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Improvement of Dissolution Rate of Repaglinide by Utilizing Solid Dispersion Technique

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ABSTRACT

The recent study's objective was to prepare and evaluate the Repaglinide (RG) solid dispersion. RG is poorly water soluble, BCS class II drug. Repaglinide solid dispersion (RG-SD) was prepared by solvent evaporation method using different proportion of PVP K30. The prepared RG-SD was evaluated for solubility studies, drug content, in vitro dissolution, DSC studies and XRD studies. DSC and XRD studies results indicate that RG exists in amorphous form in solid dispersion. The solubility of pure RG was enhanced from 34.41±0.68 to 370.3±1.52 µg/mL in distilled water at 37^0 C. RG-SD (RG:PVP K30) (1:10) showed high burst release (65%) in the first 30 min. Current research concludes that Repaglinide solid dispersions using PVP-K30 (1:10) as a carrier in solid dispersions showed promising results in enhancement of repaglinide properties.

Key words: Repaglinide, Solid Dispersion, PVP K30, Dissolution Rate, Solvent evaporation

1. INTRODUCTION

Poor aqueous solubility[1] of drugs is a significant issue for pharmaceutical researchers. The *in vivo* effectiveness of the drugs is hampered by poor aqueous solubility, which results in low bioavailability, an abnormal pharmacokinetic profile, and inter-subject and inter-species variation, which results in expensive and time-consuming development.[2] Repaglinide is a member of the meglitinide class of medications, which are frequently prescribed to treat type II diabetes mellitus. It lowers blood glucose levels by encouraging the pancreas to produce more insulin.[3] Repaglinide, a BCS class II drug with a water solubility of roughly 34 g/mL and a relatively low bioavailability (50–60%), is a poorly water-soluble compound. A carbamoyl methyl benzoic acid derivative called repaglinide (RPG) has two functional groups, one of which is weakly basic (pKa = 6.01) and the other is weakly acidic (pKa = 4.16) in nature.[4]

Many pharmaceutical techniques can be used to increase the solubility of drugs in aqueous solutions, including solid dispersion, surfactant solubilization, co-solvent use, particle size reduction, hydrotropy, and the use of derivatives or salts that are soluble in aqueous solutions.[5] One of the most efficient methods for increasing the solubility, rate of dissolution, and consequently the bioavailability of poorly water-soluble drugs is solid dispersion.[6] One of the methods for increasing the rate at which drugs that are poorly water-soluble dissolve is solid dispersion with a hydrophilic carrier matrix. In this approach, the carrier or matrix is dispersed with one or more active ingredients, resulting in the formation of straightforward eutectic mixtures, solid solutions, or amorphous precipitates. To achieve high dissolution, this process may alter the degree of drug crystallinity. Furthermore, the formation of solid dispersion can reduce drug particle size, increase surface area, and wettability, all of which can improve water solubility and dissolution rate.[7]

The purpose of this study was to prepare and characterize repaglinide solid dispersion to improve its dissolution property and bioavailability. To assess the efficacy of the carriers for repaglinide, solubility and dissolution tests were performed.

2. MATERIALS AND METHODS

Repaglinide was purchased from Yarrow Chem Products Mumbai. PEG 4000, PEG 6000, PEG 8000, polyvinylpyrrolidone (PVP K30) were obtained from Colorcon Co., Ltd India. all other ingredients and chemicals used were of analytical grade.

2.1 Preparation of Solid Dispersions and Physical Mixtures

2.1.1 Preparation of Physical Mixtures

Repaglinide was combined with PVP K30, PEG 4000, PEG 6000, and PEG 8000 in a mortar and pestle until a homogeneous mixture was obtained. The physical mixtures were collected for further study after being put through a 150 µm sieve.

2.1.2 Preparation of Solid Dispersion by Solvent Evaporation Method [8]

Weighed precisely, repaglinide and PVP K30 were dissolved in anhydrous ethanol. At 80°C in a water bath, the solvent was evaporated, and at 60°C in a vacuum oven, it was dried. For the subsequent study, the dried materials were then ground up and sieved through a 150 µm mesh.

2.2 Evaluation of Solid Dispersion

2.2.1 Solubility Studies

To figure out the saturation solubility of pure RG, physical mixtures, and RG-SD, a solubility study[9] was conducted. A conical flask with an excess sample and 25 ml of distilled water was shaken for 24 hours at 37±0.5 °C. After that, a 0.45 µm membrane filter was used to filter the dispersion. Following the proper dilution with distilled water, the drug concentration was then determined by UV Spectrophotometer (Shimadzu-1800, India) at 241 nm, and the drug solubility was measured.

2.2.2 Drug Content of Solid Dispersions[10]

Solid dispersions containing 2 mg of the drug were taken, dissolved in a minimum amount of methanol, and diluted to a volume of 50 ml. 5 ml of this solution was taken, and it was then diluted once more with methanol to make 50 ml. Whatman filter paper 0.45 µm was used to filter the samples. The filtrate was analyzed using a UV spectrophotometer at 241 nm against a blank after appropriate dilutions.

2.2.3 In vitro Dissolution Studies[11-12]

The RG-SD equivalent to 10 mg RG was weighed and added to the dissolution medium (pH 7.4 phosphate buffer, 900 ml) at 37 ± 0.5 ºC. 5 mL samples were withdrawn using a syringe filter at the specified times and then assayed for RG content by measuring the absorbance at 241 nm using a UV-Visible spectrophotometer (UV- 1800, Shimadzu, India). Dissolution studies were performed in triplicate (n = 3), and mean values were taken.

2.2.4 Drug Release Kinetics

Several mathematical models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations were investigated to determine the best mathematical model for determining the kinetics of drug release and mechanism of drug release from RG-SD. The drug release data obtained from the RG-SD was fitted into the various models in the current study, as shown in Figure 1.

2.2.5 DSC Studies

The measurements of DSC were carried out using a differential scanning calorimeter. (Mettler Toledo). The 2–5 mg sample was placed in aluminum pans, subjected to a 10 °C/min temperature scan between 30 °C to 200 °C, and then examined under an inert nitrogen atmosphere.

2.2.6 XRD Measurement

The XRD studies of RG and RG-SD were conducted using an X-ray diffractometer (D8 Advance XRD) with a 2.2 kw sealed X-Ray tube (Cu-Kα). A scanning rate of 10°/min over a 2θ angular range of 5–80° with an increment of 0.05° was used for obtaining X-ray powder diffraction patterns.

3. RESULT AND DISCUSSION

3.1 Solubility Studies

In the present investigation, the solubility of RG, physical mixtures and RG-SD using other carriers such as PEG 4000, PEG 6000, PEG 8000, and PVP K30 were determined and are summarized in Tables 1 and 2. Pure RG intrinsic aqueous solubility was calculated, and it was found to be 34.41±0.68 µg/ml when compared to the physical mixture of PVP K-30, the solubility of PEG 4000, PEG 6000, and PEG 8000 did not improve.

PVP K30 had the highest solubility of physical mixtures. Yet, compared to the physical mixture, the solubility of the solid dispersion made with PVP K30 by the solvent method was significantly higher. According to the results, PVP K30 was the best carrier out of all those tested for Repaglinide solid dispersion.

Finally, solid PVP K30 dispersion in various ratios developed as shown in Table 2. RG-SD solubility was increased up to 1:10 ratio of RG and PVP K30. The drug solubility enhanced with the increase in the proportion of PVP K30 up to 1:10 ratio and further increase of PVP K30 did not enhance drug solubility significantly. PVP was shown to increase the solubility of a hydrophobic drug after its solid dispersion was prepared. The solubility of RG-SD was enhanced from 161.4±1.25 µg/ml to 370.3±1.52 µg/ml and the maximum solubility (370.3±1.52 µg/ml) was found in RG: PVP K-30 (1:10).

3.2 Drug Content of Solid Dispersions

The drug content (n=3) of RG-SD was found between 97.45 ± 0.11% and 99.42 ± 0.93%. The outcomes show that the methods used to make the solid dispersions in this study were able to create formulations with consistent drug content.

3.3 *In vitro* Dissolution Studies

Figure 1, shows the dissolution profiles of RG and RG-SD with PVP K30 at different ratio. The dissolution patterns of the RG and RG-SD differed significantly, as was to be expected. PVP K30 with PVP K30 in 1:10 ratio showed the fastest drug release from others. The dissolution rate of RG-SD with PVP K30 (1:10) showed high burst release (65%) in the first 30 min. Pure RG dissolved slowly, as evidenced by the average percent of RG dissolved after 60 minutes being 5%, which gradually increased between 120 and 180 min., the mean percentages of drug dissolved were 14% and 21%, respectively. At the end of the dissolution study after 240 min., the mean percentage of drug dissolved amounted to 29%. On the opposite hand, after two hours, only 85% of the drug had been dissolved. The relative concentration of the drug to PVP K30 ratio had a significant impact on the rate of RG-SD dissolution. The dissolution rates increased as PVP K30 proportions increased up to a ratio of 1:10 and after that dissolution rate decreased by increasing the proportion of PVP K30. This finding suggested that the leaching out of the carrier during dissolution, which could form a concentrated layer of solution around the drug particles, might be the cause of the solid dispersion's slower rate of dissolution. Amorphous drug forms in polymeric carriers may be present in solid dispersion systems, which may lead to better solubility and dissolution rates than crystalline material.

3.4 Drug Release Kinetics

Drug release data for RG-SD (1:10) was fitted into various kinetic equations to find out the order and mechanism of drug release. The correlation coefficient showed that the release profile followed the Korsmeyer peppas model (R^2= 0.986), and the release exponent, n was found to be 0.521, indicating non-Fickian transport, suggesting that RG-SD follows both diffusion and erosion mechanism. From the aforementioned findings, it is clear that the Korsmeyer-Peppas model's regression coefficient value, which is closer to unity, indicates that the drug releases exponentially as time passes. When the data are plotted using the first order, zero order, and Higuchi equations, they show less linearity. First-order, zero-order, and higuchi model correlation coefficients are 0.615, 0.951, and 0.954, respectively.

3.5 DSC Studies

DSC thermograms of pure RG and RG-SD with PVP K30 (1:10) are shown in Figure 2, Pure RG exhibited an endothermic peak at around 137 °C, which was consistent with the melting point of Repaglinide. Conversely, the RG peak showed a considerable drop and no similar peaks were seen in the solid dispersion, indicating that the drug had changed from its crystalline state to an amorphous state.

3.6 XRD Measurement

The XRD diffractograms of pure RG and RG-SD were studied. The diffraction pattern of pure RG shows the different peaks at 2 Theta = 7.60 20.26, 22.90, 23.96, 30 and 33. The crystal character of the pure RG was amply demonstrated by these peaks. Furthermore, a significant decrease in characteristic peaks suggests the presence of amorphous forms.

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

Sample (Physical mixtures)	Drug & Polymer ratios	Solubility (µg/ml)
Pure RG	-	34.41±0.68
RG: PEG 4000	1:1	41.32±0.72
RG: PEG 6000	1:1	68.21±0.88
RG: PEG 8000	1:1	74.38±0.93
RG: PVP K-30	1:1	83.57±0.42

Table 2: Effect of drug/carrier ratio on solubility of repaglinide in water (n = 3)

Sample (Solid Dispersion)	Drug & Polymer ratios	Solubility (µg/ml)
RG: PVP K-30	1:1	161.4±1.25
RG: PVP K-30	1:3	207.1±1.34
RG: PVP K-30	1:5	302.4±1.19
RG: PVP K-30	1:10	370.3±1.52
RG: PVP K-30	1:15	344.7±1.41

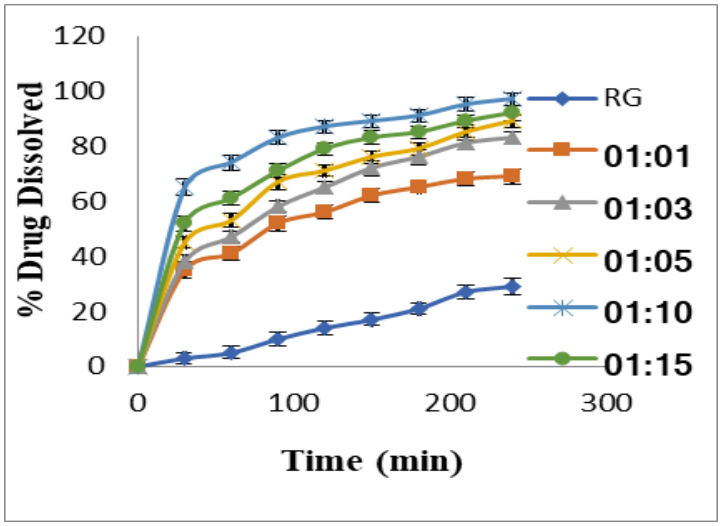

Figure 1: Dissolution profile of Repaglinide solid dispersion

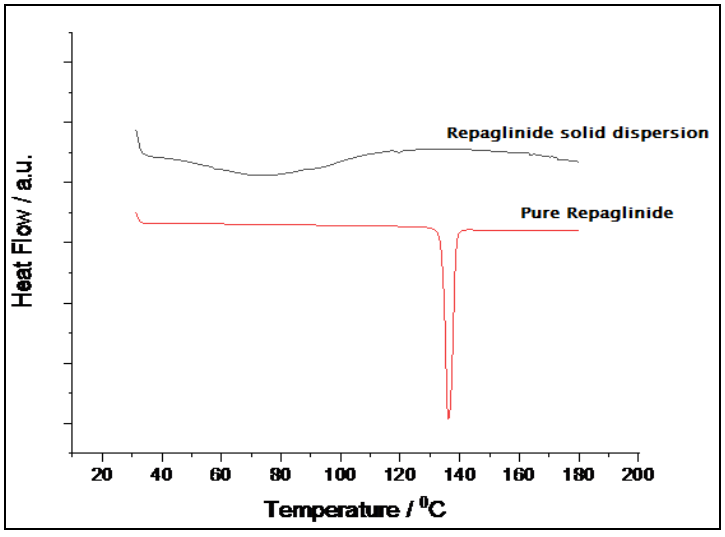

Figure 2: DSC thermograms of Pure Repaglinide and Repaglinide solid dispersion (1:10)

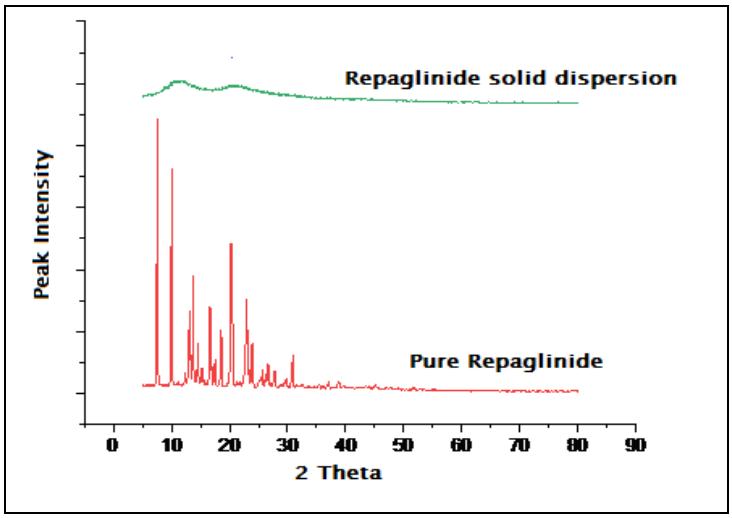

Figure 3: Diffractogram of Pure Repaglinide and Repaglinide solid dispersion (1:10)

4. CONCLUSION

It is concluded that solid dispersion of repaglinide and PVP K30 (1:10) was successfully prepared by the solvent evaporation method. In comparison to the pure drug or its physical mixture, the solubility and dissolution of repaglinide from this dispersion system were significantly higher. Studies using DSC and XRD showed that this system contained a drug in an amorphous form. In this study PVP K30 in a ratio 1:10 was chosen as the best formula due to a marked increase of drug release after 30 min than pure RG.

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