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Original Article

# DEVELOPMENT AND ASSESSMENT OF THE CILOSTAZOL SOLID DISPERSION EMPLOYING MELT AND SOLVENT EVAPORATION METHOD AND ITS COMPARISON

**MAROOR NARAYANANKUTTY ANJANA[1*], M. KUMAR[1], VENKATESWARLU B. S.[1], SANTHOSH M. MATHEWS[2], SAMPATH KUMAR K. P.[3]**

**[1]Department of Pharmaceutics and Pharmaceutical Chemistry, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation, (Deemed to be University) Salem-636008, Tamil Nadu, India. [2]Department of Pharmaceutics, Pushpagiri College of Pharmacy, Thiruvalla-689101 India. [3]Department of Pharmaceutics, Coimbatore Medical College, Coimbatore-641018, Tamil Nadu, India**
**[*]Corresponding author: Maroor Narayanankutty Anjana; [*]Email: anjanaprathibha@gmail.com**

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**ABSTRACT**

**Objective:** Development and assessment of the Cilostazol solid dispersion employing melt and solvent evaporation method and its comparison. BCS class II and IV drugs are low solubility and low permeability properties. Most of the active drugs are pharmacologically ineffective due to a lack of solubility and permeability. To overcome these problems Solid Dispersion (SD) is one of the best conventional methods. The objective of this study is to improve the dissolution rate of Cilostazol using economical and simple solid dispersion technique.

**Methods**: Physicochemical properties of Cilostazol was studied. Cilostazol and polymers (PEG 6000 and PVPK30) interactions were studied by FT-IR spectroscopy. SD was prepared using PVP K30 polymer by melt and solvent evaporation, and the polymer interactions of Cilostazol, Physical Mixture (PM), and SD were studied using FT-IR. Using a USP dissolution type 2 test apparatus (n=3) and settings of 50 rpm and 37 °C 0.5 °C, *in vitro* dissolution experiments for Cilostazol, PM and SD were conducted. Dissolution study and saturation solubility study was the main evaluating parameters.

**Results:** The FTIR study confirmed sharp peaks in the spectrum without merging, indicating that no drug interactions were present in the PM and SD formulations. Solubility and dissolution studies confirmed that drug release patterns of the pure drugs Cilostazol, PM (1:3), and SD (1:3) resulted in a markedly higher release rate. SD (1:3) released 97.2% of the drug after 60 min. PM (1:3) released 68.6% of the drug in 60 min, and the pure drug released 35.4% in 60 min. The formulation stability study confirmed that there was no significant loss of the drug under the storage conditions. The cilostazol SD was formulated using a conventional method. The solubility and drug release increased significantly ($p$<0.05) compared with Cilostazol and PM. FT-IR studies confirmed that there were no interactions between the drug and the polymer.

**Conclusion:** The present study concluded that cilostazol and PVP K30 Solid Dispersion (SD) was one of the choice used to enhance the solubility and drug release properties. However, *in vivo* studies are required before clinical application.

**Keywords:** Cilostazol, FT-IR, Physical mixture, Solid dispersion, Compatibility, *In vitro* dissolution


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## INTRODUCTION

Cilostazol is derivative of quinoline ((6-[4-(1-cyclohexyl-1H-tetrazol-5-y1) butoxy]-3, 4-dihydro-2(1H)–quinolinone). Cilostazol inhibits phosphodiesterase III enzyme activity and increases the levels of Adenosine Diphosphate (ADP) and collagen. Owing to its phosphodiesterase III enzyme inhibitory activity, cilostazol is used as an inhibitor of platelet aggregation, a vasodilator, and enhances the function of endothelial cells [1-3]. The current study confirmed that cilostazol is a safer and more effective medication than aspirin for the long-term treatment of ischemic stroke. Experimental studies have shown that cilostazol has low solubility and high permeability (BCS class II drugs) [4]. Poor drug solubility results in very low bioavailability, which causes defects during dosage form development. The solubility and dissolution rate of poorly soluble drugs can be improved by solid dispersion technique and it is widely used in the pharmaceutical field. Particle size reduction and, consequent increase in the surface area, and improved wettability are the main advantages of solid dispersion technique.

Solid dispersion (SD) refers to the process of incorporating a poorly water-soluble drug into a water-soluble carrier to form a homogenous mixture. This technique has become highly significant for pharmaceutical formulations and provides a promising approach for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs. SD involves dispersion of one or more active pharmaceutical ingredients in an inert carrier or matrix in the solid state. This often results in molecular-level mixing, which can alter the physical and chemical properties of drug. Many drugs are hindered by poor water solubility, which limits their therapeutic effectiveness.

Solid dispersions can modify the crystalline structure of a drug to an amorphous form or a different crystalline form, thus enhancing its dissolution rate and solubility. By increasing the solubility and dissolution rate of a drug, solid dispersion enables more of the drug to be absorbed into the systemic circulation. This leads to higher bioavailability, which means that a therapeutic effect can be achieved with a lower dose. Various water-soluble carriers such as polymers, surfactants, and lipids used. Polymers, such as PVP and PEG, are common carriers that interact with drugs, preventing them from recrystallizing and maintaining their improved solubility. Several methods, such as melt mixing, solvent evaporation, spray drying, and supercritical fluid technologies, have been employed to create solid dispersions. The choice of method depends on the properties of the drug and carrier and the desired end-product characteristics. Stability issues can arise because amorphous forms tend to revert to their less soluble crystalline forms over time. The development of appropriate manufacturing processes and formulation strategies to ensure long-term stability is a key challenge.

Cilostazol has a half-life of 11 h [5, 6] and its absorption from the gastrointestinal tract is variable and incomplete. According to BCS Cilostazol falls into Class II based on its poor solubility and high permeability. The Incomplete absorption of cilostazol from tablets in humans is likely due to poor dissolution. A low dose of the drug that is not effective and a higher dose of the drug will increase toxicity. To obtain good bioavailability, low-solubility medicines need to increase their solubility before forming a solid dosage form. The main objective of this study was to increase the solubility of cilostazol using the solid dispersion technique.

## MATERIALS AND METHODS

### Materials

Cilostazol, PVPK30, methanol, and PEG6000 were purchased from Yarrow Chemicals, Mumbai, while sodium hydroxide, ethanol, sodium hydrogen phosphate, n-octanol, and HCl were purchased from Sigma Aldrich, Mumbai.

### Pre-formulation studies and determination of $\lambda_{max}$ of cilostazol

Physicochemical characteristics (color, taste, odor), melting point (capillary method), and solubility (Solubility of Cilostazol was evaluated using aqueous and organic solvents) of the cilostazol molecule were studied using the method described by Doile *et al.* [7], with minor changes. Cilostazol organic molecules with various functional groups. When exposed to the UV light spectrum, cilostazol solution absorbs a certain wavelength of light based on the type of electronic transition connected with absorption. The absorbed wavelength of the compound is denoted as λmax.

### I. R. spectrophotometry of cilostazol, PEG 6000 and PVP K30

The FT-IR spectra of Cilostazol, PEG 6000, and PVP K30 were studied using a Shimadzu IR affinity spectrophotometer, with a range of 300 to 3500 $cm^{-1}$. Fourier transform infrared spectroscopy (FT-IR) studies of Cilostazol, PEG 6000, and PVP K30 were performed. Cilostazol, PEG 6000, and PVP K30 were dispersed individually in KBr and compressed into pellets. The prepared KBr Cilostazol, PEG 6000 and PVP K30 pellets are placed in the path length and obtained the IR spectrum of the individual Cilostazol, PEG 6000 and PVP K30 [8].

### Quantitative estimation of the cilostazol

Quantitative estimation of cilostazol was performed using the UV spectrophotometric method because of its sensitivity, specificity, simplicity, reproducibility, rapidity, and accuracy. Cilostazol (50 mg) was dissolved in simulated gastric fluid (100 ml) at a pH 1.2 (stock solution). Ten milliliters of solution was collected from the stock solution and volume makeup with gastric solution (pH 1.2 gastric solution up to 100 ml (50 µg/ml). From the 100 ml (50 µg/ml) solution, 2, 4, 6, 8, and 10 serial volumes were transferred into a volumetric flask (10 ml) and volume makeup with gastric fluid solution (10 ml). The OD was measured at 258 nm along with a blank solution. A standard graph was drawn between the absorbance and concentration. A straight line is obtained that passes through the origin [9].

### Partition coefficient

The partition coefficient has a direct influence on the permeability of medication through different membranes. The important function of this study was to determine the partition coefficient of the drug in a simulated gastric fluid (pH 1.2) and n-octanol. The separating funnel shake flask method was used to calculate the cilostazol partition coefficient between n-octanol and the simulated gastric fluid (pH 1.2). Cilostazol (10 mg) was dissolved in one of the phases and shaken for 30 min with another partitioning solvent. Spectrophotometry was used to estimate the partition coefficient and drug concentration in the aqueous and n-octanol phases at 258 nm [10].

$$\text{Partition coefficient} = \frac{\text{Conc: of the drug in the oil phase}}{\text{Conc: of the drug in the aqueous phase}}$$

### Drug and polymer compatibility

Drug and polymer compatibility were studied using FT-IR spectroscopy. FT-IR spectroscopy of cilostazol-PEG 6000 and cilostazol-PVP K30 was performed using a Shimadzu IR affinity spectrophotometer in the range of 300 to 3500 cm-1. An FT-IR study of Cilostazol with PEG 6000 and Cilostazol-PVPK30 studied. The cilostazol-PEG 6000 and cilostazol-PVP K30 mixtures were individually dispersed in KBr and compressed in the pellets. The prepared KBr Cilostazol-PEG 6000 mixture and Cilostazol-PVP K30 mixture pellets are placed in the path length and obtained the IR spectrum [8].

### Preparation of the physical mixture

Cilostazol and PVP K30 were mixed in various weight ratios of 1:1, 1:2, 1:3, and 1:4 to produce Cilostazole-PVPK30 physical combinations,using mortar and pestle. The resulting combinations were blended, and put through sieve no. 80, gathered and kept out of the light and humidity in tightly-closed amber-coloured containers until they were needed again [11].

### Preparation of solid dispersion

The conventional fusion method was used to prepare the Solid Dispersion (SD) of Cilostazol and PVPK30. The 1:1, 1:2, 1:3 and 1:4 (Code: SD1, SD2, SD3 and SD4) W/W Cilostazol and PVPK30 ratio were selected for the preparation of SD. Cilostazol and PVPK30 were dissolved in an adequate amount of methanol. The methanol solvent was rapidly evaporated using mild heat and surface airflow with vigorous stirring to form a uniform solid mass. The co-precipitate was crushed to form fine particles, and the moisture was removed and stored in a vacuum desiccator for 24 h. The solid particles were sieved (sieved: 80) and stored in a desiccator until further use.

### FT-IR spectroscopy

The SD was studied using FT-IR spectroscopy. FT-IR spectroscopy of cilostazol-PVP K30 was performed using a Shimadzu IR affinity spectrophotometer in the range of 300 to 3500 $cm^{-1}$. The FT-IR study of cilostazol-PVP K30 was performed using the method of Muddukrishnaiah *et al.* with minor modifications. The cilostazol-PVP K30 mixture was individually dispersed in KBr and compressed into pellets. The prepared KBr cilostazol-PVP K30 mixture pellets were placed in the path length, and the IR spectrum was obtained to observe the polymer and excipient interactions [8].

### Percentage of drug content

Drug content determined by solid dispersion formulation. SD (50 mg) was dissolved in ethanol (50 ml) using a mechanical shaker for 30 min. The drug content in the diluted solution was determined by UV spectroscopy using absorbance at 258 nm.

SD saturation solubility and pH-dependent solubility determination

Saturation and pH solubility were determined using the shake flask method and 0.1N HCl for pH-dependent solubility was used. Cilostazol-prepared S and PMs pure excess amounts of were added in 25 ml of distilled water contained conical flask and incubated at 37 °C and 100 rpm for 72 hr in an orbital shaker. By using a UV spectrophotometer, absorbance was obtained at 258 nm.

### *In vitro* dissolution studies

Using a USP type 2 test apparatus (n=3) with settings of 50 rpm and 37 °C 0.5 temperature, *In vitro* dissolving experiments of produced SDs were conducted. For the entire experiment, 5 ml of the experimental sample was collected at every 5 min interval and filtered using a 0.45-mm Whatman filter [10, 11]. Fresh medium (5 ml) was placed in the experimental chamber. Experimental samples were analysed at 258 by using a UV spectrophotometer [8].

### Stability studies of SD

The stability of the SD was studied following the International Conference on Harmonization (ICH) guidelines for three months. SD formulations were stored at 40±0.5 °C to 75±5% °C. The time interval samples were collected and tested for drug content. Statistical differences were analyzed and compared with those of the standard fresh formulation (n=3).

### Statistical analysis

The data obtained from the experimental study, reported as mean standard errors of the mean and difference between groups, were tested using Prism software (Student's *t*-test at $p<0.05$). Analysis of variance was used to compare all groups, and the difference was considered significant at $p<0.05$.

## RESULTS AND DISCUSSION

### Pre-formulation studies

Pre-formulation studies of cilostazol have also been conducted. Cilostazol is a white crystal with a distinct and faint odor. Table 1 are reported the physico-chemical properties of the Cilostazol [7].

### I. R. spectrophotometry of cilostazol, PEG 6000 and PVP K30

The results of a Cilostazol, PEG 6000 and PVP K30 FT-IR study were studied and analysed [8]. Cilostazol: 3301.3 $cm^{-1}$ (amide, NH

stretch), 1661.8 $cm^{-1}$ (amide, C=O stretch), 1240.3 $cm^{-1}$ (Aryl-O, stretch vibration) and 2936.8 $cm^{-1}$, 2860.0 $cm^{-1}$ ($CH_2$, stretch vibration) (fig. 1A). PEG 600: FT-IR results confirmed that the stretching and bending vibrations were limited to C-C, C-O, CH stretching (methylene absorption), and C-H bending. 2803 $cm^{-1}$ (-CH3 vibration in the stretching), 1474 $cm^{-1}$ (binding vibration of-CH2), and 1362 $cm^{-1}$ and 1287 $cm^{-1}$ (C-O stretching vibration) (fig. 1B). The FTIR spectrum of pure PVP K30 showed a characteristic absorption band at 1634 $cm^{-1}$. This can be attributed to the carbonyl group14. The broad band at 3440 $cm^{-1}$ indicate the presence of moisture, revealing the hygroscopic nature of PVP K30 (fig. 1C).

**Table 1: Physicochemical properties of cilostazol.**

| Organoleptic character | Characteristic |
|---|---|
| Colour | White crystals |
| Taste | Bitter |
| Odour | Slight and characteristic |
| Melting point | 160 °-165 °C (Std-160 °C) |
| Freely soluble | Acetic acid, chloroform, n-methyl-2-pyrrolidone, DMSO |
| Slightly soluble | Methanol, ethanol |
| Practically insoluble | Ether |
| $\lambda_{max}$ | 258 nm |

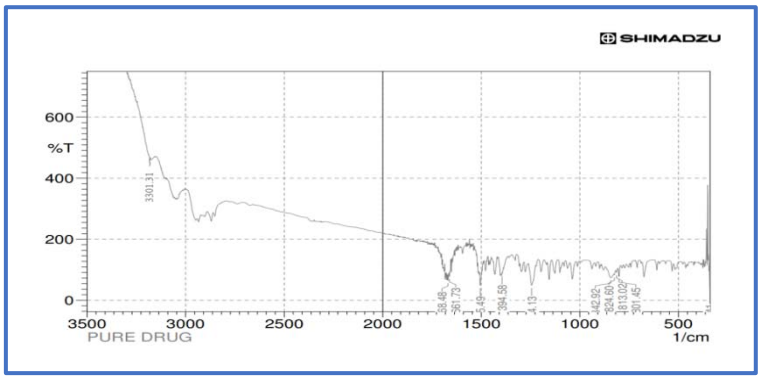


**Fig. 1A: FT-IR spectrum of cilostazol**

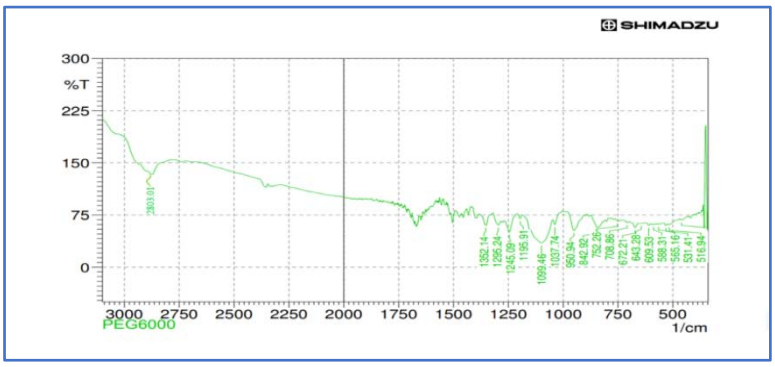


**Fig. 1B: FT-IR spectrum of PEG6000**

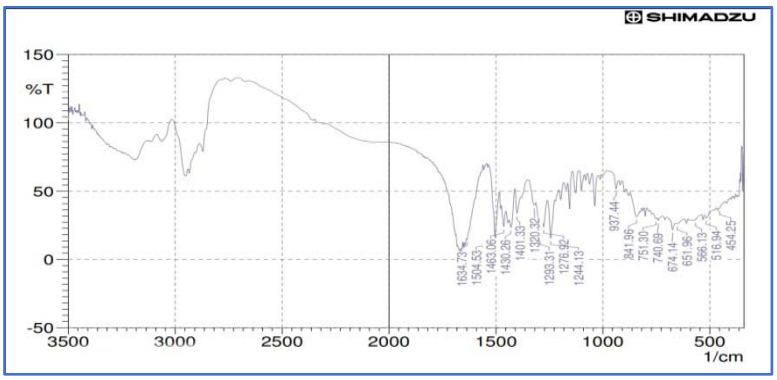


**Fig. 1C: FT-IR spectrum of PVP K30**

**Quantitative estimation of the cilostazol [9]**

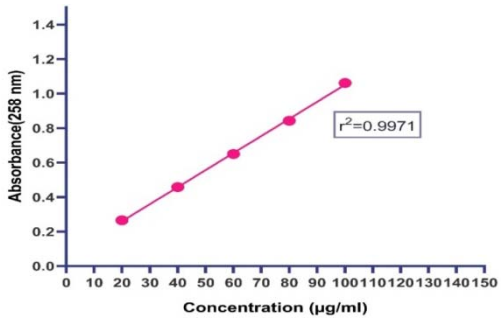


**Fig. 2: Calibration curve of cilostazol**

**The experiment was conducted three times (n=3)**

**Partition coefficient**

Partition coefficient equilibrium partitioning of a solute with a single, specified charge state between two liquid phases in contact. Drug discovery typically uses octanol-water partition coefficients as a metric of lipophilicity [10]. The Cilostazol partition coefficient was determined to be 2.2.

**Drug and polymer compatibility**

The FT-IR results of PG6000 and Cilostazol (fig. 3A), PVP K30 and Cilostazol (fig. 3B) provide information about the molecular stretching and bending vibrations limited to C-C, C-O, CH stretching (methylene absorptions), C-H bending, (amide, NH stretch), (Aryl-O, stretch vibration), (CH2, stretch vibration). 1661.8 $cm^{-1}$ (amide, C=O stretch), 1240.3 $cm^{-1}$ (aryl-O, stretch vibration), 2936.8 $cm^{-1}$, 2860.0 $cm^{-1}$ (CH2-stretch vibration), 2803 $cm^{-1}$ (-CH3 vibrate in the stretching), 1474 $cm^{-1}$ (Binding vibration of-CH2), 1362 $cm^{-1}$ and 1287 $cm^{-1}$ (C-O stretching vibration). Fig. 3B: 3301.3 $cm^{-1}$ (amide, NH stretch), 1661.8 $cm^{-1}$ (amide, C=O stretch), 1240.3 $cm^{-1}$ (Aryl-O, stretch vibration) and 2936.8 $cm^{-1}$, 2860.0 $cm^{-1}$ (CH2, stretch vibration). PVP-K30 exhibited significant bands at 2934 $cm^{-1}$ (C-H stretch) and 1667 $cm^{-1}$ (C=O) [8].

**Physical mixture and solid dispersion preparation**

The physical mixture and solid dispersion of cilostazol were prepared and stored in a desiccator until further use. Tables 2 and 3 list the ratios of Cilostazol and PVP K30.

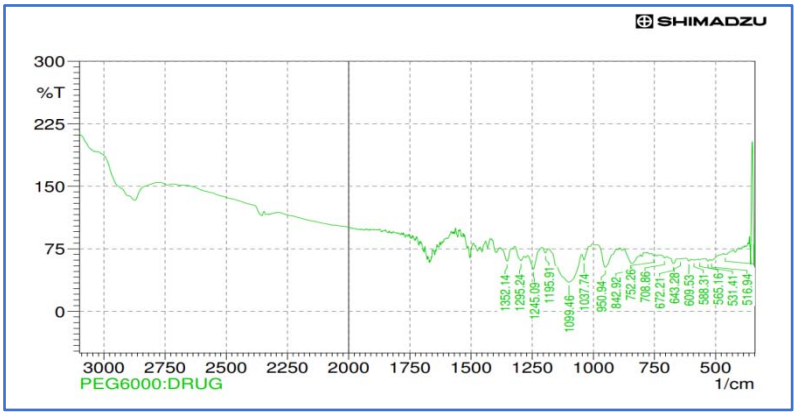


**Fig. 3A: FT-IR spectrum of PEG6000 and cilostazo**

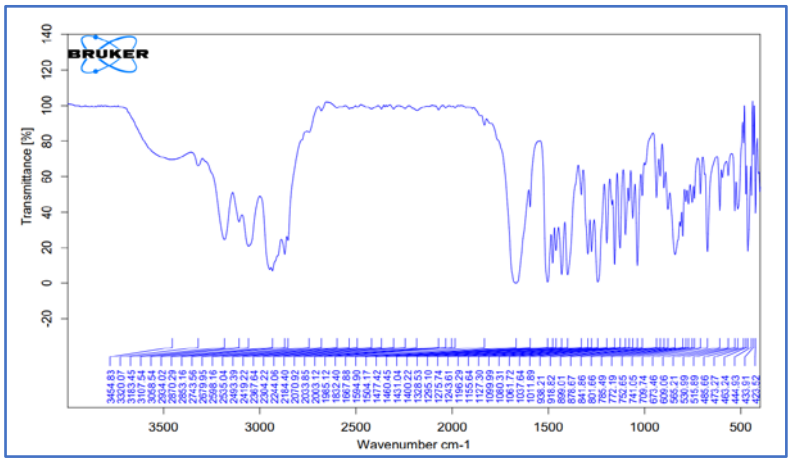


**Fig. 3B: PVP K30 and cilostazol FT-IR spectra**

**Table 2: Composition of the physical mixture and there assign batch code**

| S. No. | Ratio (Cilostazol: pvpk30) | Batch code |
|---|---|---|
| 1 | 1:1 | PM1 |
| 2 | 1:2 | PM2 |
| 3 | 1:3 | PM3 |
| 4 | 1:4 | PM4 |

**Table 3: Composition of solid dispersion and there assign batch code**

| S. No. | Ratio (Cilostazol: pvpk30) | Batch code |
|---|---|---|
| 1 | 1:1 | SD1 |
| 2 | 1:2 | SD2 |
| 3 | 1:3 | SD3 |
| 4 | 1:4 | SD4 |

**FT-IR spectroscopy SD (Cilostazol and PVP K30)**

The resulting spectra were compared with the individual spectral spectra. The FTIR spectra of the drug, carrier, and surface solid dispersions are shown in fig. 4. Although the location of the functional groups in the carrier (PVP K30) was unaltered by the introduction of cilostazol, no appreciable alteration was observed in the spectrum of the solid dispersions.

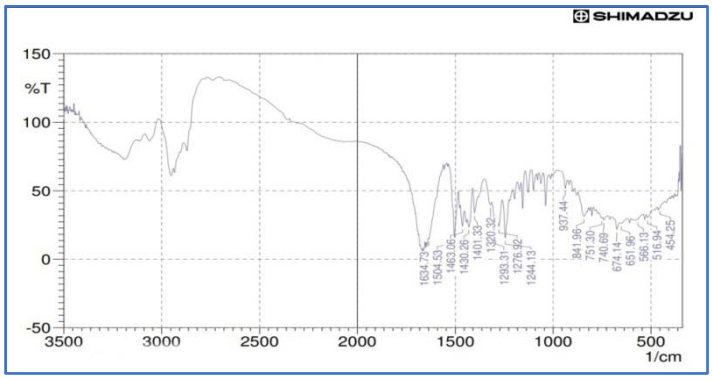


**Fig. 4: FT-IR spectra of SD, Cilostazol and PVP K30**

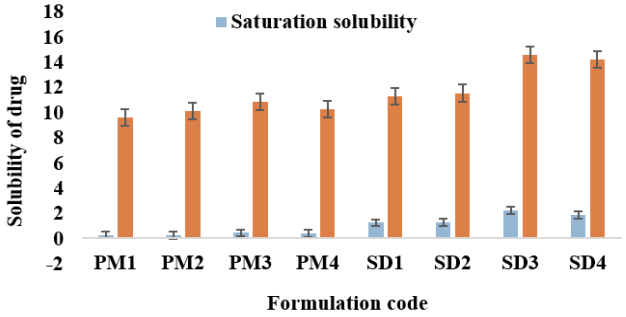


**Fig. 5: PM and SD saturation solubility and pH-dependent solubility studies, the experiment was conducted three times (n=3), and the standard deviation (SD) of the data was obtained. The standard deviation was a measure of the amount of variation**

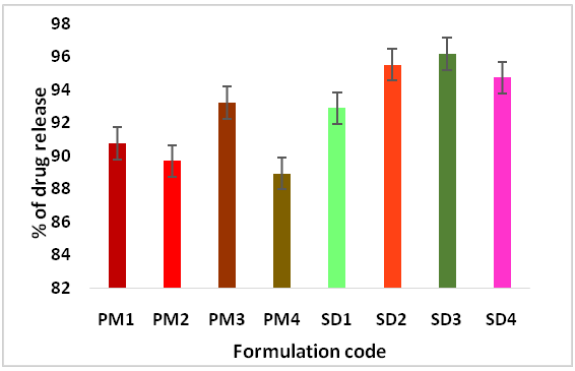


**Fig. 6: Percentage drug content of pure PM and SD, the experiment was conducted three times (n=3), and the standard deviation (SD) of the data was obtained. The standard deviation was a measure of the amount of variation**

**Determination of SD saturation pH-dependent solubility**

The SDs saturation, pH-dependent solubility, and percentage of drug release were studied using UV spectroscopy. Table S4 and fig. 5 and 6 show the saturation solubility of the physical mixture, SD, pH-dependent solubility, and percentage of drug content, respectively.

***In vitro* dissolution studies**

Solid dispersions can be characterized using dissolution studies, which are essential tools. The Maximum homogeneity and amorphous drug content of the formulation should result in maximal dissolution. Cilostazol had the lowest rate of dissolution, whereas

formulations with the highest ratio of polymer had the highest rate of release. PVP K30 is a water-soluble carrier that, when dissolved, increases the solubility of SD and, consequently, increases the amount of dissolution. Due to the carrier effect in dissolving, the physical mixture had less dissolution than pure Cilostazol but more than SD. In the fusion approach, molecular dispersion is created by mixing the drug and carrier molecules, whose molecular mobility is the greatest at their respective melting points. While gradual cooling at room temperature gives the drug and polymer molecules plenty of time to segregate and set with their densities, quench cooling a fused product causes molecular motion to be arrested when mixing is at its maximum [12]. This results in a highly heterogeneous and recrystallized product. Fig. 7, 8, and 9 depict the dissolution drug release patterns of PM, SD, and Cilostazol, which were carried out in 900 ml of 0.1N HCl. Fig. 9 shows that the drug release patterns of the pure drugs Cilostazol, PM (1:3), and SD (1:3) resulted in markedly higher release rate. SD (1:3) released 97.2% of the drug after 60 min. PM (1:3) released 68.6% of the drug in 60 min, and pure drug released 35.4% in 60 min [8]. Zhang *et al.* in 2020 [13] reported significant advancement in cilostazol *in vitro*/*in vivo* performance through the creation of osmotic pump tablets. The research team enhanced the solubility and bioavailability of the drug by synergizing hydrophilic polymers and mesoporous silica in the solid dispersions. In 2021, Jin *et al.* [14]. focused on the use of surfactant micellization to enhance the dissolution of cilostazol. Utilizing Poloxamer 407-based solid dispersion via the anti-solvent method, they succeeded in significantly improving the dissolution rate of the drug, aligning with the objective of achieving better solubility.

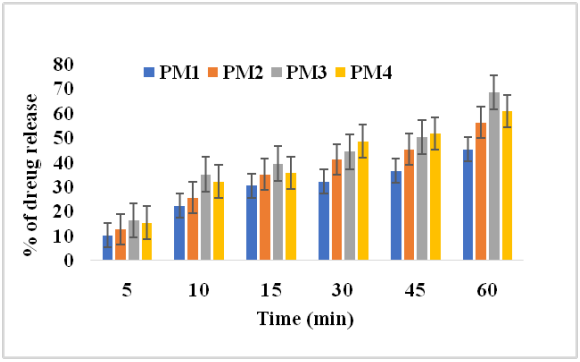


**Fig. 7: PM drug release percentage, the experiment was conducted three times (n=3), and the standard deviation (SD) of the data was obtained. Standard deviation is a measure of the amount of variation**

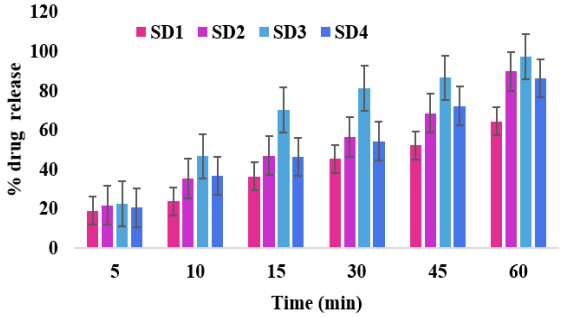


**Fig. 8: SD drug release percentage, the experiment was conducted three times (n=3), and the standard deviation (SD) of the data was obtained. The standard deviation was a measure of the amount of variation**

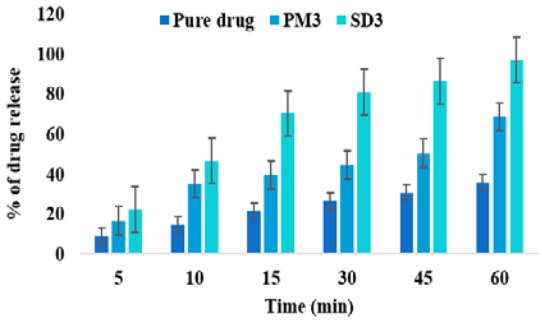


**Fig. 9: Cilostazol, PM3, and SD3 release percentages, the experiment was conducted three times (n=3), and the standard deviation (SD) of the data was obtained. The standard deviation was a measure of the amount of variation**

### Stability studies of SD

Cilostazol, PM (1:3), and SD (1:3) formulations were used in stability studies. No significant differences ($P$<0.05) were observed in the experimental results. The stability study confirmed that the SD prepared using PVP K30 were stable under various storage conditions.

### Statistical analysis

The data are presented as mean±standard deviation. To assess statistical significance, one-way ANOVA was conducted to compare the values both within and between groups. The results were considered statistically significant at *p<0.05, indicating differences compared to the control group and among the groups.

## CONCLUSION

The cilostazol SD was formulated using a conventional method. The solubility and drug release increased significantly ($p<0.05$) compared with cilostazol and the physical mixture. Cilostazol, PEG 6000, PVP K30, Cilostazol with PEG 6000, Cilostazol with PVP K30 and SD were characterised by FT-IR, resulting in sharp peaks. Sharp peaks without any interactions were observed (fig. 3 and 4). Sharp peaks in FT-IR without merging indicate that there is no drug polymer interaction between Cilostazol and PEG 6000 and PVP K30. PVP K30 was selected for the SD because it did not form high consistency during heating compared to PEG 6000. Cilostazol, PM, and SD dissolution studies confirmed that SD (97.2%) had the highest dissolution rate compared with PM (68.6%) and cilostazol (35.4%). The formulation stability study confirmed that there was no significant loss of the drug under the storage conditions. The present work concluded that cilostazol and PVP K30 Solid Dispersion (SD) was one of the choice used to enhance the solubility and drug release properties. *However, in vivo* studies are required before clinical application.

## ACKNOWLEDGEMENT

The authors would like to thank the Vinayaka Mission Research Foundation and Pushpagiri College of Pharmacy for providing research facilities.

## ABBREVIATIONS

AD: Solid Dispersion, PEG: Polyethylene glycol, PVPK: Polyvinyl Pyrolidone

FT-IR: Fourier Fourier Transform infrared, PM: Physical Mixture, BCS: Biopharmaceutical classification system.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

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