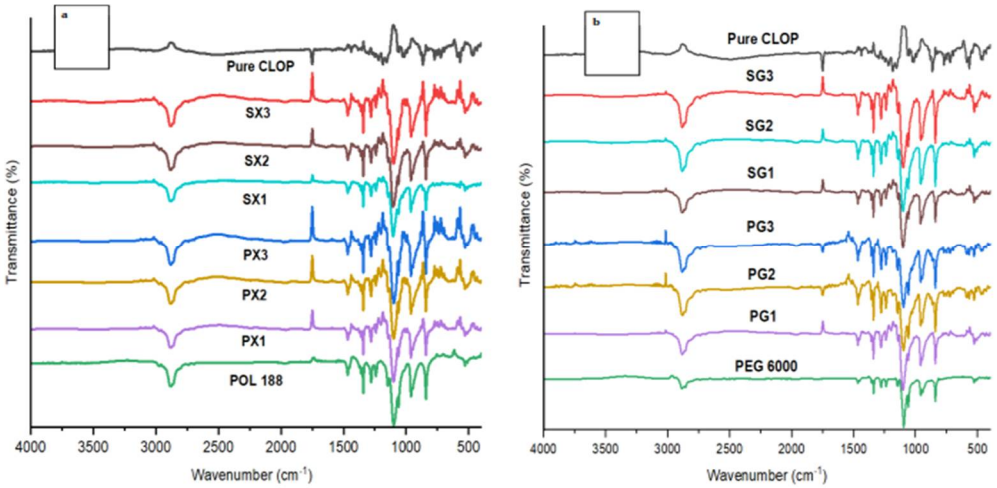

Figure 4. (a) FTIR spectra overlay of pure CLOP, poloxamer 188 (POL 188) and SE and PM solid dispersion formulations of CLOP: POL188. (b) FTIR spectra overlay of pure CLOP, PEG 6000 and PM and SE solid dispersion formulations of CLOP: PEG 6000.

Scanning electron microscopy (SEM). SEM was used to analyze the surface morphology of prepared SDs. These were then compared with pure CLOP and the polymer individually. SEM was performed only for the formulations with the highest dissolution values (SX3 and PX3). From the SEM images, it was observed that pure CLOP was present as spheres having a size of about 100 µm in crystalline form and poloxamer 188 was present as crystalline spheres of about 200 µm having very smooth surfaces (Figure 5). The solid dispersion SX3 (SE CLOP: POL 188 1:5) prepared by solvent evaporation method had a size diameter ranging from 500-1000 µm whereas, PX3 prepared by physical mixing of CLOP with poloxamer 188 had a diameter ranging from 200-500 µm. Both solid dispersions appeared to have very different, irregular and non-uniform shapes, with no similar morphological and surface properties to the pure drug and polymer. The surface of prepared solid dispersions was highly porous compared to the smooth surface of POL 188. This irregular shape, rough contour and porous nature of the surfaces of the SDs resulting in enhanced effective surface area is responsible for the higher dissolution rate that was observed in the dissolution studies.[27]

Differential scanning calorimetry (DSC). The DSC of pure CLOP demonstrated endothermic graphs with a sharp peak at 180.1°C at 68.7 J/g, and a minor peak at 209.4°C at 20.1 J/g enthalpy, indicating degradation temperature (Figure 6). The peaks and enthalpy gained confirm that form II of pure CLOP was used for formulation. The DSC thermogram of the polymer poloxamer 188 exhibited an endothermic peak at 59.8°C with an enthalpy of 136.5J/g (Figure 6). The DSC of the formulation SX3 (SE CLOP: POL 188 1:5) showed a single peak at 60°C with 111.4J/g enthalpy and that for formulation PX3 (PM CLOP: POL 188 1:5) exhibited a single sharp peak at 57.1°C with 126.1 J/g enthalpy (Figure 6). Thermograms of prepared solid dispersions were very close to the peak of POL 188 (59.8°C), with no presence of the sharp peak for pure CLOP (180.1°C) which strongly suggests that either CLOP is completely soluble in the liquid phase of the polymer used or the crystalline nature of pure CLOP is completely absent.[12]

Thermogravimetric analysis (TGA). The mass loss of the sample was represented as a function of temperature using TGA in a DTG vs temperature

graph (Figure 7). TGA curve for pure CLOP exhibited mass loss corresponding to the first endothermic peak of DSC which continued until 240°C (Figure 7), whereas the mass losses of prepared PM and SE solid dispersions (PX3 and SX3, respectively) were presented within a small peak at around 60°C, which was very similar to that the thermogram of poloxamer 188. The thermograms of the prepared formulations remained relatively stable without any loss of mass up to around 200°C where a slight decline in mass was observed, whereas an exponential decline was observed for pure CLOP at the same region probably due to degradation. The differential thermal analysis data proved that an amorphous form of the BCS class II drug was achieved, which ultimately led to an increased drug dissolution and oral bioavailability.[28]

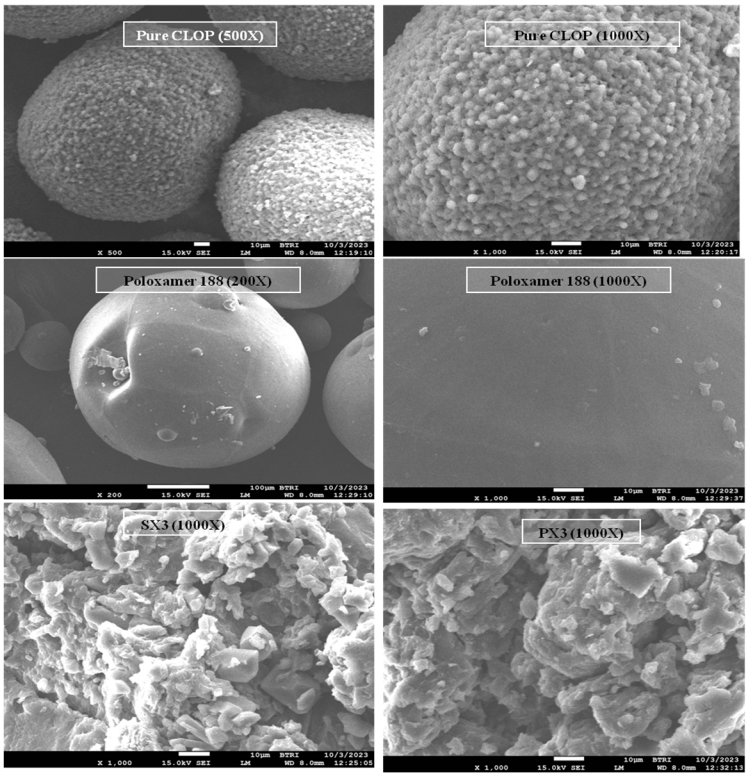

Figure 5. Morphological observation of the surface of pure CLOP, poloxamer 188 and solid dispersions SX3 (SE CLOP: POL 188 1:5) and PX3 (PM CLOP: POL 188 1:5) at 1000X magnification.

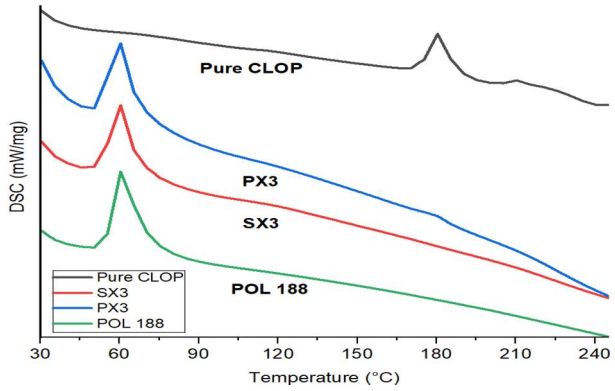

Figure 6. Differential scanning calorimetry (DSC) thermograms of pure CLOP, POL 188 and solid dispersion formulations of clopidogrel PX3 (PM CLOP: POL 188 1:5) and SX3 (SE CLOP: POL 188 1:5).

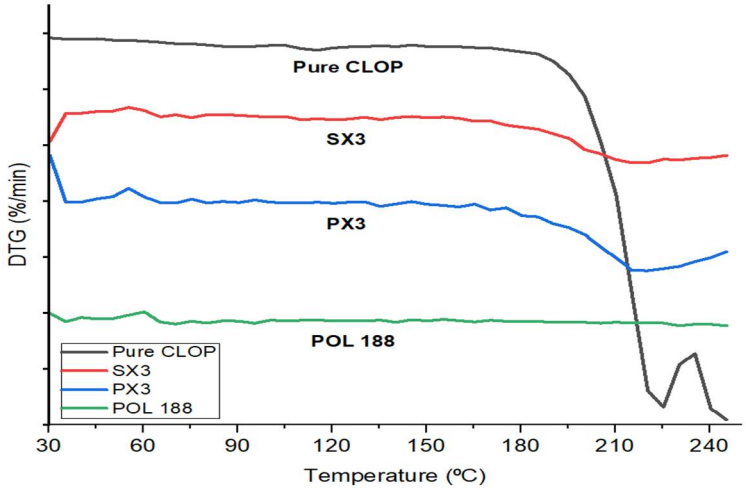

Figure 7. Differential thermogravimetric analysis (DTG) for pure CLOP, POL 188 and solid dispersion formulations of clopidogrel PX3 (PM CLOP: POL 188 1:5) and SX3 (SE CLOP: POL 188 1:5).

Table 3. Kinetic modelling for dissolution profiles of the pure clopidogrel and its solid dispersion formulations.

Formulation	Zero order model		First order model		Higuchi model		Hixon-Crowell model		Korsmeyer-Peppas	
	K_0	R^2	K_1	R^2	K_h	R^2	K_{hx}	R^2	n	R^2
Pure CLOP	0.345	0.956	0.006	0.939	4.072	0.984	-0.008	0.945	0.196	0.993
PX1	0.332	0.953	0.005	0.940	3.907	0.977	-0.006	0.945	0.162	0.985
PX2	0.365	0.977	0.005	0.965	4.287	0.997	-0.007	0.969	0.171	0.999
PX3	0.402	0.949	0.006	0.932	4.745	0.981	-0.008	0.938	0.183	0.992
PG1	0.353	0.938	0.006	0.919	4.176	0.974	-0.008	0.926	0.191	0.988
PG2	0.289	0.979	0.004	0.972	3.358	0.985	-0.006	0.975	0.142	0.986
PG3	0.284	0.926	0.004	0.913	3.378	0.97	-0.006	0.918	0.141	0.99
SX1	0.402	0.937	0.006	0.918	4.766	0.975	-0.008	0.924	0.188	0.99
SG1	0.231	0.734	0.004	0.725	2.828	0.815	-0.005	0.728	0.124	0.88
SG2	0.252	0.886	0.004	0.872	3.008	0.937	-0.005	0.877	0.126	0.966
SG3	0.334	0.888	0.005	0.874	3.998	0.943	-0.007	0.879	0.162	0.973

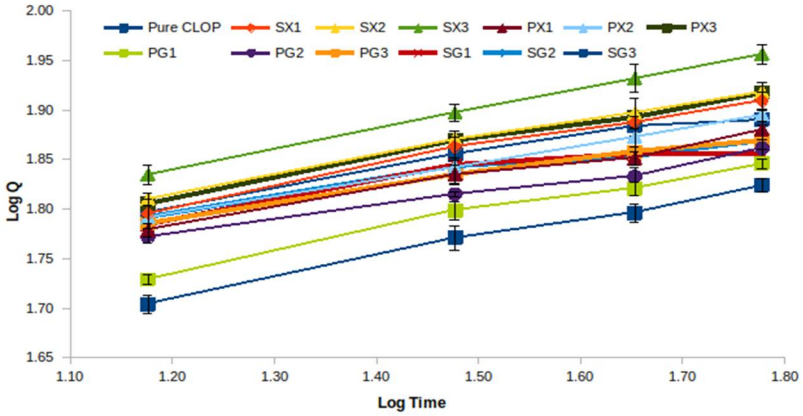

Figure 8. Korsmeyer-Peppas kinetic model (Log cumulative percent drug release vs log time) for pure CLOP and SE and PM solid dispersion formulations of both CLOP: POL 188 and CLOP: PEG 6000 at ratios of 1:1, 1:2 and 1:5 (n=3).

Analysis of drug release kinetics. The dissolution results of all the formulations were fitted using the zero order, first order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas models. All the models gave satisfactory correlation coefficient values (R^2) for the prepared clopidogrel solid dispersion formulations as well as for pure drug (Table 3).

Korsmeyer-Peppas model was developed to explain drug release from polymeric systems using an empirical equation to describe both Fickian and non-Fickian kinetics from either swellable or non-swellable polymeric delivery systems. The drug release data was fitted in the equation: $Q_t/Q_\infty = K_k t^n$, where Q_t/Q_∞ is the fraction of drug released at time t and K stands for the rate constant which includes the structural and geometrical characteristics of the delivery system (Figure 8). Here, 'n' is the release exponent which determines the mechanism of drug transport from the polymer.[29] A value of n less than or equal to 0.45 determines Fickian diffusion (Class I diffusional) where non-swellable matrix diffusion acts as the drug release mechanism. In this study, release exponents turned out to be Fickian diffusion.

CONCLUSION

The study involves the development and characterization of solid dispersion of a BCS class II drug, clopidogrel bisulfate to enhance its aqueous solubility. A UV-Vis spectroscopic analytical method for clopidogrel was also developed and validated according to ICH guidelines to be used for all quantitation purposes. Solid dispersion is a relatively economical and unambiguous formulation technology compared to other novel drug delivery systems which can be used to resolve the complex problem regarding the solubility of BCS class II drugs. A careful and validated selection of carrier matrix and the use of its appropriate ratio is vital for successful formulation development. In this study, compatibility and efficacy between two polymers, PEG 6000 and poloxamer 188, were investigated in terms of carrier matrix for the development of solid dispersion for clopidogrel. Poloxamer 188 was found to be superior to PEG 6000 in enhancing the dissolution profile of clopidogrel. Interestingly, the manufacturing methods of solid dispersion also play a significant role in carrier polymer efficacy in enhancing the solubility of clopidogrel. Poloxamer 188 showed better results with a higher dissolution profile of solid dispersion formulation when prepared by solvent evaporation method compared to simple physical mixing. The characterization of the developed formulation using FTIR, SEM, DSC and TGA confirmed a conversion of the crystalline active ingredient clopidogrel into an amorphous form, which is supposed to be mainly responsible for the improvement of drug dissolution.

ACKNOWLEDGEMENT

The author is thankful to the Ministry of Science and Technology (MoST) for funding the project and also grateful to the Department of Pharmaceutical Technology, University of Dhaka and Bangladesh Council of Scientific and Industrial Research (BCSIR) where the research project has been carried out.

CONFLICT OF INTEREST

The authors declare 'no conflict of interest'.

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