Formulation and enhancement of dissolution rate of poorly aqueous soluble drug Aceclofenac by solid dispersion method: In vitro study

Sumana Neupane and Chhitij Thapa*

Department of Pharmacy, Universal College of Medical Sciences, Tribhuwan University, Siddhartha Nagar, Rupandehi 32900, Nepal.

Received 19 November, 2019; Accepted 19 December, 2019

Solid dispersion technique was successfully used to enhance the dissolution of poorly aqueous soluble drugs aceclofenac. Four carriers Hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA), Mannitol and Dextrose in two ratios (1:2, 1:3 w/w) were used to prepare solid dispersion. Eight different formulations were designed by the varying carrier and the drug: Carrier ratio and solvent wetting method was used for preparing solid dispersion. Acquired formulations were used for various micrometric and in vitro drug release studies. The solubility of aceclofenac in distilled water was 0.0753±0.021 mg/ml. The study shows that aceclofenac solubility is pH-dependent where the solubility observed was greater in phosphate buffer (pH 7.4) at 5.76±1.23 mg/ml compared to acid buffer (0.1 N HCl) at 0.0214±0.012 mg/ml. The percentage yield measured in F5 was higher at 85.18±6.02% and lower at 70.43±5.028% in F1. Micrometric study suggest that the Carr’s index and Hausner’s ratio value was smallest for F4 with 5.018±0.0025 and 1.06±0.0025 respectively, indicating an excellent flow property and greatest for F6 with 15.35±0.0022 and 1.18±0.0022, indicating relatively poor flow. The angle of repose value was lower for F5 with 20.77±2.9º and higher for F2 with 30.77±2.1º. Both acid buffer (pH 1.2) and phosphate buffer (pH 7.4) were undertaken for in vitro drug release study of pure drug aceclofenac and eight separate formulations. The in vitro drug release after 180 min for aceclofenac in acidic buffer (pH 1.2) was 3.89±0.41% and was highest in F8 with 54.73±6.60 % and lowest in F5 with 31.75±3.10 %. Drug release was significant compared to pure drug aceclofenac (p<0.05) in acidic buffer. Similarly, in vitro drug release after 180 min for aceclofenac in phosphate buffer (pH 7.4) was 23.79±2.20% and was highest in F8 with 76.65±6.50% and lowest in F5 with 64.09±5.70%. The data was analyzed by Dunnett’s multiple comparison tests while statistical significance was predefined at p<0.05.

Key words: Aceclofenac, hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA)

INTRODUCTION

Among all newly discovered chemical entities, about 40% of drugs are lipophilic and fail to reach the market due to...
their poor aqueous solubility (Ganesan et al., 2015). Drugs weak aqueous solubility and dissolution rate is one of the major problems in pharmaceutical growth and has become more prevalent among current drug candidates over the past two decades owing to the use of elevated-performance and combinatorial screening techniques during the drug discovery and selection phase (Mooter, 2011). A drug compound seems to be poorly soluble according to the Biopharmaceutical Classification System (BCS) if the utmost dose strength is insoluble in 250-ml aqueous media over the pH range at 37ºC (FDA, 2017). These compounds are mostly categorized into Class II compounds that seem to be poorly soluble and extremely permeable depending on the pH of the gastrointestinal fluid and tend to deliver dissolution rate-limited absorption (Kawabata et al., 2011). Drugs assigned to BCS Class II are marked by elevated permeability of the membrane, slow dissolution rate (owing to low water solubility) and elevated oral dose. Consequently, a drug’s solubility or dissolution rate is a crucial factor in determining its rate and magnitude of absorption. Improving the dissolution rate is essential to achieving an appropriate blood concentration for therapeutic effect since their dissolution rates are typically the rate-limiting step for bioavailability (Al-Hamidi et al., 2010). One of the most problematic aspects of drug development exists in the improvement of oral bioavailability of poorly aqueous soluble drugs. Though salt formation, co-solubilization, and decrease of particle size have been frequently used to boost the rate of dissolution and thus the oral absorption and bioavailability of such drugs, these methods have practical constraints (Bharti et al., 2015). The strategy of salt formation is not viable for neutral compounds and the synthesis of suitable salt forms of drugs that are weakly acidic or weakly basic may often not be functional (Choi et al., 2017). In many cases, although salts can be prepared, an enhanced rate of dissolution in the digestive tract might not be fulfilled due to the transformation of salts into aggregates of their corresponding acid or base forms (Frizon et al., 2013). The solubilization of drugs in organic solvents or aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are generally unwanted from patient acceptance and marketing.

Although a decrease in particle size is frequently used to raise the dissolution rate, there is a practical limit to size reduction obtained through frequently used techniques such as controlled crystallization, grinding, pearl milling, etc. The use of very fine powders in a dosage form can sometimes be troublesome due to hardships in handling and weak wettability due to the development of charges (Mogal et al., 2012). In 1961, Sekiguchi and Obi created a practical technique by which most of the constraints with the improvement of achieved, which was named as “Solid Dispersion” (Leonardi et al., 2007). The dissolution rate in conventional capsules and tablets is restricted by the size of the principal particles created after the dosage forms are disintegrated. In this situation, an average particle size of 5 µm is generally the reduced limit, although greater particle sizes are favored for ease of handling, formulation, and production (Pande et al., 2014). On the other side, if a solid dispersion or a solid solution is used, a part of the drug will immediately dissolve to saturate the gastrointestinal fluid and the surplus drug will precipitate as fine colloidal particles or submicron-sized. Solid dispersion has, therefore, become one of the most influential exploration fields in the pharmaceutical sector owing to the promising rise in the bioavailability of poorly water-soluble drugs (Kurmi et al., 2016; Leuner et al., 2000). Solid dispersion technology is the science of diffusing one or even more principal components in a solid-state in an inert matrix to obtain enhanced dissolution or constant discharge of drugs, modified solid-state properties as well as increased stability (Leonardi et al., 2007). The word solid dispersion relates to a set of solid components composed of at least two distinct parts, a soluble matrix and a low aqueous-soluble drug in general. The matrix can be either crystalline or amorphous and the drug may be molecularly dissipated in amorphous particles (clusters) or crystalline particles (Mogal et al., 2012).

Aceclofenac is a derivative of phenyl acetic acid with powerful anti-inflammatory and analgesic properties. It is a novel NSAIDs that displays a multifactor mechanism of action. ACE’s mode of action is based primarily on prostaglandin synthesis (PG) inhibition. ACE inhibits the enzyme of cyclooxygenase (Cox) involved in PG synthesis and also hinders synthesis inflammatory cytokines, interleukins, and tumor necrosis factors. The reduced nitrous oxide synthesis in human articular chondrocytes is also associated with its anti-inflammatory action. The aim of the study is focused on formulating the solid dispersion of poorly aqueous soluble drug aceclofenac by using different hydrophilic polymers to enhance the aqueous solubility and dissolution rate of the drug. The study also dwells on the effect of various polymers on drugs dissolution when formulated individually in different ratios.

MATERIALS AND METHODS

Aceclofenac (API) was gifted from Quest Pharmaceuticals Pvt. Ltd. Pipara, Bara, Birgunj, Nepal. Hydroxyl propyl methylcellulose (HPMC) was purchased from Kemphasol. Mannitol and polyvinyl alcohol (PVA) were purchased from SD- Fine Chemicals. Dextrose was purchased from Qualigens and Isopropyl alcohol (IPA) was purchased from Rankem. All the chemicals used were of analytical grade.

Formulation of solid dispersion

Solid dispersion of Aceclofenac was prepared by using four carriers...
Table 1. Formulation design involving different Aceclofenac loaded solid dispersions.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug</th>
<th>Carrier</th>
<th>Ratio (Drug: Carrier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Aceclofenac</td>
<td>Mannitol</td>
<td>1:2</td>
</tr>
<tr>
<td>F2</td>
<td>Aceclofenac</td>
<td>Dextrose</td>
<td>1:3</td>
</tr>
<tr>
<td>F3</td>
<td>Aceclofenac</td>
<td>HPMC</td>
<td>1:2</td>
</tr>
<tr>
<td>F4</td>
<td>Aceclofenac</td>
<td>PVA</td>
<td>1:3</td>
</tr>
<tr>
<td>F5</td>
<td>Aceclofenac</td>
<td>PVA</td>
<td>1:2</td>
</tr>
<tr>
<td>F6</td>
<td>Aceclofenac</td>
<td>HPMC</td>
<td>1:3</td>
</tr>
<tr>
<td>F7</td>
<td>Aceclofenac</td>
<td>Dextrose</td>
<td>1:2</td>
</tr>
<tr>
<td>F8</td>
<td>Aceclofenac</td>
<td>Mannitol</td>
<td>1:3</td>
</tr>
</tbody>
</table>

HPMC, PVA, Mannitol, Dextrose in two ratios (1:2, 1:3 w/w). Eight different formulations were designed by the varying carrier and the drug: carrier ratio as depicted in Table 1. The Solvent wetting method was used for preparing solid dispersion.

A weighed quantity of Aceclofenac was dissolved in an appropriate quantity of isopropyl alcohol. The amount of isopropyl alcohol used was 5 ml/gm polymer. The required amount of carrier was placed in the mortar, and then the drug solution was dropped into the carrier and was constantly stirred. Finally, the solvent was removed by evaporation at ambient temperature (25°C). The powder so obtained was ground in a mortar, dried and stored in a vacuum oven at 40°C for 24 h (Weerapol et al., 2017).

Characterization

Melting point determination

A small amount of the drug sample was taken and inserted in a thin-walled capillary tube; at one end, the tube was closed. The capillary comprising the sample was placed in the melting point apparatus and heated, and the melting point of the sample powder was observed when the drug sample was melted (Kala et al., 2016).

Solubility study

An excess quantity of aceclofenac was placed in 100-ml conical flask containing 50 ml of different solutions (distilled water, 0.1 N HCl and phosphate buffer PH 7.4). The sample was stirred for 24 h at 37°C in magnetic stirrer. The supernatant solution was then passed through a Whatmann filter paper 0.45 μm. The filtrate was appropriately diluted and the concentration of the Aceclofenac in the filtrate was determined by UV spectrophotometer at 273 nm (Samal et al., 2012).

Percentage yield

The percent yield was helpful to observe the efficiency of the method of preparation and was evaluated as the ratio of the practical mass obtained (g) concerning the total theoretical mass of drug and carrier considered during formulation. The final yield was expressed in terms of percentage (Gaur et al., 2014; Patel et al., 2006).

\[
\text{% Yield} = \frac{\text{Practical mass}}{\text{Theoretical mass}} \times 100
\]

Micrometric property

Bulk density: Appropriately weighted solid dispersions were transferred to a measuring cylinder (100 ml) and the true volume of the powder (bulk volume) was noted in the cylinder. The bulk density of the powder was measured as the ratio of the weight of the sample taken to the bulk volume of the loaded solid dispersion (Milling, 1991).

\[
\text{Bulk density} = \frac{\text{Mass of solid dispersion}}{\text{Bulk volume of solid dispersion}}
\]

Tapped density: Appropriately weighted solid dispersions were transferred to a measuring cylinder (100 ml). The measuring cylinder was subjected for 100 tapings or till constant volume was achieved. The achieved constant volume was considered as the tapped volume of solid dispersions. The tapped density of the powder was measured as the ratio of the weight of the solid dispersion taken to the tapped volume of the loaded solid dispersion (Singh et al., 2000).

\[
\text{Tapped density} = \frac{\text{Mass of solid dispersion}}{\text{Tapped volume of solid dispersion}}
\]

Carr’s (compressibility) index: Carr’s index value of solid dispersion was computed considering the tapped and the bulk density of the solid dispersion and was computed according to the following equation (Srivastava et al., 2005).

\[
\text{% compressibility} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100
\]

Powder with Carr’s index value below 15% is usually considered to have good flow characteristics, while above 25% is considered to have poor flow ability.

Hausner’s ratio: Hausner’s ratio of solid dispersion was determined as the ratio of tapped density to bulk density using the following equation (Kannan et al., 2009).

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

A decent flow is shown by a Hausner ratio higher than 1.25, and a weak flow maybe 1.5.

Angle of repose: The angle of repose (α) of solid dispersion which measures the resistance of particle flow was determined by a fixed
funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of blends. Accurately weighed solid dispersion was allowed to pass through the funnel freely on the surface. The height and radius of the powder were measured and the angle of repose was calculated using the following equation (Bhardwaj et al., 2012).

\[ \alpha = \tan^{-1} \frac{h}{r} \]

Where,
\( \alpha \) = angle of repose
\( h \) = height
\( r \) = radius of the heap of powder or granule

**In vitro drug release study**

*In vitro* dissolution studies were carried out in a USP type II dissolution apparatus in both medium 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) for both pure drug and prepared formulations. Sample equal to 50 mg of Aceclofenac was introduced to 900 ml dissolution medium at 37±0.5ºC and stirring rate of 50 rpm. An aliquot sample (2 ml) was taken at 10, 20, 30, 40, 50, 60, 90, 120 and 180 min intervals with new medium substitute to retain sink condition. The sample was filtered and 1 ml of the sample was taken and diluted to 10 ml with the medium. Each sample was analyzed for Aceclofenac content by UV-Visible spectrophotometer at 273 nm.

**Statistical analysis**

All the experiments were run in triplicate and results were expressed as mean±SD. Statistical analysis was carried out using Graph-Pad prism version 7 software (GraphPad software Inc., La Jolla, CA). The data was analyzed by Dunnett’s multiple comparison tests. Statistical significance was predefined at p<0.05.

**RESULTS AND DISCUSSION**

**Melting point and solubility**

The melting point of the drug was observed at 149.66ºC. The melting point of the drug was within the range of literature specification, 149-150ºC indicating the identity and purity of the drug sample as Aceclofenac (Kala et al., 2016). The solubility of aceclofenac was 0.0753±0.021 mg/ml in distilled water. The study suggests that the solubility of aceclofenac was pH-dependent where the observed solubility was higher in Phosphate buffer (pH 7.4) with 5.76±1.23 mg/ml compared to acidic buffer (0.1 N HCl) with 0.0214±0.012 mg/ml. This might be because aceclofenac being weakly acidic remains unionized in lower pH while it remains ionized in higher pH value rendering the remarkable increase of drug solubility in aqueous media.

**Percentage yield**

The percentage yield was conducted in eight different formulations. The results for the percentage yield of eight different formulations are depicted in Figure 1. The
Table 2. Summary result of micrometric properties of different Aceclofenac loaded solid dispersions.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr's index</th>
<th>Hausner's ratio</th>
<th>Angle of repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.6250±0.0024</td>
<td>0.7259±0.0022</td>
<td>13.89±0.0025</td>
<td>1.16±0.0024</td>
<td>29.03±2.7</td>
</tr>
<tr>
<td>F2</td>
<td>0.6122±0.0027</td>
<td>0.7031±0.0024</td>
<td>12.92±0.0019</td>
<td>1.14±0.0025</td>
<td>30.77±2.1</td>
</tr>
<tr>
<td>F3</td>
<td>0.6271±0.0023</td>
<td>0.7305±0.0023</td>
<td>14.15±0.0018</td>
<td>1.16±0.0022</td>
<td>27.88±1.9</td>
</tr>
<tr>
<td>F4</td>
<td>0.6165±0.0024</td>
<td>0.6544±0.0026</td>
<td>5.79±0.0025</td>
<td>1.06±0.0025</td>
<td>25.81±2.2</td>
</tr>
<tr>
<td>F5</td>
<td>0.6250±0.0022</td>
<td>0.7258±0.0029</td>
<td>13.88±0.0022</td>
<td>1.16±0.0022</td>
<td>20.77±2.9</td>
</tr>
<tr>
<td>F6</td>
<td>0.6338±0.0019</td>
<td>0.7438±0.0024</td>
<td>14.78±0.0022</td>
<td>1.17±0.0022</td>
<td>21.56±1.5</td>
</tr>
<tr>
<td>F7</td>
<td>0.6315±0.0024</td>
<td>0.7275±0.0022</td>
<td>13.19±0.0019</td>
<td>1.15±0.0029</td>
<td>30.61±2.9</td>
</tr>
<tr>
<td>F8</td>
<td>0.6428±0.0020</td>
<td>0.7408±0.0027</td>
<td>13.22±0.0022</td>
<td>1.15±0.0022</td>
<td>29.43±3.1</td>
</tr>
</tbody>
</table>

Figure 2. Cumulative percentage release of pure aceclofenac and aceclofenac from solid dispersion in 0.1 N HCl (pH 1.2).

observed percentage yield was highest in F5 with 85.18±6.02% while the percentage yield of F1 was the lowest of all the formulations accounting value of 70.43±5.028%.

Micrometric study

The different micrometric study was conducted for eight different formulations. The summary result of the micrometric properties of eight different formulations is depicted in Table 2. The observed response indicated that the bulk density of F8 was greatest with 0.6428±0.002 g/ml while bulk density was the smallest for F2 with 0.6122±0.0027. The observed tapped density was highest for F6 with 0.7438±0.0024 g/ml while tapped density was lowest for F4 with 0.6544±0.0026. The Carr’s index and Hausner’s ratio value was smallest for F4 with 5.018±0.0025 and 1.06±0.0025 respectively indicating an excellent flow property, while Carr’s index and Hausner’s ratio value was greatest for F6 with 15.35±0.0022 and 1.18±0.0022 indicating relatively poor flow. The angle of repose value was lower for F5 with 20.77±2.9º while the angle of repose value was higher for F2 with 30.77±2.1º. The solvent wetting method was found to be an efficient method to produce solid dispersions with good flow properties.

In vitro drug release study

The test on in vitro drug release was undertaken in both acid buffer (pH 1.2) and phosphate buffer (pH 7.4) for pure drug aceclofenac and eight separate formulations. The cumulative percentage drug release of pure aceclofenac in 0.1 N HCl and phosphate buffer is depicted in Figures 2 and 3 respectively. The cumulative in vitro drug release after 180 min for aceclofenac in acidic buffer (pH 1.2) was 3.89±0.41%, while according to observed study of cumulative percentage drug release
Cumulative percentage drug release was highest in F8 with 54.73±4.60% and lowest in F5 with 31.75±3.10% as found under the same dissolution medium and interval. The in vitro drug release of different formulations in acidic buffer (pH 1.2) were significant compared to pure drug aceclofenac (p<0.05). Similarly, the cumulative in vitro drug release after 180 min for aceclofenac in phosphate buffer (pH 7.4) was 23.79±2.20% while, as per the observed result depicted in Figure 3, cumulative percent drug release was highest in F8 with 76.65±6.50% and lowest in F5 with 64.09±5.70% as in the same dissolution medium and interval. The in vitro drug release of different formulations in phosphate buffer (pH 7.4) were not significant compared to pure drug aceclofenac (p>0.05). The study also suggests that the intrinsic solubility as well as the rate of aceclofenac dissolution is poor, which may be attributed due to poor wettability and agglomeration of particles, so there is a strong need to enhance its solubility and dissolution. Meanwhile, when formulated as a solid dispersion relative with pure aceclofenac as a whole, there was a significant increase in the dissolution rate of aceclofenac. The probable mechanism might be due to the reduction of particle size of aceclofenac and increase in effective surface area of drug, amorphization and improved wettability of aceclofenac by hydrophilic carrier at diffusion layer (Yadav et al., 2013). In the order of Mannitol > dextrose > HPMC > PVA, the rise in dissolution rate was noted. The release profile was higher with the formulation containing mannitol in the ratio 1:3 (F8) in both the medium which might be due to generation of fine crystals of the drug when it comes in contact with dissolution medium resulting increase in wettability of the crystals, while release profile was lower with the formulation containing HPMC and PVA which might be due to the result of formation of viscous layer at the interface of drug and dissolution medium that hinders the diffusion of drug from the diffused layer to bulk layer (Rane et al., 2007; Zaini et al., 2017; Madgulkar et al., 2016). Similarly, the lower dissolution rate of PVA may be attributed to the weaker drug-polymer interaction in the PVA system that leads to the lower degree of amorphization and also due to its higher viscosity in solution, might hinder the transformation of the drug domain during dissolution (Chan et al., 2015).

Conclusion

Aceclofenac solid dispersion was prepared by the solvent wetting method. The aqueous solubility of the drug aceclofenac was considerably lower resulting in its poor dissolution rate. Moreover, the solubility of the drug aceclofenac was found to be pH-dependent as a result of which the in vitro drug release of aceclofenac was higher.
in phosphate buffer (pH 7.4) and lower in acidic buffer (pH 1.2) with the value of 23.79±0.0022 and 3.89±0.0024% respectively. The formulation of aceclofenac in a solid dispersion resulted in significant increase in in vitro drug release in both acidic and phosphate buffer. A comparative study of in vitro drug release of eight different formulations was carried. The observed result suggested that the percent cumulative drug release in acidic buffer was highest in F8 and lowest in F5 with 54.73±0.0020 and 31.75±0.0022% respectively. Similarly, the percent cumulative drug release in phosphate buffer was highest in F8 and lowest in F5 with 76.65±0.0018 and 64.09±0.0019%, respectively.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

The authors sincerely appreciate Quest Pharmaceuticals (Birgunj, Nepal) for their kindness in providing the sample of the drug Aceclofenac. Heartfelt thanks to Professor Dr. Ananda Kumar, The Principal, Universal College of Medical Sciences (Siddhartha Nagar, Nepal) for the valuable support to make this research possible, and to Universal College of Medical Sciences (Siddhartha Nagar, Nepal) for allocating necessary laboratory premises for successful conduct of this work.

REFERENCES


