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

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INTRODUCTION

Cilostazol is a 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 in vivo.

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 are 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.

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, 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 drug 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
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 \( \lambda_{\text{max}} \) 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 \( \lambda_{\text{max}} \).

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 compacted 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-PVP K30 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 Cilostazol-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 observed to observe the polymer and excipient interactions [8].

Per centage 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 water 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 dissolution 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% RH. 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 the 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\(^{-1}\) (\(-\mathrm{CH}_3\) vibration in the stretching), 1474 cm\(^{-1}\) 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 group\(^{14}\). 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.

<table>
<thead>
<tr>
<th>Organoleptic character</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>White crystals</td>
</tr>
<tr>
<td>Taste</td>
<td>Bitter</td>
</tr>
<tr>
<td>Odour</td>
<td>Slight and characteristic</td>
</tr>
<tr>
<td>Melting point</td>
<td>160(^\circ) - 165 (^\circ) C (Std 160 (^\circ) C)</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>Acetic acid, chloroform, n-methyl-2-pyrrolidone, DMSO</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>Methanol, ethanol</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>Ether</td>
</tr>
<tr>
<td>(\lambda_{max})</td>
<td>258 nm</td>
</tr>
</tbody>
</table>
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.

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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ratio (Cilostazol: PVP K30)</th>
<th>Batch code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>PM1</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>PM2</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>PM3</td>
</tr>
<tr>
<td>4</td>
<td>1:4</td>
<td>PM4</td>
</tr>
<tr>
<td>S. No.</td>
<td>Ratio (Cilostazol: pvpk30)</td>
<td>Batch code</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>1:1</td>
<td>SD1</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>SD2</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>SD3</td>
</tr>
<tr>
<td>4</td>
<td>1:4</td>
<td>SD4</td>
</tr>
</tbody>
</table>

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

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.

![FT-IR spectra of SD, Cilostazol and PVP K30](image)

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

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 **In vitro** dissolution studies

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.

![Percentage drug content of pure PM and SD](image)

**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**

![Percentage drug release of pure PM and SD](image)

**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**
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 0.1 N 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.

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, and PVP K30 and SD were characterised by FT-IR, resulting in sharp peaks. Sharp peaks without any interactions were observed ([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 polymer interaction between Cilostazol and PEG 6000 and PVP K30. 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: Polylethylene glycol, PVPK: Polyvinyl Pyrolidone

FUNDING
Nil

AUTHORS CONTRIBUTIONS
All the authors have contributed equally.

CONFLICT OF INTERESTS
Declared none

REFERENCES