Enhancement of Repaglinide Dissolving Rate by the Application of the Solid Dispersion Method

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ABSTRACT

The recent work primarily set out to evaluate and synthesize the Repaglinide (RG) solid dispersion. The medicine rifampicin is classified as a class II biopharmaceutical due to its low water solubility. Through the use of solvent evaporation and a range of PVP K30 ratios, a Repaglinide solid dispersion (RG-SD) was produced. A battery of tests, including in vitro dissolution testing, drug content analysis, X-ray diffraction (XRD), and differential scanning calorimetry (DSC), were performed on the produced RG-SD. Research using Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) has shown that the solid dispersion of the examined material, RG, is amorphous. Purified RG's solubility in distilled water was enhanced from 34.41±0.68 to 370.3±1.52 μg/mL when the temperature was maintained at 37°C. Within the first half an hour, the RG-SD (RG:PVP K30) (1:10) formulation showed a notable surge release of 65%. A recent scientific study found that Repaglinide's characteristics were improved when PVP-K30 (1:10) was used as a carrier in solid dispersions of the drug.

Keywords: Repaglinide, Solid Dispersion, PVP K30, Dissolution Rate, Solvent evaporation

INTRODUCTION

The low solubility of drugs in water is a major concern for researchers in the pharmaceutical field.¹ The in vivo effectiveness of the drugs is hindered by inadequate aqueous solubility, leading to reduced bioavailability, atypical pharmacokinetic profile, and variability between subjects and species, resulting in costly and time-consuming development.² Repaglinide belongs to the meglitinide class of drugs, commonly used for the treatment of type II diabetes mellitus. The mechanism of action involves the stimulation of insulin production by the pancreas, resulting in a reduction of blood glucose levels.³

Repaglinide, a Biopharmaceutics Classification System (BCS) class II drug with a water solubility of approximately 34 g/mL and a bioavailability of 50-60%, is considered a compound with low solubility in water. A compound known as repaglinide (RPG), which is a derivative of carbamoylmethyl benzoic acid, contains two functional groups. One of these functional groups is weakly basic with a pKa value of 6.01, while the other functional group is weakly acidic with a pKa value of 4.16.⁴

Various pharmaceutical techniques can be employed to enhance the solubility of drugs in aqueous solutions. These techniques include solid dispersion, surfactant solubilization, co-solvent utilization, particle size reduction, hydrotropy, and the utilization of derivatives or salts that exhibit solubility in aqueous solutions.⁵ One of the most effective techniques for enhancing the solubility, dissolution rate, and thus the bioavailability of drugs with low water solubility is solid dispersion.⁶

One of the techniques employed to enhance the dissolution rate of drugs with low water solubility is solid dispersion using a hydrophilic carrier matrix. In this methodology, the carrier or matrix is
dispersed with one or more active ingredients, leading to the creation of simple eutectic mixtures, solid solutions, or amorphous precipitates. In order to attain a high dissolution rate, this process has the potential to modify the level of drug crystallinity. Moreover, the process of solid dispersion formation can lead to a decrease in drug particle size, an increase in surface area, and enhanced wettability. These factors collectively contribute to the improvement of water solubility and dissolution rate.[7-8]

The objective of this study was to synthesize and analyze a solid dispersion of repaglinide in order to enhance its dissolution kinetics and bioavailability. In order to evaluate the effectiveness of the carriers for repaglinide, solubility and dissolution tests were conducted.

MATERIALS AND METHODS

The compound repaglinide was acquired from the supplier Yarrow Chem Products in Mumbai. PEG 4000, PEG 6000, PEG 8000, and polyvinylpyrrolidone (PVP K30) were procured from Colorcon Co., Ltd India. All other ingredients and chemicals utilized were of analytical grade.

Preparation of solid dispersions and physical mixtures

Preparation of physical mixtures

The drug Repaglinide was mixed with PVP K30, PEG 4000, PEG 6000, and PEG 8000 using a mortar and pestle until a uniform blend was achieved. The physical mixtures were collected for subsequent analysis following their passage through a 150μm sieve.[9-10]

Preparation of Solid dispersion by solvent evaporation method

The repaglinide and PVP K30 were accurately measured and dissolved in anhydrous ethanol. At a temperature of 80°C in a water bath, the solvent underwent evaporation. Subsequently, at a temperature of 60°C in a vacuum oven, the solvent was subjected to drying. In preparation for the following investigation, the dehydrated substances were subsequently pulverized and filtered using a 150μm mesh.[11-13]

Evaluation of Solid dispersion

Solubility studies

A solubility study was conducted to determine the saturation solubility of pure RG, physical mixtures, and RG-SD. An Erlenmeyer flask containing an excess sample and 25 mL of distilled water was agitated for 24 hours at a temperature of 37±0.5 °C. Subsequently, a 0.45 meter membrane filter was employed to effectively filter the dispersion. After diluting the drug with distilled water according to the appropriate ratio, the drug concentration was subsequently assessed using a UV Spectrophotometer (Shimadzu-1800, India) at a wavelength of 241 nm. Additionally, the solubility of the drug was measured.[14-16]

Drug content of solid dispersion

Solid dispersions comprising 2 mg of the pharmaceutical compound were administered, dissolved in a minimal quantity of methanol, and subsequently diluted to a total volume of 50 ml. A volume of 5 milliliters (ml) of this solution was extracted and subsequently further diluted with methanol to achieve a final volume of 50 ml. A 0.45 μm Whatman filter paper was utilized to perform sample filtration. The filtrate underwent analysis using a UV spectrophotometer at a wavelength of 241 nm, compared to a blank sample, following appropriate dilutions.[17]

In vitro Dissolution studies

The RG-SD equivalent to 10 mg of RG was measured by weight and introduced into the dissolution medium, consisting of a pH 7.4 phosphate buffer with a volume of 900 ml, at a temperature of 37 ± 0.5°C. A total of 5 mL samples were extracted using a syringe filter at the designated time intervals. The samples were then analyzed for RG content by measuring the absorbance at 241 nm using a UV-Visible spectrophotometer (UV-1800, Shimadzu, India). Dissolution studies were conducted in triplicate (n = 3), and the average values were obtained.[18-20]

Drug release kinetics

Various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations, were analyzed to identify the most
suitable mathematical model for quantifying the kinetics and mechanism of drug release from RG-SD. The drug release data acquired from the RG-SD device was fitted into different models in the present study.

**DSC studies**

The DSC measurements were conducted utilizing a differential scanning calorimeter. Mettler Toledo is a leading provider of precision instruments and services for laboratory and industrial applications. The 2–5 mg sample was placed in aluminum pans, subjected to a temperature scan with a heating rate of 10°C/min between the temperature range of 30°C to 200°C, and then analyzed under a nitrogen atmosphere that was free from reactive gases.

**XRD measurement**

The X-ray diffraction (XRD) analyses of RG and RG-SD samples were performed using a D8 Advance XRD instrument equipped with a 2.2 kW sealed X-ray tube that emits Cu-Kα radiation. A scanning rate of 10°/min was employed to collect X-ray powder diffraction patterns. The scanning was performed over a 20 angular range of 5–80° with an increment of 0.05°.

The solubility of physical mixtures was found to be highest in PVP K30. However, when compared to the physical mixture, the solubility of the solid dispersion prepared using PVP K30 through the solvent method exhibited a significantly greater value. Based on the findings, PVP K30 demonstrated superior performance as a carrier for Repaglinide solid dispersion compared to other carriers tested. Finally, a solid PVP (polyvinylpyrrolidone) K30 dispersion was developed in various ratios, as indicated in Table 2.

The solubility of RG-SD was observed to increase when the ratio of RG to PVP K30 reached 1:10. The solubility of the drug was found to be enhanced as the proportion of PVP K30 increased up to a ratio of 1:10. However, further increases in the amount of PVP K30 did not result in a significant enhancement of drug solubility. Polyvinylpyrrolidone (PVP) was demonstrated to enhance the solubility of a hydrophobic pharmaceutical compound following the preparation of its solid dispersion. The solubility of RG-SD was increased from 161.4±1.25 to 370.3±1.52, with the highest solubility (370.3±1.52) observed in RG:PVP K-30 (1:10) formulation.

**Table 1: Solubility studies of Repaglinide in different carriers (n=3)**

<table>
<thead>
<tr>
<th>Sample (Physical mixtures)</th>
<th>Drug &amp; Polymer ratios</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure RG</td>
<td>-</td>
<td>34.41±0.68</td>
</tr>
<tr>
<td>RG : PEG 4000</td>
<td>1:1</td>
<td>41.32±0.72</td>
</tr>
<tr>
<td>RG : PEG 6000</td>
<td>1:1</td>
<td>68.21±0.88</td>
</tr>
</tbody>
</table>
Table 2: Effect of drug/carrier ratio on solubility of repaglinide in water (n = 3)

<table>
<thead>
<tr>
<th>Sample (Solid Dispersion)</th>
<th>Drug &amp; Polymer ratios</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG : PEG 8000 1:1</td>
<td></td>
<td>74.38±0.93</td>
</tr>
<tr>
<td>RG : PVP K-30 1:1</td>
<td></td>
<td>83.57±0.42</td>
</tr>
<tr>
<td>RG : PVP K-30 1:3</td>
<td></td>
<td>161.4±1.25</td>
</tr>
<tr>
<td>RG : PVP K-30 1:5</td>
<td></td>
<td>207.1±1.34</td>
</tr>
<tr>
<td>RG : PVP K-30 1:10</td>
<td></td>
<td>302.4±1.19</td>
</tr>
<tr>
<td>RG : PVP K-30 1:15</td>
<td></td>
<td>370.3±1.52</td>
</tr>
</tbody>
</table>

Drug content of solid dispersions
The drug content (n=3) of RG-SD was determined to be between 97.45 ± 0.11% and 99.42 ± 0.93%. The results indicate that the techniques employed for the production of solid dispersions in this investigation successfully generated formulations with uniform drug content.

In vitro Dissolution studies
Figure 2 depicts the dissolution profiles of RG and RG-SD with PVP K30 at various ratios. The dissolution patterns of the RG and RG-SD exhibited significant differences, as anticipated. The drug release rate was found to be the fastest when using a 1:10 ratio of PVP K30 to PVP K30 compared to other ratios. The dissolution rate of RG-SD (Rapidly Disintegrating Solid Dosage) with PVP K30 (Polyvinylpyrrolidone K30) at a ratio of 1:10 exhibited a significant burst release of 65% within the initial 30 minutes. The dissolution rate of Pure RG was observed to be slow, as indicated by the average percentage of RG dissolved after 60 minutes being 5%. This percentage gradually increased between 120 and 180 minutes, with mean dissolution percentages of 14% and 21%, respectively. Upon completion of the dissolution study after 240 minutes, the average percentage of drug dissolved was found to be 29%. On the contrary, following a duration of two hours, only 85% of the drug had undergone dissolution. The ratio of the drug concentration to PVP K30 concentration had a notable effect on the dissolution rate of RG-SD.

The dissolution rates exhibited a positive correlation with the increasing proportions of PVP K30 up to a ratio of 1:10. However, beyond this ratio, the dissolution rate showed a decrease with the increasing proportion of PVP K30. This observation indicates that the carrier may undergo leaching during dissolution, resulting in the formation of a concentrated solution layer around the drug particles. This phenomenon could be responsible for the reduced dissolution rate of the solid dispersion. Amorphous drug forms embedded in polymeric carriers can be found in solid dispersion systems, resulting in enhanced solubility and dissolution rates compared to crystalline material.

Drug release kinetics
The drug release data for RG-SD (1:10) was analyzed using different kinetic equations in order to determine the order and mechanism of drug release. The correlation coefficient (R2= 0.986) indicated a strong relationship between the release profile and the Korsmeyer peppas model. The release exponent, n, was determined to be 0.521, suggesting non-Fickian transport. This implies that the RG-SD substance exhibits a combination of diffusion and erosion mechanisms. Based on the aforementioned findings, it is evident that the
regression coefficient value of the Korsmeyer-Peppas model, which is closer to unity, signifies that the drug follows an exponential release pattern over time. When the data is plotted using the first order, zero order, and Higuchi equations, it exhibits reduced linearity. The correlation coefficients for the first-order, zero-order, and Higuchi models are 0.615, 0.951, and 0.954, respectively.

**DSC studies**

DSC thermograms of the pure RG and RG-SD with PVP K30 in a ratio of 1:10 are displayed in Figure 3. The pure RG sample displayed an endothermic peak at approximately 137 °C, which corresponds to the known melting point of Repaglinide. On the other hand, the RG peak exhibited a significant decrease and no corresponding peaks were observed in the solid dispersion, suggesting that the drug underwent a transition from its crystalline form to an amorphous form.

**CONCLUSION**

The successful preparation of a solid dispersion of repaglinide and PVP K30 (1:10) was concluded using the solvent evaporation method. Compared to the pure drug or its physical mixture, the solubility and dissolution of repaglinide from this dispersion system exhibited a notable increase. Experiments utilizing Differential Scanning Calorimetry and X-ray Diffraction techniques demonstrated that this particular system contained a pharmaceutical substance in an amorphous state. In this study, Polyvinylpyrrolidone K30 in a ratio of 1:10 was determined to be the optimal formula. This choice was based on the observation of a significant enhancement in the release of the drug after 30 minutes compared to pure RG.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest.

**Acknowledgement:** NA.

**REFERENCES**


