Improvement of Solubility of Repaglinide by Physical Mixing and Melt Solvent Method

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Abstract: This study focused on an investigation and assessment of solubility and dissolution rate of the drug repaglinide, a practically water-insoluble antidiabetic drug and the main purpose of this study was to enhance the dissolution rate by solid dispersion (SD) system consisting of drug, excipients and carrier. Solid dispersion formulations were prepared by using the physical mixing (PM) and melt solvent method. Physical mixtures (PMs) of repaglinide and hydrophilic polymer Kollicoat IR, HPMC, Kollidon 90F, Poloxamar 407 and PVK 30 were prepared at 1:1, 1:3 and 1:5 ratios. Melt Solvent method was used to prepare solid dispersion of repaglinide with hydrophilic excipients Kollicoat IR, HPMC, Kollidon 90F, Poloxamar 407 and PVK 30 at 1:1, 1:3 and 1:5 ratios. All formulations were characterized by scanning electron microscopy (SEM) and dissolution tests. Characterization studies revealed that SD prepared by melt solvent methods displayed better dissolution property compared to physical mixing and pure API repaglinide due to the conversion into a less crystalline and/or amorphous form. The order of dissolution rate enhancement was Kollicoat IR > PVK30 > Kollidon 90F > Poloxamar 407 > HPMC in solid dispersions. In all cases enhancement of dissolution rate was significantly superior in solid dispersions prepared by melt solvent method than the physical mixtures. The SEM studies influenced that a decreased crystallinity of the solid dispersions revealed that a portion of repaglinide was in an amorphous state. This was because of Kollicoat IR, Kollidon 90F, Poloxamar 407, HPMC and PVK 30 modified the crystallinity that could be considered as an important factor in enhancement of the dissolution rate.

Keywords: Melt Solvent method; Repaglinide; hydrophilic excipients; poorly water-soluble drug; dissolution rate.

INTRODUCTION

Repaglinide is a water insoluble antidiabetic drug which belongs to the class of medications known as meglitinides [1]. It lowers the blood glucose by stimulating the release of insulin from the pancreatic β-cell [2-4]. Repaglinide is a poorly water-soluble approximately 20 μg/mL, high lipophilicity and relatively low oral bioavailability (56 %) which is attributed to poor dissolution release (BCS class II) and however once it dissolved, it can be absorbed rapidly and completely in the gastrointestinal tract [5,6].

Repaglinide has very low and erratic oral bioavailability due to its inferior water solubility. Therefore, it is indispensable to design effective methods to boost dissolution profile, hence its oral absorption which will eventually increase bioavailability. The improvement of bioavailability of poorly aqueous soluble drugs in oral route remains one of the most challenging aspects of formulation development [7]. Though salts formation, micronization, prodrug, particle size reduction and solubilization have commonly been used to raise dissolution rate and thereby oral absorption and bioavailability of such drugs, there are some practical downsides of these techniques [8]. Solid dispersions have been considered as a fruitful method for enhancing drug dissolution rate and saturation solubility in the gastrointestinal fluids [9]. Solid dispersion (SD) is defined as the dispersion of one or more API in inert carriers at solid state prepared by melt solvent, fusion, solvent, or solvent melt solvent methods [10, 11]. Solid dispersion system provides the possibility of reducing the API particle size and altering the drug crystal structure to the shapeless amorphous state, and/or to locally increase the saturation aqueous solubility [12, 13].

Solid dispersion (SD) formulations of a poorly soluble drug have been prepared by mixing with hydrophilic polymers is a promising method for improving the dissolution profile characteristics and bioavailability of the drug [14, 15]. Water-soluble carriers such as polyvinylpyrrolidone (PVP) [16, 17], mannitol, poloxamer [18], hydroxypropyl methylcellulose (HMC) [19] and polyethylene glycols etc. have been employed for preparing solid dispersions of different drugs to improve dissolution rate. In the
current study, an effort has been made to boost solubility of repaglinide by solid dispersion using physical mixing (PM) and melt solvent technique using a series of hydrophilic excipients/carriers Kollidion 90F, Poloxamar 407, HPMC and PVK 30.

MATERIALS AND METHODS

Materials

Repaglinide, Kollidion 90F and Kollidion 90F was provided as generous gift from Beximco Pharmaceutical, Bangladesh (Analytical grade). Poloxamar 407, HPMC and PVK 30 were obtained from BASF (Germany). All other materials including solvents and reagents were of analytical grade of purity.

Preparation of Physical Binary Mixtures of Repaglinide–polymer

Physical mixtures (PM) of repaglinide with Poloxamar 407, Kollidion 90F, PVK 30, Kollidion 90F, and HPMC were prepared by properly mixing in a mortar and pestle for 15-20 minutes. The binary mixtures of drug–polymer carrier were then stored in desiccators at a room temperature until further test and were letter-coded as PM (physical mixture) (Table-1) [20].

Preparation of Solid Dispersion by Melt Solvent Method:

Polyethylene glycol 6000 was precisely weighed and placed in an aluminum pan on a hot plate and molten at a temperature around 55–60 °C [20]. Then correctly weighed repaglinide & polymer were added in the molten PEG with continuous stirring to assure homogenous mixing. The mixtures were then allowed to cool-down to room temperature to get the dry and solid mass of the mixtures [20]. The ternary mixtures (SD) were then powdered in a mortar-pestle and sieved through a 40-mesh sieve to have uniform-size. The SD powders were then preserved in desiccator at the ambient temperature for further use. SD powders were letter-coded as MS (melt solvent) (Table-1).

Scanning Electron Microscopy (SEM)

The scanning electron microscopy (SEM) analysis was accomplished using scanning electron microscope (JSM 6100, Jeol, Japan). Samples of Pure repaglinide, physical mixtures (PM) formulations and solid dispersion (SD) were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of gold palladium alloy (150–200Å) [20]. The scanning electron microscope was operated at an acceleration voltage of 20 KV, working distance (12–14 mm). The selected magnification was ×500. SEM was used to investigate particle shape of formulations [20].

In vitro release studies

In vitro dissolution studies of API, PM, and SD formulations equivalent to 2 mg of repaglinide were performed in USP type II paddle type apparatus (ELECTRO LAB, India) using 900 mL distilled water maintaining at 37 ± 0.5°C as dissolution medium and 50 rpm as the paddle rotation speed [20]. Each time, 10 mL of dissolution medium was withdrawn at predetermined time intervals and 10 mL fresh distilled water was added immediately to maintain the sink condition [20]. The withdrawn medium samples were filtered through 0.45 μm filter paper and analysed for pure drug content by a UV-VIS (Varian Cary 5000 or Agilent Cary 60) spectrophotometers at a of 243 nm.

RESULTS AND DISCUSSION

Scanning Electron Microscopy (SEM)

SEM studied indicated that pure drug repaglinide particles were asymmetrical in shape, while the physical mixture (PM) of the API and hydrophilic excipients demonstrated that drug particle remains distributed and physically adsorbed on the surface of the hydrophilic carrier particles. The solid dispersion of repaglinide, Kollidion 90F, Kollidion 90F, Poloxam 407 and HPMC presented a homogeneous dispersion demonstrating that the repaglinide molecules were disseminated uniformly in carrier of solid dispersion prepared by fusion/melt method at 1:5 ratios, assuming reformed to amorphous form.

Fig-1: Chemical structure of repaglinide [4]
Table 1: Different Formulations Prepared by Physical Mixing and Melt Solvent Method

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Polymer</th>
<th>Formulation Combination</th>
<th>Assigned Code of the Formulated Batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kollicoat IR</td>
<td>1:1</td>
<td>5:1:1</td>
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<tr>
<td>2</td>
<td></td>
<td>1:3</td>
<td>5:1:3</td>
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<tr>
<td>3</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>PVP K30</td>
<td>1:1</td>
<td>5:1:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1:3</td>
<td>5:1:3</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1:5</td>
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</tr>
<tr>
<td>7</td>
<td>Poloxamar 407</td>
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<td>5:1:1</td>
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<td>8</td>
<td></td>
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<td>13</td>
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<td>1:3</td>
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<tr>
<td>15</td>
<td></td>
<td>1:5</td>
<td>5:1:5</td>
</tr>
</tbody>
</table>

RpG = Repaglinide; P = polymer; C = Carrier, PEG 6000; PM = physical mixing; MS = melt-solvent

Fig-2: standard curve of repaglinide

Fig-3: Scanning Electron Microscopy (SEM) of the formulations
In vitro release studies

In vitro dissolution profile studies were carried out three times of each of the formulations (formulations PM₁, PM₂, PM₃, PM₄, PM₅, PM₆, PM₇, PM₈, PM₉, PM₁₀, PM₁₁, PM₁₂, PM₁₃, PM₁₄, PM₁₅, MS₁, MS₂, MS₃, MS₄, MS₅, MS₆, MS₇, MS₈, MS₉, MS₁₀, MS₁₁, MS₁₂, MS₁₃, MS₁₄ & MS₁₅). The cumulative released of repaglinide in dissolution media was 50.8% after 60 minutes which is presented in figure 4. The mean cumulative percent of repaglinide released from PM₁, PM₂, PM₃, PM₄, PM₅, PM₆, PM₇, PM₈, PM₉, PM₁₀, PM₁₁, PM₁₂, PM₁₃, PM₁₄ and PM₁₅ formulations prepared by physical mixing (PM), at various time intervals is shown in figure 4. It was witnessed that the rate of API release for PM₃, PM₆, PM₉, PM₁₂ and PM₁₅ was superior than 1:1 and 1:3 formulations. As 75%, 80% and 78% repaglinide was found to be released in case PM₁₂, PM₃ and PM₆ (1:5 ratio) after 60 minutes of dissolution study. The greater dissolution rate of API due to presence of carriers’ polymers which boosted effective solubilisation process and transformation of unstructured/amorphous phases, the dissolution percentage (%) was very higher. Therefore, the improve aqueous solubility and dissolution profile of repaglinide increased significantly in the presence of Kollicoat IR, Kollidon 90F, PVK 30, HPMC and Poloxamar 407. On the other hand, the formulations MS₁, MS₂, MS₃, MS₄ and MS₁₅, produced by melt solvent technique exhibited maximum release after 60 minutes which were nearly 95% for Kollicoat IR (MS₃), 92% for PVP K30 (MS₆) and 88% for Kollidon 90F (MS₁₂), 82% for Poloxamar 407 (MS₁₂), 79% for HPMC (MS₁₅), respectively which were much improved than MS₁, MS₂, MS₃, MS₄, MS₅, MS₆, MS₁₀, MS₁₁, MS₁₃, MS₁₄ and all other PM formulations shown in Figure 4. Various studies have also reported that Kollicoat IR, Kollidon 90F Poloxamar 407, HPMC and PVK30 reduce crystallinity of drugs and resulting in amorphous nature of API in the solid dispersions [20, 21, 22]. Crystallization inhibition was attributed to two effects: the interactions between the drug molecule and the hydrophilic polymer due to hydrogen bonding and the entrapment of the drug molecules in the hydrophilic polymeric matrix. In presence of hydrophilic excipients, drug had better wettability; hence the dissolution of drug was greater in the form of solid dispersion [20, 23, 24]. The order of dissolution enhancement was Kollicoat IR>PVK30>Kollidon 90F>Poloxamar 407> HPMC in solid dispersions as well as in physical mixtures.

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CONCLUSIONS

The study has demonstrated that binary and ternary dispersions of repaglinide into water-soluble carriers like Kollicoat IR, PVK30, Kollidon 90F, Poloxamer 407 and HPMC changed/transformed the crystallinity of repaglinide according to type and amount of the polymer. The formation of repaglinide–Kollicoat IR/PVK 30/Kollidon 90F solid dispersion destroyed/reduced almost completely the crystallinity of the drug and represent a suitable modification for improving its availability. Increase dissolution rate likely increase bioavailability of repaglinide which would be beneficial for better glucose control in diabetic patients. However, further studies are required especially in vivo studies to confirm bioavailability.

Acknowledgement

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REFERENCES


