Formulation and Evaluation of Obeticholic Acid Solid Dispersion Tablet

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Authors' contributions
This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Obeticholic acid is a farnoside X receptor agonist that was recently licenced by the US Food and Drug Administration. In a solvent, solubility is lower, therefore it is necessary to improve solubility. Solid dispersion is one of the most effective methods for increasing Obeticholic acid's solubility. Solid dispersion can be prepared in a variety of ways. Fusion (Hot Melting) is one of the most straightforward and cost-effective methods for producing solid dispersion. Poloxamer is one of the finest polymers for solid dispersion production. Poloxamer 188 and Poloxamer 407 are widely accessible. Above solid dispersion is made using the fusion or hot melting procedure. The solubility of the prepared solid dispersion has increased to 0.347 mg/ml. In comparison to the polymer combination, which has a drug release rate of 99.63 percent, the percent drug release is also superior. Precompression settings were found to be within a reasonable range. Post compression parameters such as Hardness, Friability, Uniformity of weight, content uniformity are in standard range. F7 formulation shows 99.63 ± 0.19 in 60 minutes of time. Phosphate buffer 7.4 is used for dissolution test apparatus. All result parameter shows that prepared solid dispersion of Obeticholic acid by using poloxamer gives improved solubility and increased drug release.

Keywords: Obeticholic acid; poloxamer 188 and 407; phosphate buffer; solid dispersion.

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1. INTRODUCTION

The oral route of drug administration is the most common and recommended mode of delivery due to its simplicity and ease of intake, yet it might be troublesome if the medication is poorly soluble or has low membrane penetrability. Although salt manufacturing, dissolution rate, and particle size reduction are commonly utilised to increase dissolution rate and, as a result, oral absorption and bioavailability of low water soluble medicines [1-4], these methods have limitations. Solid dispersion of the medication in a water soluble polymer is one of the potential approaches for enhancing drug solubility. The solid dispersion (SD) of one or more active components in inert carriers created by fusion, solvent, or solvent fusion procedures is defined as the dispersion of one or more active ingredients in one or more inert carriers prepared by fusion, solvent, or solvent fusion methods [5-7]. The Biopharmaceutical Classification system divides drugs into four categories based on in vitro and in vivo permeability data. I (high solubility, high permeability), II (low solubility, high permeability), III (high solubility, low permeability), and IV (low solubility, low permeability) are the four categories of compounds [6]. With Class I medications, it’s typical to skip bioequivalence testing. During the selection phase, new chemical compounds with low water solubility and permeability are screened out since they may present problems during pharmaceutical development. Dissolution / solubility in class II pharmaceuticals and permeability in class III pharmaceuticals restrict oral medicine absorption [8-10]. Class II medications’ poor capacity to dissolve is definitely a stronger limiting factor in their overall speed and higher bioavailability than their ability to pass through the intestinal epithelia. Some of the pharmacological approaches available for enhancing the water solubility of poorly soluble medicines include solid dispersion, surfactant solubilization, co-solvent usage, particle size reduction, hydrotropy, and the use of highly soluble derivatives or salts. Solid dispersion (SD) is the most effective technique of dispersion in carrier, described as a system in which one or more active chemicals are dispersed in an inert matrix at a solid state using a melting method, a solvent evaporation method, or a melting solvent [11]. For a long time, many researchers have investigated SDs of poorly water soluble medicines with various pharmacologically inert carriers in order to increase dissolution and oral absorption of poorly water soluble treatments, but only a few systems are economically feasible. Polymer has recently gained popularity as a wetting and solubilizing agent, as well as a surface adsorption excipient. Many different ways have been explored to increase the solubility, dissolution, and bioavailability of hydrophobic drugs. Poloxomer provided a larger improvement in solubility for several medications than other melanx polymers like PEGs and complex-forming chemicals like cyclodextrin [12]. Poloxomer was chosen as a polar carrier in this study experimentally because of its superior surfactant properties and oral safety. According to the study, the main ways to improve dissolution are to reduce the particle size of the solid compound and/or optimise the wettability characteristics of the compound surface, reduce the boundary layer thickness, ensure sink conditions for dissolution, and, last but not least, improve the apparent solubility of the drug under physiologically relevant conditions.

Obeticholic Acid is a hydrophobic semi-synthetic BA analogue. This is a highly selective FXR agonist with revitalization power comparable to the endogenous one. However, BA chenodeoxycholic acid is 100 times more powerful. Intestinal production hormones, particularly FGF19, are also induced by the powerful 5OCA. OCA has beneficial effects on the resultant glucose and lipid metabolism, particularly in the liver. It’s a possible possibility because of the inflammation. PBC and non-alcoholic steatohepatitis are two illnesses that require pharmaceutical therapy (NASH). Obeticholic acid is a modified synthetic bile acid that acts as a farnesoid X-activated receptor (FXR) agonist. The principal cells that express farnesoid X-activated receptors are human enterocytes and hepatocytes. The most prevalent ligands for FXRs are bile acids, which are present in nature. In enterocytes, FXRs control bile acid synthesis and release fibroblast growth factor, particularly FGF-19, into the hepatic portal circulation. FXRs regulate hepatic triglyceride production, fibrosis, and a range of other metabolic processes in hepatocytes. When FGF-19 is released into the portal vein, it interacts to the FGFR-4 receptor on hepatocytes [13]. This receptor causes the enzyme responsible for turning cholesterol to bile acids, cholesterol 7 alpha-hydroxylase (CYP7A1), to be inhibited. Obeticholic acid is a modified synthetic bile acid that acts as a farnesoid X-activated receptor (FXR) agonist. The principal cells that
express farnesoid X-activated receptors are human enterocytes and hepatocytes. The most prevalent ligands for FXRs are bile acids, which are present in nature. In enterocytes, FXRs control bile acid production and release fibroblast growth factor, particularly FGF-19, into the hepatic portal circulation. FXRs regulate hepatic triglyceride production, fibrosis, and a range of other metabolic processes in hepatocytes. Once released into the portal vein, FGF-19 interacts to the FGFR-4 receptor on hepatocytes. This receptor complex causes a decrease in cholesterol 7 alpha-hydroxylase (CYP7A1), the enzyme responsible for turning cholesterol to bile acids. While Obeticholic acid (OCA) is not approved for use in NASH, current research suggests that OCA’s activity in suppressing hepatic triglyceride synthesis and promoting insulin sensitivity and insulin-dependent activities decreases the risk of lipid deposition in hepatocytes, thus also reducing the occurrence and progression of NASH [14].

1.1 Advantages

1. Solid dispersion has made it possible to improve drug bioavailability by modifying their water solubility.
2. Increased dissolution rate and absorption extent, as well as a decrease in pre-systemic metabolism.
3. The transformation of a medication from a liquid to a solid state.
4. Solid dispersions are much more efficient than particle size reduction approaches that have a particle reduced size limit of 2-5 mm, which is typically insufficient to improve medication solubility or release in the small intestine significantly.
5. When parameters including carrier molecular weight and composition, drug crystallinity, particle porosity, and wettability are adequately regulated, bioavailability can be improved.

1.2 Disadvantages

1. It absorbs moisture which result in phase separation, crystal growth, sometimes there is change in state of material.
2. It has poor Scale up for their manufacturing on large scale.

1.3 Applications of Solid Dispersion

1. It make stable drug from un-stabilized drug.
2. Convert liquid or gas into solid form.
3. Get homogeneous mixture of small amount of drug in solid form.
4. To produce fast release drug in slow release formulation.
5. It mask unpleasant taste of drug.
6. It reduces undesirable incompatibility.
7. It reduces presystemic inactivation of drug.

1.4 Techniques for Preparation of Solid Dispersion

Different techniques are there to prepare Solid Dispersions are,

1. Kneading Method
2. Co-Milling Method
3. Hot-Melt Method (Fusion Method)
4. Solvent Evaporation Method
5. Solvent Based Method
6. Melting Solvent Evaporation Method
7. Supercritical Fluid

![Fig. 1. Solid dispersion method](image)
2. MATERIALS AND METHODS

Obeticholic acid obtained as gift sample from Amneal Pharma, Gujrat. Poloxomer polymer was purchased from Vishal Chemical Supplier Mumbai. Lactose, Mg Stearate was obtained as gift sample from GSK Laboratories, Gujrat.

2.1 Drug Profile

2.1.1 Obeticholic acid

\[ C_{26}H_{44}O_4 \]

Molecular Weight - 420.6

Melting Point – 108 - 110°C

Fig. 2. Obeticholic acid

2.1.2 Mechanism of action of obeticholic acid

Fig. 3. Mechanism of action

2.2 Poloxamer Profile

Molecular Weight – 162.3

Molecular Formula- \( C_8H_{18}O_3 \)

Fig. 4. Polymer profile

2.3 Physical Mixture Preparation

By fully combining correctly weight drug and Poloxamer in a glass mortar and pestle, a physical mixture of Obeticholic Acid and Poloxamer in the ratio of 1:1 was formed. After passing through sieve no. 40, the mixture was put in a desiccator for two days.
2.4 Solid Dispersion Preparation

The physical combination is heated immediately till it melts. With fast stirring, the melted fluid is quickly cooled and hardened in an ice bath. After that, the solid mass is crushed to reduce particle size so that it may be put into an appropriate dosage form.

2.5 Drug Content Determination

Dissolve solid dispersion corresponding to 2 mg drug transfer in 100 ml volumetric flask, dissolve in methanol, and make up volume with phosphate buffer up to 100 ml to determine drug content. Filter it and use a UV spectrophotometer to measure the absorption.

2.6 Drug Release *In vitro*

In USP dissolution apparatus II, 2 mg of drug was carefully weighed and added to 900 ml of dissolving fluid (7.4 phosphate buffer), which was agitated at a speed of 50 rpm at 370.5°C. Five millilitre aliquots were taken and replaced with 5 millilitres of fresh dissolving medium (37°C) at 10, 20, 30, 40, 50, and 60 minutes. The collected samples were evaluated against the blank using a UV-visible spectrophotometer after appropriate dilution at 228 nm. Pure Glimepiride was also dissolved in the same way.

2.7 Formulation and Evaluation of Obeticholic Acid Solid Dispersion Tablet

Obeticholic acid 5 mg containing solid dispersion is prepared and by direct compression tablet is prepared. Blend was compressed on 6 station rotary machine using round shape concave punches.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Solid Dispersion</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Polyvinyl</td>
<td>08</td>
</tr>
<tr>
<td>3</td>
<td>Pyrrolidone</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Lactose</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Sodium Starch</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Glycolate</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Magnesium Stearate</td>
<td>04</td>
</tr>
</tbody>
</table>

Table 1. Composition of tablet

2.8 Evaluation of Obeticholic Acid Solid Dispersion Tablet

All prepared tablet were evaluated for content uniformity, friability, hardness, weight variation, *In-vitro* drug release. Friability test performed on Roche Fraibilator and Hardness tested on Pfizer Hardness tester.

2.9 Content Uniformity of Tablets

Tablet were weighted and crushed in small morter. Fine powder equivalent to 2 mg of drug transfer to 100 ml volumetric flask, containing 10 ml methanol and dissolved, volume made up to 100 ml by NaOH. Solution is filtered and dilute with 100 ml for UV absorbance.

2.10 *In-vitro* Drug Dissolution

Prepared Obeticholic acid tablet added to 900 ml of dissolution medium (PH 7.4 Phosphate Buffer) contained in USP dissolution apparatus II and stirred at speed 50 rpm at 37 ± 0.5°C. 5 ml sample is withdrawal after 10, 20,30,40,50 and 60 minutes and same quantity of buffer is replaced. Collected sample then send for UV absorbance.

3. RESULTS AND DISCUSSION

The drug content of Obeticholic Acid solid dispersion was found to be in range 98.24 to 99.72 and these values are within the acceptable range. Low values of standard deviation in respect of with respect to drug content, as given in Table 2.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Drug Content</th>
<th>Solubility mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>96.15</td>
<td>0.122</td>
</tr>
<tr>
<td>F2</td>
<td>97.14</td>
<td>0.186</td>
</tr>
<tr>
<td>F3</td>
<td>97.85</td>
<td>0.216</td>
</tr>
<tr>
<td>F4</td>
<td>98.26</td>
<td>0.286</td>
</tr>
<tr>
<td>F5</td>
<td>98.95</td>
<td>0.292</td>
</tr>
<tr>
<td>F6</td>
<td>98.97</td>
<td>0.310</td>
</tr>
<tr>
<td>F7</td>
<td>99.63</td>
<td>0.347</td>
</tr>
<tr>
<td>F8</td>
<td>99.55</td>
<td>0.298</td>
</tr>
<tr>
<td>F9</td>
<td>99.40</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Table 2. Indicating uniform drug distribution in all the solid dispersions
3.1 Solubility Studies

Obeticholic Acid has a solubility profile of 0.0087 mg/ml, indicating that it has a lot of room for improvement in terms of solubility and dissolution. Obeticholic Acid’s solubility and dissolution were improved using a solid dispersion technique including Poloxamer in the current investigation. With an increase in the weight percentage of surface-active carrier, the solubility of all solid dispersions improved. The Fusion technique was utilised to create a 1:5 ratio of Obeticholic Acid to Poloxamer 188, which resulted in the most solubility increase. 0.347 mg/ml is the concentration in millilitres.

3.2 In-vitro Drug Dissolution Studies

The in vitro release profile of Obeticholic Acid from Poloxamer 188 and Poloxamer 407 solid dispersions (produced using the Fusion Method) and physical mixture formulation are shown in the figure and graph. According to the data, drug dissolution rose gradually when both grades of Poloxamer concentrations were raised up to a point, after which it practically became constant. The dispersion of drug molecules and colloids in the hydrophilic carrier matrix of poloxamer was shown to be quicker than that of physical mixtures and drug. This may be due to the drug’s molecular and colloidal dispersion in the poloxamer’s hydrophilic carrier matrix.

3.3 Pre Compression Evaluation of Drug-Excipient Blend

Table shows the pre-compression results as well as the drug-excipients mix evaluation. The angle of repose was determined to be less than 29, indicating favourable flow properties. It was discovered that the bulk density and tapped density values were both less than one. Similarly, all batches percentage compressibility (Carr’s Index) values were less than 15%, indicating that all batches of tablet blend have good flow properties.

<table>
<thead>
<tr>
<th>Table 3. Evaluation parameter</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of Repose</td>
<td>24.11</td>
</tr>
<tr>
<td>Bulk Density</td>
<td>0.53</td>
</tr>
<tr>
<td>Tapped Density</td>
<td>0.56</td>
</tr>
<tr>
<td>% Compressibility</td>
<td>6.78</td>
</tr>
<tr>
<td>Hausner Ratio</td>
<td>1.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Post compression study of prepared tablet</th>
<th>Prepared Tablet Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight (mg)</td>
<td>148.5 ± 0.45 mg</td>
</tr>
<tr>
<td>Content Uniformity %</td>
<td>99.63</td>
</tr>
<tr>
<td>Friability %</td>
<td>0.5 ± 0.50</td>
</tr>
<tr>
<td>Hardness (kg/cm2)</td>
<td>3.8 ± 0.38 (kg/cm2)</td>
</tr>
</tbody>
</table>

Fig. 5. Evaluation of solid dispersion tablet dosage form
3.4 Dissolution Study of Prepared Tablet

The polymeric particles may have quickly hydrated when the combination came into touch with water, solubilizing the adjacent drug particles and releasing the drug into the medium. The reason for improved Obeticholic Acid release from solid dispersion as the ratio of Poloxamer 188 to Poloxamer 407 increases is that the poloxamer monomers are thought to form monomolecular micelles through a change in solution configuration at low concentrations, similar to those at which more conventional nonionic detergents release from micelles. At larger concentrations, these monomolecular micelles mix to create aggregates of various sizes, which have a stronger potential to solubilize medications.

4. CONCLUSION

Without any physical or chemical interaction, solid dispersions created by the Fusion Method using poloxamers increased the solubility rate of Obeticholic Acid. Solid dispersions of Poloxamer 188 with Obeticholic acid outperformed physical mixes and solid dispersion with poloxamer 407 in terms of dissolving profile. In vitro experiments demonstrated that the 188, 1:5 ratio of Obeticholic Acid to Poloxamer generated the greatest results of all formulations. Furthermore, tablets created with that mixture had a better dissolving profile and were not affected by compression mechanical shocks.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

10. Attia MS, Hasan AA, Ghazy FES, Gomaa E. Solid dispersion as a technical solution


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