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UTILIZATION OF DISSOLUTION RATE IMPROVEMENT EFFECT OF DIFFERENT HYDROPHILIC POLYMERS ON ANTIPLATELET DRUG (CILOSTAZOL) VIA SOLID DISPERSION TECHNIQUE

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ABSTRACT
Solid dispersions of a poorly water-soluble drug cilostazol in poloxamer188, polyvinylpyrrolidone (PVP-K25) and PEG 4000 were prepared by solvent evaporation technique. Physicochemical properties of the prepared systems were characterized by in vitro dissolution, powder X-ray diffraction, fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and scanning electron microscope (SEM). Cilostazol was found amorphously dispersed in solid dispersion system with the drug to poloxamer188 weight ratio of 1:5. FT-IR spectra data indicated that there was no interaction between cilostazol and the polymer. Solid dispersion prepared by the mentioned method showed an improvement of cilostazol dissolution. By comparison, solid dispersions of drug with Poloxamer188 showed distinctly superior performance in that cilostazol dissolved 67.6 ±3.1% within 120 min and the dissolution rate was at least 15 times faster than pure cilostazol. Poloxamer188 in 1:5 w/w drug/ polymer ratio could provide an effective pharmaceutical formulation method to improve the bioavailability of poorly water-soluble cilostazol.

KEYWORDS: Cilostazol, Solid dispersion technique, Poloxamer188, Dissolution rate.

INTRODUCTION
Pharmaceutical solid dispersion (SD) is an important method used to enhance the dissolution rate of poorly water soluble pharmaceutically active ingredients.[1] SD has been used widely to improve the dissolution of biopharmaceutical classification system class II drugs (BCS).[2] The enhanced dissolution rates of SD are due to reduction in the drug particle size or conversion of the drug from the crystalline to the amorphous state and the consequent increase in the surface area[3], and improved wettability resulting from intimate contact with a hydrophilic carrier.[4] The formation of a higher energy solid-state form (amorphous state) of the drug which doesn't require energy to break up the crystal lattice of a drug during dissolution process may also improve the drug dissolution rate.[5] Solvent evaporation method has been utilized to prepare SDs which involves dissolution of both drug and carrier in a volatile solvent. The solvent was allowed to evaporate which resulted in formation of amorphous dispersion of the drug in the hydrophilic carrier.[6][7]

Peripheral arterial disease is common in ~ twenty percent of the general population aged over 70 years.[8] Cramping pain in the legs or buttocks with muscle exertion occurs due to the weak blood circulation in the arteries of the patient's legs.[9] Cilostazol "Fig. 1" (6-[4-(1-cyclohexyl-1H-tetrazol- 5-yl) butoxy]-3, 4-dihydro-2(1H)-quinolinone) is a cAMP phosphodiesterase III inhibitor was used for patients with intermittent claudication. Cilostazol increases cAMP in platelets and blood vessels, resulting in inhibition of platelet aggregation and vasodilation.[10]

Cilostazol is also effective in coronary artery restenosis prevention.[11] Cilostazol was marketed as oral tablet under the trade name Pletal ®. The recommended dosage is 100 mg twice per day. Cilostazol solubility in water is 3.34µg/ml.[12] According to BCS, cilostazol belongs to class II based with poor solubility and high permeability. Therefore, improving cilostazol dissolution would enhance its bioavailability.[12] Therefore, the present work aimed to improve dissolution rate of cilostazol using economical and simple SD technique.

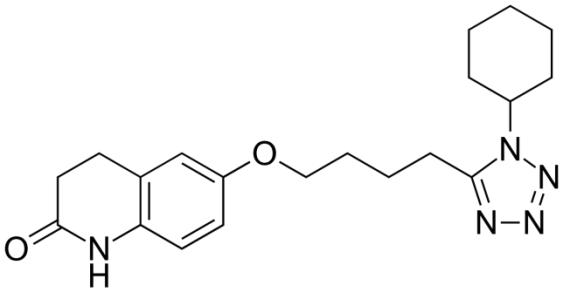

Figure 1: The chemical structure of cilostazol.

MATERIAL AND METHODS

Materials

Cilostazol (CLZ) was kindly provided by SEDICO Pharmaceuticals, Egypt. Poloxamer188, Polyvinyl pyrrolidone-K25 (PVP-K25), and PEG 4000 were purchased from FLUKA Chemika, Switzerland. Methanol was purchased from ELNASR Pharmaceutical chemicals Co., Egypt. Potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate were kindely provided by NICE Chemicals, India. All other chemicals are of analytical grades.

Preparation of cilostazol SDs via solvent evaporation technique

Different hydrophilic carriers were employed for preparing cilostazol SDs. These polymers are poloxamer188, PVP-K25 and PEG 4000. SDs were prepared by solvent evaporation method. Three different ratios of drug and polymer were prepared (1:1, 1:3, and 1:5 w/w). The calculated amounts of cilostazol and the polymers were dissolved in a minimum amount of methanol. The solvent was allowed to evaporate at room temperature. The resultant residue was kept for 48 hours in a desiccator at room temperature. The residue was ground, sieved and kept for further investigations.[13]

Preparation of physical mixtures

Physical mixtures were prepared by efficient blending of cilostazol with poloxamer 188 at ratios 1:1, 1:3, and 1:5 w/w using porcelain mortar and a pestle. The physical mixtures were sieved and stored in a well closed brown glass bottle for further investigations.[13]

Methods of analysis

Cilostazol was identified by using UV spectrophotometric technique in phosphate buffer pH 6.8 at wavelength 258.5 nm.

Dissolution study

The dissolution rate of unprocessed cilostazol was determined by the USP Class II apparatus at 37°C and a rotating speed of 50 rpm. Cilostazol (50 mg), physical mixture and solid dispersions equivalent to 50 mg of cilostazol were placed into a vessel containing 900 ml of phosphate buffer pH 6.8 as dissolution medium.[14] Dissolution samples (5ml) were withdrawn through volumetric pipette, using cotton plug as a filter at 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes and the samples were replaced by the same amount of phosphate buffer pH 6.8 at the same temperature. The concentration of cilostazol was determined spectrophotometrically at 258.5 nm. The measurement was performed in triplicate. The percent released of cilostazol in each formulation was calculated and plotted versus time.[15]

Fourier Transform Infra-Red spectroscopy (FT-IR)

The interaction between cilostazol and the polymers was investigated by FT-IR spectroscopy. FT-IR spectra were obtained by mixing pure drug, physical mixture and SDs with dry potassium bromide using shimadzu SSP-CoA IR compression machine and Infrared spectrophotometer, IR-476 (Shimadzu Co., Japan). The samples were scanned from 4000 to 400 cm^{-1}.[16]

Differential scanning calorimetry (DSC)

Thermal analysis was carried out using DSC unit (DSC-60, Shimadzu, Kyoto, Japan). Indium was used to calibrate the temperature scale and enthalpy response. Samples of 5 mg of cilostazol, poloxamer, SD or physical mixture were charged into appropriate aluminum pans sealed with lids. DSC thermograms of the samples were assessed under nitrogen at 10 °C/min between 25 and 300°C.[17]

Powder X-ray diffraction (PXRD)

The x-ray diffraction patterns for different samples were determined using the Philips 1710 automated diffractometer. The relation was provided by CuKα radiation operating at 40 KV and current of 30 mA (λKα = 1.5418 Å). The system was calibrated using standard polycrystalline silicon. The differential patterns were achieved using continuous scan mode with 2θ ranging from 4^o to 60^o. The output data achieved were represented by 2θ, d Å, intensities are determined via the microprocessor of the PW /1710.[18]

Scanning electron microscopy (SEM)

The morphology of the samples was examined by SEM (S4800, Hitachi, Japan). The samples were mounted onto an aluminum stub and sputter coated with platinum particles for 60 seconds in an argon atmosphere.[19]

RESULTS AND DISCUSION

Preparation of cilostazol SDs and physical mixtures

The different cilostazol SDs and physical mixtures with different polymers are illustrated in table 1. The trials (Data not supplied) revealed that drug: polymers with ratios namely 1:1, 1:3, and 1:5 w/w were the most ratios effective in enhancement of cilostazol dissolution rate.

Table 1: The Compositions of The Prepared Binary Physical Mixture and Solid Dispersion Systems.

Formula	Cilostazol	Poloxamer 188	PVP-K25	PEG 4000
Control	1	0	0	0
A1	1	1	0	0
A2	1	3	0	0
A3	1	5	0	0
B1	1	0	1	0
B2	1	0	3	0
B3	1	0	5	0
C1	1	0	0	1
C2	1	0	0	3
C3	1	0	0	5
D1	1	5	0	0

In Vitro Dissolution Study

Dissolution profiles of cilostazol, physical mixture and solid dispersions in phosphate buffer pH 6.8 are shown in "table 2 and Fig. 2 - 5". Amorphous form of cilostazol in the prepared solid dispersions shows significant increased dissolution rate compared to pure cilostazol. The amount dissolved in 120 minutes was 67.6 ± 3.12% for solid dispersion with poloxamer188 (1:5 w/w), whereas it was only 20.8 ± 2.4% and 22.17 ± 1.5 % for pure cilostazol and physical mixture with poloxamer188 (1:5 w/w), respectively. All solid dispersions and physical mixture with poloxamer 188 (1:5 w/w) showed improved dissolution rate over the pure cilostazol. The enhancement in dissolution rate of cilostazol from the solid dispersions might be attributed to the following factors such as a reduction in cilostazol particle size, increasing in the surface area, reducing crystallinity and increasing in the solubility of the drug in the presence of the poloxamer188, PVP-K25, and PEG 4000. Similar observations have been reported for solid dispersions of naproxen in polyethylene glycols. The results showed that, as the concentration of the used polymers increased, the dissolution rate of cilostazol was increased until 1:5 w/w drug to polymers ratio.[20] Poloxamer188 solid dispersion showed significant an increasing in cilostazol dissolution rate comparing with PVP-K25 and PEG 4000. Also, the physical mixture of cilostazol with poloxamer188 in 1:5 w/w drug to polymer was showed higher dissolution rate than the pure drug.[21]

Regarding the results of the in-vitro dissolution of cilostazol from the prepared SDs with PVP-K25 in different ratios, it was found that the percent of dissolved drug was increased by increasing PVP amounts. This effect might be due to the hydrophilicity of PVP-K25 which could enhance the wettability of drug and hence improved the dissolution rate of SD samples.[22] The reduction in dissolution rate of solid dispersion samples containing poloxamer188 at lower drug/ carrier ratios could be attributed to the polymer nature. In solid dispersions with low amount of poloxamer 188, the presence of poloxamer is not sufficient to disperse cilostazol molecularly among carrier molecules and hence cilostazol molecules form aggregates due to their lipophilicity and make amorphous clusters. This corresponds to glass suspension type of solid dispersion systems.[23] When this system comes into contact with the dissolution medium, poloxamer forms a viscose gel layer around cilostazol clusters. This viscose gel slows down the diffusion of dissolution medium through it and therefore, small lumps appear in dissolution vessels which are difficult to dissolve. In solid dispersions with higher amount of poloxamer188, cilostazol molecules could be dispersed molecularly among polymer chain and therefore, the formation of glassy solution type of solid dispersion system would be easy. This type of solid dispersion system could dissolve quickly after contact with dissolution medium.[24]

Table 2: Percent Cumulative Cilostazol Amount Dissolved From Different Solid Dispersion and Physical Mixture:

Time	Percent cumulative amount dissolved from:										
	Control	A1	A2	A3	B1	B2	B3	C1	C2	C3	D1
0	0	0	0	0	0	0	0	0	0	0	0
5	0.2 ± 0.0	23.2 ±1.4	35 ±2.3	42 ±3.1	7.2 ±1.2	9.3 ±2.1	17.2 ±3.4	1.2 ±1.6	1.9 ±0.8	3.4 ±1.5	0.3 ±0.0
10	0.9 ±0.03	26.8 ±2.1	39.4 ±3.6	46.3 ±4.8	11.9 ±2.1	17.3 ±4.6	27.9 ±3.9	3.1 ±1.3	4.2 ±1.6	6.2 ±2.2	0.75 ±0.0
15	2 ±0.6	29.5 ±2.4	41.5 ±4.1	47.92 ±2.3	16.4 ±1.1	22.7 ±2.9	33.8 ±5.8	6.4 ±1.5	7.2 ±1.4	9.8 ±2.1	3.18 ±1.9
20	5.2 ±1.6	33.7 ±3.1	47.2 ±3.3	54.6 ±2.5	19.3 ±3.5	26.3 ±2.2	37 ±5.3	7.3 ±1.4	8.5 ±1.1	12.1 ±2.5	7.33 ±1.4
30	8.3 ±1.2	34.8 ±2.5	49.6 ±2.3	56.7 ±5.6	22.5 ±2.4	29.2 ±1.3	41.7 ±3.4	9.5 ±1.1	11.4 ±1.7	16.4 ±1.0	11.45 ±2.5
45	10.7 ±2.3	36.4 ±4.6	53.8 ±3.5	61.98 ±5.1	24.8 ±2.8	30.6 ±2.0	44.2 ±2.8	12.1 ±1.4	14.2 ±2.6	19.6 ±1.3	13.15 ±1.8
60	14.6 ±2.3	38.9 ±1.8	55.8 ±3.3	63.46 ±5.5	27.9 ±2.1	32.8 ±3.2	47.4 ±4.4	13.9 ±1.6	17.6 ±2.0	22.9 ±1.5	18.39 ±5.0
90	17.9 ±1.3	41.3 ±3.2	58.7 ±4.2	64.86 ±5.2	31.6 ±3.7	35.9 ±3.6	48.2 ±2.7	18.1 ±1.5	20.1 ±1.2	28.1 ±2.5	20.9 ±3.7
120	20.8 ±2.4	42.6 ±3.1	60.9 ±4.7	67.6 ±3.1	32.8 ±2.4	37.1 ±1.7	50.8 ±2.3	22.2 ±1.9	24.3 ±3.4	36.5 ±3.5	22.17 ±1.5

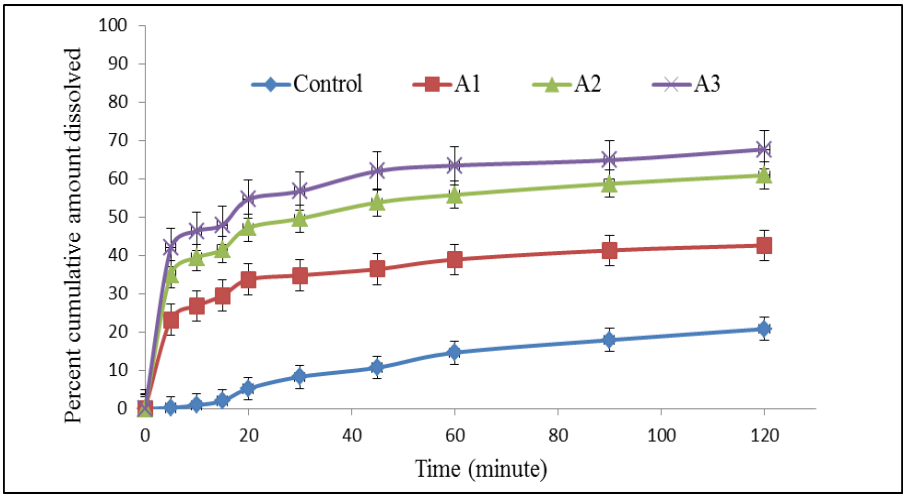

Figure 2: Dissolution profiles of pure cilostazol (control), 1:1 (A1), 1:3 (A2), and 1:5 (A3) w/w cilostazol/ poloxamer188 solid dispersions (n = 3).

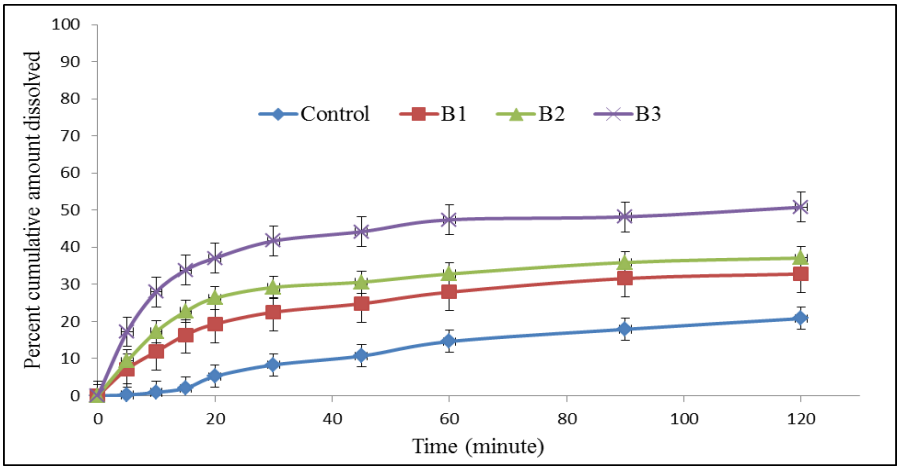

Figure 3: Dissolution Profiles of Pure Cilostazol (Control), 1:1 (B1), 1:3 (B2), And 1:5 (B3) W/W Cilostazol/ Pvp K25 Solid Dispersions (N = 3).

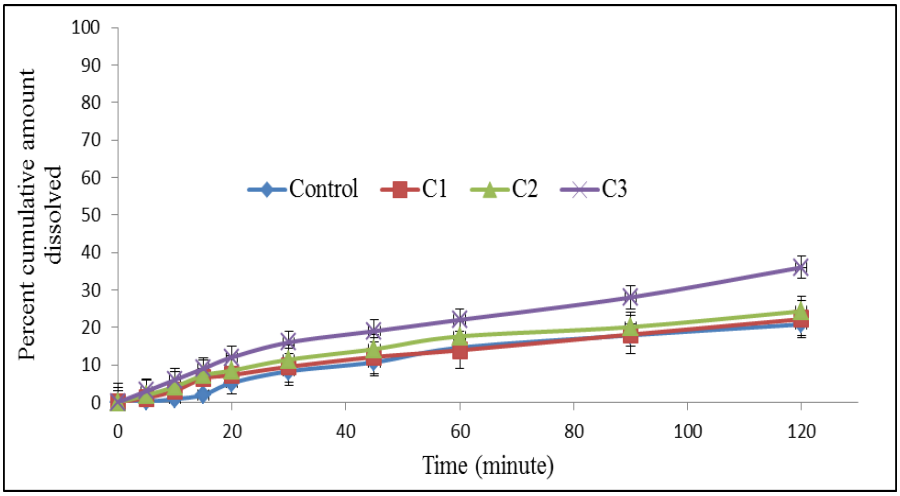

Figure 4: Dissolution Profiles of Pure Cilostazol (Control), 1:1 (C1), 1:3 (C2), And 1:5 (C3) W/W Cilostazol/ Peg 400 Solid Dispersions (N = 3).

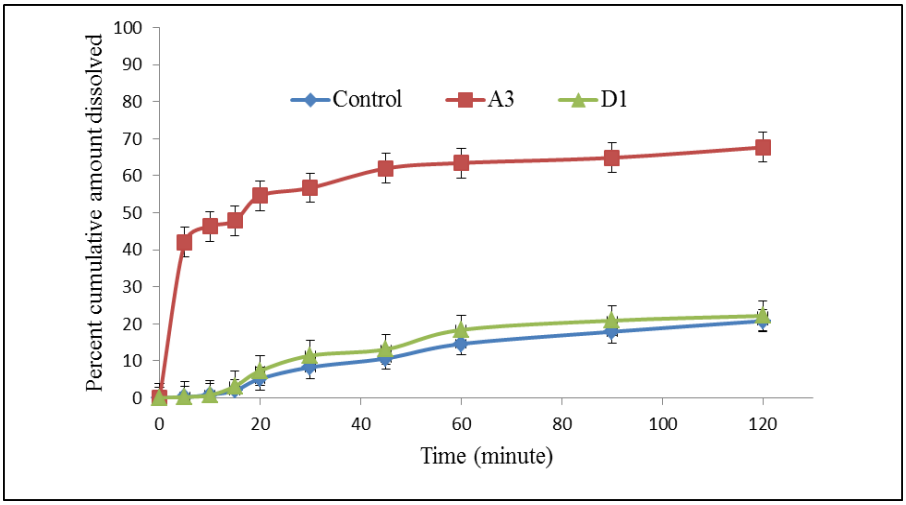

Figure 5: Dissolution Profiles of Pure Cilostazol (Control), 1:5 Cilostazol/ Poloxamer188 (A3), And 1:5 Cilostazol/ Poloxamer188 Physical Mixture (D1) (N = 3).

Fourier Transform Infra-Red spectroscopy (FT-IR)

The chemical interaction between the drug and polymer in solid dispersion systems usually results in noticeable changes in the FT-IR spectra. So, FT-IR has been conducted to study the molecular interactions between the drug and polymer. As it is shown in "Fig. 6 ", The FT-IR spectra of cilostazol showed the presence of following peaks: 3311,3180 cm^{-1} (N-H stretching); 3049, 3040 cm^{-1} (Aromatic C-H stretching), 1451, and 1426 cm^{-1} (C-H bending) 1238, 1193, 1155 cm^{-1} (C-N stretching) and 1085 cm^{-1} (C-O stretching). The FT-IR spectra of SDs and the corresponding physical mixture were the superposition of spectra of the individual components. Analysis of the spectra for both SDs as well as the physical mixtures did not showed any changes for the specific absorption bands for poloxamer or cilostazol, suggesting that there were no chemical interactions between cilostazol and polymer.[25] In FT-IR spectra of cilostazol/ poloxamer188 physical mixture (1:5), the N-H stretching band appeared at 3315, 3190 cm^{-1} along with hydroxyl group band appeared at 3435, 3419 cm^{-1} suggesting partial or little interaction of the drug with poloxamer 188 molecules. In FT-IR spectra of cilostazol/ poloxamer188 solid dispersion (1:5), the N-H stretching band at 3170 cm^{-1} and the aliphatic C-H stretching band at 2890, 2755, 2682 cm^{-1} suggesting the formation of solid dispersion. The N-H stretching vibration at 3322 cm^{-1} could not be detected which might be due to co-occurrence of aromatic C-H stretching band with O-H intensified band at 3409 cm^{-1}.[26]

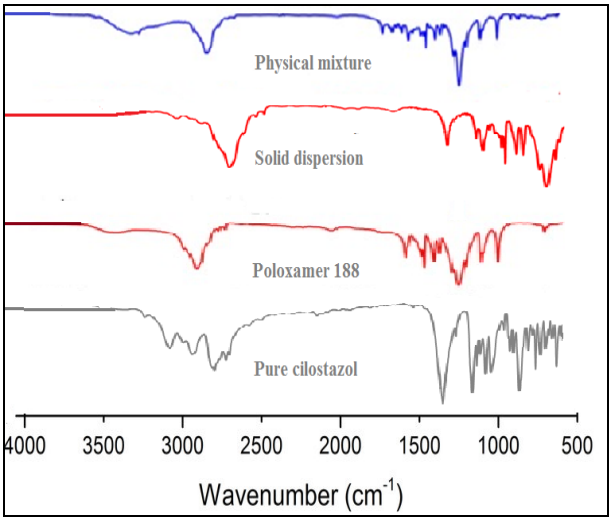

Figure 6: FT-IR spectrum of pure cilostazol, poloxamer188, 1:5 w/w cilostazol/ poloxamer188 solid dispersion and physical mixture.

Differential scanning calorimetry (DSC)

The DSC thermograms of cilostazol, poloxamer188, physical mixture and solid dispersion are shown in "Fig. 7". The DSC thermogram of pure cilostazol and poloxamer revealed the melting points at 161.50 (Trace A) and 54.74°C (Trace B), respectively.[27] The cilostazol/ poloxamer188 physical mixture (Trace C) showed a melting peak of poloxamer188 at 51.35°C and large broad peak around 158.12°C. It was suggested that relatively more crystalline part of cilostazol existed in the physical mixture compared its solid dispersion with poloxamer188. The 1:5 w/w cilostazol/ poloxamer188 solid dispersion (Trace D) showed a melting peak of poloxamer188 at 53.88°C and a small broad peak around 160.29°C. It was suggested that a small crystalline portion of cilostazol which still existed in this tested solid dispersion melted at lower than melting point of pure cilostazol.[28]

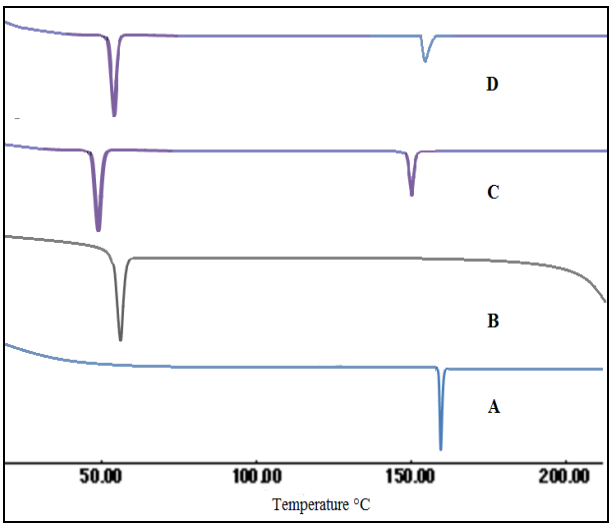

Figure 7: DSC peaks of: Pure cilostazol (A), Poloxamer188 (B), Cilostazol/ poloxamer188 (1:5 w/w) physical mixture (C) and cilostazol/ poloxamer188 (1:5 w/w) solid dispersion (D).

Powder X-ray diffraction (PXRD)

The powder X- ray diffraction patterns of cilostazol, poloxamer188, physical mixture and solid dispersions (1:5 w/w) are illustrated in "Fig. 8". PX-RD pattern of cilostazol at a diffraction angle of 5.1, 8.7, 10.1, 12.2, 14.0, 16.2, 17.3, 18.9, 19.8, 20.6, 21.0, 22.5, 23.0, 24.8, 26.8, 27.5, 30.4, 31.9, 33.6, 37.1, 39.9, 41.0, 43.3, 45.8, 46.1, 47.0, 48.8, 50.1 and 53.4° suggesting that cilostazol was present in the crystalline form.[29] The physical mixture of cilostazol with poloxamer188 at 1:5 w/w cilostazol/ poloxamer188 ratio showed both the characteristic diffraction peaks of cilostazol and poloxamer188. In case of cilostazol/ poloxamer188 solid dispersion (1:5 w/w), the diffraction peaks of cilostazol was not observed whereas the diffraction peaks of poloxamer188 was noted. This indicated that cilostazol in solid dispersion system was in amorphous state.[30]

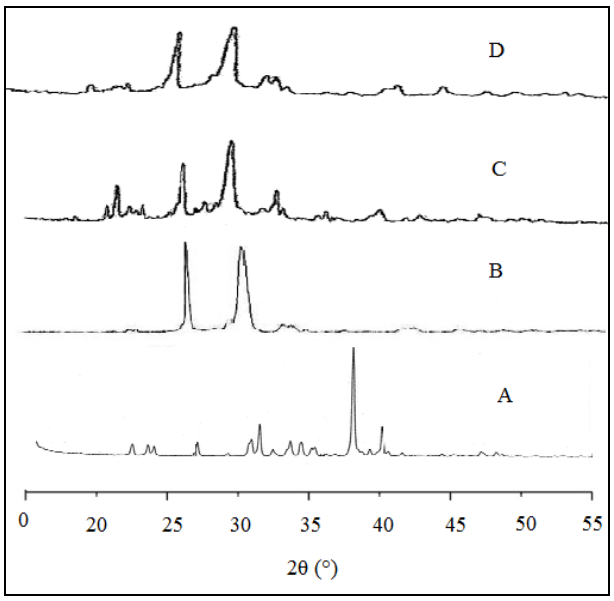

Figure 8: X-ray Thermograms of Cilostazol (A), Poloxamer188 (B), 1:5 W/W Physical Mixture (C) And 1:5 W/W Solid Dispersion (D).

Scanning electron microscopy (SEM)

SEM of pure cilostazol, poloxamer188, physical mixture and solid dispersion are illustrated in "Fig. 9 and 10". SEM of cilostazol and poloxamer188 showed crystal and globular form respectively.[33] In solid dispersion the structure of cilostazol crystal or mixture is completely different which revealed formation of a new structure in solid dispersion of cilostazol with poloxamer188. These findings demonstrated that the drug was thoroughly mixed in the carriers with the loss of little crystallinity. In case of pure cilostazol rod shaped crystals can be seen, whereas in SEM of poloxamer188, large globular particles are seen. In case of solid dispersions, it was difficult to distinguish the presence of cilostazol crystals. Cilostazol crystals appeared to be incorporated into the poloxamer188 particles. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of poloxamer188.[31]

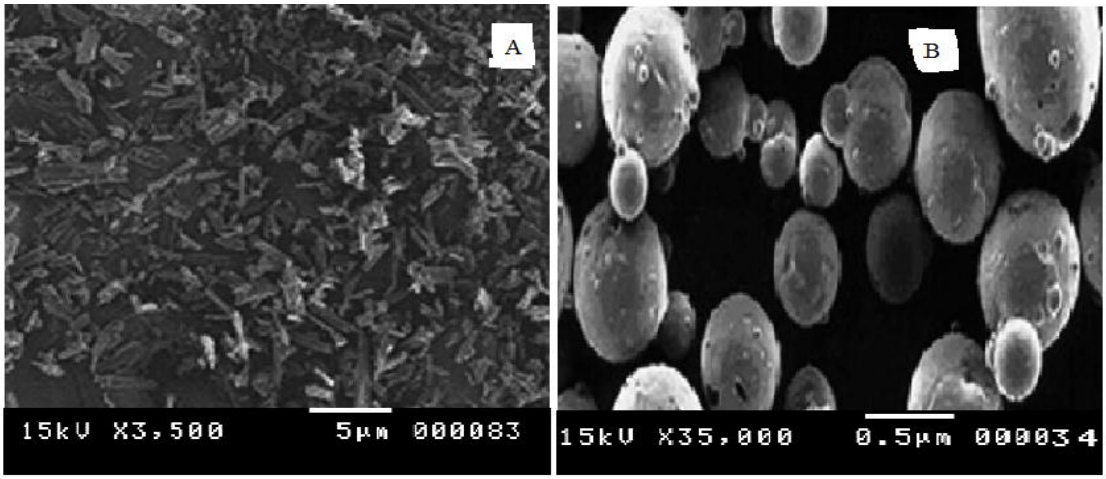

Figure 9: SEM of (A) Pure cilostazol and (B) Pure poloxamer 188.

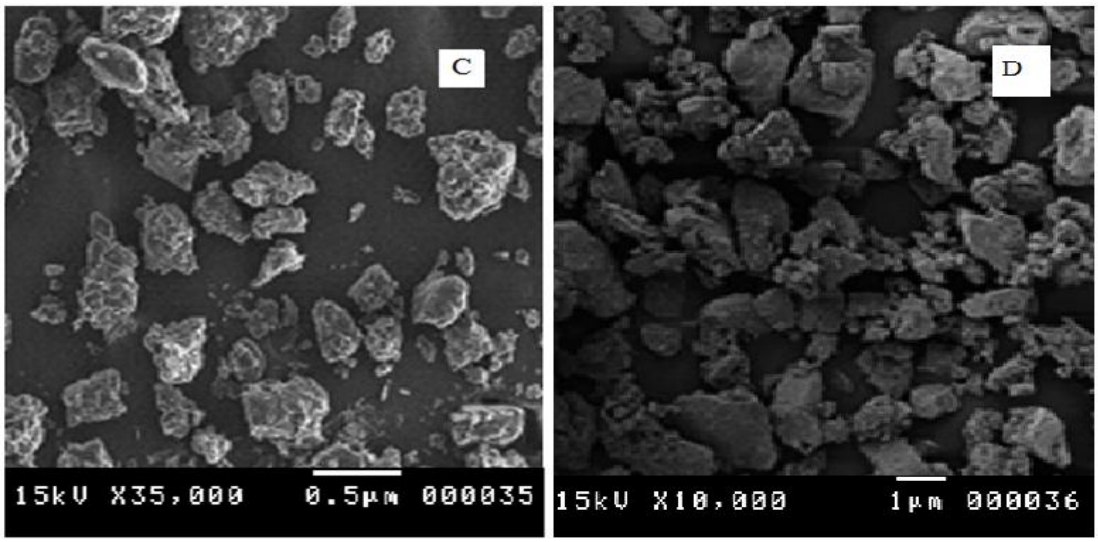

Figure 10: SEM of (C) Cilostazol/ poloxamer188 physical mixture and (D) Cilostazol/ poloxamer188 1:5 w/w solid dispersion.

CONCLUSION

The previous results revealed that poloxamers 188, PVP-K25 and PEG 4000 are suitable for the fabrication of solid dispersions with cilostazol by solvent evaporation method. Solid dispersions with all the used polymers have increased the dissolution rate of cilostazol, with poloxamer 188 showed greater solubilization efficiency. Increased poloxamer ratio in solid dispersions was increased the dissolution rate of cilostazol as well as other polymers. FT-IR study results showed that there was no interaction between the drug and poloxamer188 in the selected solid dispersion. DSC and PXRD thermograms revealed that cilostazol was converted from the crystalline form to the amorphous one.

Conflict of Interest: The authors declare that they have no competing interests.

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