A Study to Increase the Bulk Density of Imatinib Mesylate

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ABSTRACT
The objective of the current study is to develop a process for the preparation of Imatinib mesylate of high bulk density from Imatinib free base. Since, crystals of the Imatinib mesylate with various forms were prepared using various reaction conditions and different solvents followed by crystallization. But, most of the process produced Imatinib mesylate with low bulk density. Since in case of Imatinib mesylate dose of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day, so use of low density Imatinib mesylate for pharmaceutical formulation as solid forms are not favorable. In view of theses facts we developed a process of mesylation in mixture of methanol, ethyl acetate and water which produce Imatinib mesylate with high bulk density which is suitable for the solid formulation. Bulk density of the produced crystals was identified by conventional method.

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Introduction

Imatinib mesylate (Gleevec, 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]phenyl] benzamide methane sulphonate, Figure 1) is indicated for the treatment of chronic myeloid leukemia (CML) and unrespectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) [1]. CML is a hematological stem cells disorder in which the neoplastic cells express an abnormal chromosome, the Philadelphia chromosome. A hallmark of this is a reciprocal chromosomal translocation involving the bcr gene from chromosome 9 and the c-abl gene from chromosome 22. The Bcr-Abl gene of the Philadelphia chromosome code for an oncoprotein that has a consecutive tyrosine kinase activity, resulting in uncontrolled blood cell proliferation [2,3]. Imatinib is an ATP-competitive selective inhibitor of Bcr-Abl protein tyrosine kinase with unprecedented efficacy for the treatment of Bcr-Abl positive CML [4-9].

The bulk density of a drug is an important factor in pharmaceutical manufacturing as well as in pharmaceutical formulation. Higher bulk density is the key physical properties involved in the formulation of solid dosage forms of various drugs and Imatinib mesylate is one such drug which is used as solid doses forms. The reaction conditions such as quantity of solvent or solvent mixture, temperature, cooling rate and crystallization pattern exhibits a key influence for the formation of crystals with a fixed bulk density. Formulation studies involve developing a preparation of the drug which is both stable and acceptable to the patient. For orally taken drugs, this usually involves incorporating the drug into a tablet or a capsule. Formulation of an oral dose considers factors like particle size, polymorphism, solubility and bulk density. Bulk density is the key factor to decide the drug load in a tablet or a capsule, if the bulk density of the drug is low it will lead to low drug load a low drug load may cause homogeneity problems and require large capsules if the compound has a low bulk density.

Since all the reported methods produce Imatinib mesylate with low bulk density which create problem in the solid doses formulation as imatinib mesylate has high doses i.e. 400 mg or 600 mg subsequently creating problem in the formation of tablet. In view of these facts a new process need to be developed for the preparation of Imatinib mesylate with high bulk density which can favor the formulation of Imatinib mesylate.

Experimental Section

Chemical and Reagent

Imatinib free base (mol. Wt. 493.6g/mol) was prepared by reported method [10]. All the chemicals used were of LR grade and commercial available in market.

Apparatus and Equipment

Bulk density was calculated manually on Bulk Density Apparatus.

Procedure of preparation of Imatinib mesylate

Example 1: Preparation of Imatinib mesylate in ethanol

Imatinib base (2.0g) was suspended in 20 ml ethanol, methanesulphonic acid (0.38 g) in 5 ml ethanol was added slowly during 30 minutes at RT. The suspension was heated to reflux temperature for one hour and was slowly
brought to RT. The suspension was stirred at RT for 30 minutes, filtered and washed with 4 ml ethanol and
dried for 6 hr at 60°C. The yield was 1.9g (79.8%), untapped density: 0.34g/ml; tapped density: 0.45g/ml.

Example 2: Preparation of Imatinib mesylate in methanol
Imatinib base (2.0g) was suspended in 10 ml methanol, methanesulphonic acid (0.38 g) in 1 ml methanol was
added slowly during 30 minutes at RT. The suspension was heated to reflux temperature for one hour and was
slowly brought to RT. The suspension was stirred at RT for 30 minutes, filtered and washed with 2 ml methanol
and dried for 6 hr at 60°C. The yield was 1.5g (63.02%), untapped density: 0.36g/ml; tapped density: 0.44g/ml.

Example 3: Preparation of Imatinib mesylate in isopropanol
Imatinib base (2.0 g) was suspended in 50 ml isopropanol, methanesulphonic acid (0.38 g) in 10 ml isopropanol
was added slowly during 30 minutes at RT. The suspension was heated to reflux temperature for one hour and
was slowly brought to RT. The suspension was stirred at RT for 30 minutes, filtered and washed with 4 ml
isopropanol and dried for 6 hr at 60°C. The yield was 2.0 g (84.03%), untapped density: 0.31g/ml; tapped
density: 0.39g/ml.

Example 4: Preparation of Imatinib mesylate in ethyl acetate
Imatinib base (2.0 g) was suspended in 50 ml ethyl acetate, methanesulphonic acid (0.38 g) in 10 ml ethyl acetate
was added slowly during 30 minutes at RT. The suspension was heated to reflux temperature for one
hour and was slowly brought to RT. The suspension was stirred at RT for 30 minutes, filtered and washed with 4 ml
ethyl acetate and dried for 6 hr at 60°C. The yield was 1.9 g (79.8%), untapped density: 0.26g/ml; tapped
density: 0.38g/ml.

Example 5: Preparation of Imatinib mesylate form β in Methanol, ethyl acetate and water mixture
Imatinib base (2.0 g) was suspended in 3.0 ml methanol and ethyl acetate (1:1) mixture, heat to 40-45°C,
methanesulphonic acid (0.38 g) in 0.25 ml purified water was added slowly during 30 minutes at 40-45°C. The
suspension was stirred at 40-45°C for 1 hr and was slowly brought to RT. The suspension was stirred at RT for
6 hr, filtered and washed with 1 ml ethyl acetate and dried for 6 hr at 60°C, The yield was 2.0 g (84.0%),
untapped density: 0.44g/ml; tapped density: 0.77g/ml.

Result and Discussion
Several methods for the preparation of Imatinib mesylate from Imatinib free base have been reported [11-19].
The first synthesis of Imatinib mesylate, reported by J. Zimmermann [11], was base on the reaction of Imatinib
free base and methane sulphonic acid in solvent Ethanol and methanol to produce alpha and beta form
respectively. The XRPD pattern of each form shows unique peaks, usable for its identification. According to
Zimmermann et al the crystalline α-form used for the pharmaceutical dosage form is characterized as needle-
shaped or rod crystals having a hygroscopic nature and is not particularly well suited to pharmaceutical
formulation as solid forms because of their physical properties; such as particle size, polymorph, solubility and
bulk density, their flow characteristics and compaction behavior are unfavorable. However, beta form is well
suited to pharmaceutical formulation as solid forms with respect to stability [11].
K. Amala et al described α-2-crystalline form of Imatinib mesylate which is stable at room temperature and
even at higher temperatures which is also suitable for pharmaceutical formulation as solid forms [15].
Despite stability of Imatinib mesylate, it was observed that the above process yields Imatinib mesylate with a
relatively low untapped and tapped bulk density (Table-1), which may result in handling difficulties during
processing and use.
Since in case of Imatinib mesylate dose of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day, so use of low density Imatinib mesylate for pharmaceutical formulation as solid forms are not favorable. A material with a higher untapped and tapped bulk density is desirable during the manufacture of oral dosage forms containing Imatinib mesylate. An improved procedure for preparation of high density Imatinib mesylate was reported in which mesylation is carried out in methanol and ethyl acetate mixture followed by the addition of a solution of methanesulphonic acid in water.

**Bulk density analysis of crystals**

Untapped density and tapped density of different crystals of Imatinib mesylate prepared by different methods, solvents and reaction conditions are tabulated in table 1

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Solvent used/ Process references</th>
<th>Untapped density</th>
<th>Tapped density</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol (J. Zimmermann, US Patent 6 894 051)</td>
<td>0.34g/ml</td>
<td>0.45g/ml</td>
</tr>
<tr>
<td>2</td>
<td>Methanol (J. Zimmermann, US Patent 6 894 051)</td>
<td>0.36g/ml</td>
<td>0.44g/ml</td>
</tr>
<tr>
<td>3</td>
<td>Isopropanol (K. Amala, US Patent 2008/0255138)</td>
<td>0.31g/ml</td>
<td>0.39g/ml</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl acetate</td>
<td>0.26g/ml</td>
<td>0.38g/ml</td>
</tr>
<tr>
<td>5</td>
<td>Mixture of methanol and ethyl acetate (Current method)</td>
<td>0.44g/ml</td>
<td>0.77g/ml</td>
</tr>
</tbody>
</table>

**Conclusion**

In summary, the results of this study reveal the role of solvents and reaction condition is important to prepare preferred high bulk density Imatinib mesylate. Since, all the reported method produced Imatinib mesylate with low bulk density. In case of Imatinib mesylate dose of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day, so use of low density Imatinib mesylate for pharmaceutical formulation as solid forms are not favorable, hence a method need to be developed which yield the high bulk density Imatinib mesylate. In this study we have devised a process for the preparation of Imatinib mesylate having untapped density of 0.44 g/ml and tapped density of 0.77 g/ml which is suitable for the formulation as solid form of the drug.
References


