Effect of Additives on the Solubility and Dissolution of Piroxicam From Prepared Hard Gelatin Capsule

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Abstract

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of musculo-skeletal and joint disorders. The problem with this drug is its poor solubility in water and hence poor bioavailability after oral administration. In order to improve its solubility and dissolution behavior, hydrophilic additives such as starch, lactose, superdisintegrants including crospovidone (C.P), cross carmellose sodium (CCS), and sodium starch glycolate (SSG) were physically dry mixed with the drug by simple trituration. The improvement in the solubility in 0.1 N HCl was obtained as the amount of starch or lactose increased in the physical mixture, while for superdisintegrants, they further improve the solubility when they are present in small amount and the best improvement was gained with SSG. To study the effect of these additives on the dissolution of the drug, piroxicam capsules were prepared by simple trituration of the drug with starch or lactose or combination of lactose: starch (2:1) by weight with or without the presence of SSG. The dissolution profiles of these preparations were analyzed using similarity factor f2. Best results were obtained when the drug was triturated with starch and SSG or with acombinaton of lactose: starch (2:1) by weight with SSG. The dissolution profiles of these preparations were similar to that of the marketed Feldene ® Pfizer 20 mg capsules with f2 74.6 and 80.37 respectively.

Key words: Piroxicam, hydrophilic additives, superdisintegrant

Introduction

Sufficient solubility is a prerequisite for effective oral delivery of any therapeutic agent. However, drugs with low solubility and high permeability fall into Biopharmaceutics Classification System (BCS) class II (3) for which the dissolution is usually the rate-limiting step for gastrointestinal absorption. To enhance the dissolution rate and thus oral absorption of such drugs numerous formulation strategies have been developed (5). Proxicam is a NSAID which is widely used for treatment of musculo-skeletal and joint disorders (3). Its absolute bioavailability is unknown since no intravenous dosage data is available in man. It is practically insoluble in water (3,4). Hence when this drug is administered orally it may cause bioavailability problems arises from its low water solubility and law dissolution rate in acid medium where the absorption takes place(5).

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Various techniques have been used in an attempt to improve the solubility and dissolution rate of piroxicam including liquisolid compacts \textsuperscript{(6)}, salt formation with ethanolamines \textsuperscript{(7)}, solid dispersion using PVP K30 \textsuperscript{(8)} or PEG 4000 \textsuperscript{(9)} as a water soluble carriers. In addition, surface solid dispersion of piroxicam in microcrystalline cellulose and in potato starch was also prepared by coevaporation method \textsuperscript{(10)}. Moreover, it was found that the solubility and dissolution of poorly water soluble drugs can be markedly improved by the use of superdisintegrants using solid dispersion technique \textsuperscript{(11,12)} or by preparation of ordered mixing or as physical mixture \textsuperscript{(11, 13)}. The aim of this study was to determine the impact of simple physical mixing of piroxicam with different amount of starch, lactose, superdisintegrants including crospovidone, cross carmelllose sodium, and sodium starch glycolate each alone on the solubility of drug in 0.1N HCl. In addition the effect of combination of piroxicam with one or more of the above additives on its dissolution from these physical mixtures enclosed in hard gelatin capsules was also explored and compared with that of pure drug and with the commercially available Feldene \textsuperscript{(8)} 20 mg Pfizer capsules.

**Materials and Methods**

**Materials**

Piroxicam, sodium starch glycolate (SSG) (Samara Drug Industry (SDI), Iraq), crospovidone (C.P), cross carmelllose sodium (CCS) (Dar Al-Dawa Pharmaceutical, Manufacturing Co., Jordan), lactose, starch (Riedel-Dehean, Ag seelze- Hannover, Germany), HCl (BDH chemicals Ltd.,Pool, England), Feldene \textsuperscript{(R)} 20 mg Pfizer capsules

**Methods**

**Solubility Study**

**Determination of piroxicam solubility**

The solubility of piroxicam in 0.1N HCl was measured using standardized shake flask method \textsuperscript{(14)}. In this method 60 mg of the drug was added to 50 ml of 0.1N HCl (saturated solution) \textsuperscript{(15)} and the mixture was shaken at 37°C for 48 hours, filtered through ordinary filter paper and the concentration of piroxicam in the filtrate, following suitable dilution, was assayed spectrophotometrically at 333 nm for piroxicam \textsuperscript{(16)}.

**Effect of additives on the solubility of piroxicam**

Starch, lactose, C.P, CCS, SSG were used to study the effect of additives on the solubility of piroxicam. Certain amounts ranging from 60-480 mg of one of the above additives was added to a bottle containing 60 mg drug. Manual bottle tumbling was used to prepare simple physical mixture, then 50 ml of 0.1N HCl was added to the mixture to determine the solubility of piroxicam in presence of specific amount of additives by shake flask method as mentioned previously.

**Preparation of piroxicam capsules**

According to the results of solubility study, six different formulas were prepared, in which piroxicam was geometrically triturated with certain amount of one or more of the additives (Table 1). The resultant powder was filled in hard gelatin capsule size 0 as 20mg/capsule.

**Table 1: Composition of piroxicam capsules**

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piroxicam</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Starch</td>
<td>480</td>
<td>---</td>
<td>160</td>
<td>420</td>
<td>---</td>
<td>140</td>
</tr>
<tr>
<td>Lactose</td>
<td>---</td>
<td>480</td>
<td>320</td>
<td>---</td>
<td>420</td>
<td>280</td>
</tr>
<tr>
<td>SSG</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

*All ingredients are in milligram

**Dissolution studies**

The dissolution profiles of the drug alone, encapsulated drug, the prepared capsules and Feldene \textsuperscript{(R)} Pfizer capsules as a reference capsules were studied using apparatus 1 (USP, basket). Dissolution medium was 900 ml 0.1N HCl maintained at 37°C ± 0.1°C and stirred at 50 r.p.m for one hour. Five ml of sample were withdrawn at specified time intervals and were replaced with an equal volume of fresh dissolution medium to maintain sink condition. The samples, following suitable dilution were assayed spectrophotometrically at 333 nm \textsuperscript{(16)}. All dissolution studies were carried in triplicate.

**Dissolution data analysis**

The dissolution profiles of the prepared formulas were compared using \(f_2\) similarity factor. The similarity factor is a logarithmic reciprocal square-root transformation of the sum of squared error and
is a measurement of the similarity in the percentage of dissolution between two curves.

\[ f_2 = 50 \times \log \left[ 1 + \left( \frac{1}{n} \right) \sum (R_t - T_t)^2 \right]^{-0.5} \times 100 \]

where \( n \) is the sampling number, \( R_t \) and \( T_t \) are the percent dissolved of the reference and test products at each time point \( t \). Two dissolution profiles are considered similar when the \( f_2 \) value is greater than or equal to 50\(^{(17)}\).

**Results and Discussion**

**Effect of additives on the solubility of piroxicam**

The effect of type and amount of additives on the solubility of piroxicam in 0.1N HCl is summarized in table (2). The solubility of piroxicam was highly improved in presence of the hydrophilic superdisintegrants more than with lactose, a soluble carrier or with starch which have limited solubility and swelling properties. This improvement in solubility can be explained to be due to the surface adsorption of drug in the physical mixtures of all carriers \(^{(10)}\), the wetted surface of the carrier promotes wettability and solubility of the drug \(^{(18, 19)}\). In addition, it was found that within the superdisintegrants, the order of improvement in the solubility is SSG > CCS > C.P which may be due to the differences in their physical properties including hydrophilicity and swelling property. On the other hand, the results in table (2) show that increasing the amount of superdisintegrants results in decreasing the solubility of the drug. This could be attributed to the formation of viscous barrier resultant from absorption of water by the superdisintegrants that decrease the wettability and thus the solubility of the drug \(^{(13)}\).

**Table 2: Effect of type and amount of additives on the solubility of piroxicam (mg/50 ml) at 37°C in 0.1 N HCl**

<table>
<thead>
<tr>
<th>Amount of Additive (mg)</th>
<th>Starch</th>
<th>Lactose</th>
<th>C.P</th>
<th>CCS</th>
<th>SSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.36 ± 0.46</td>
<td>6.36 ± 0.46</td>
<td>6.36 ± 0.46</td>
<td>6.36 ± 0.46</td>
<td>6.36 ± 0.46</td>
</tr>
<tr>
<td>60</td>
<td>6.39 ± 0.02</td>
<td>10.23 ± 0.04</td>
<td>11.47 ± 0.12</td>
<td>13.42 ± 0.01</td>
<td>14.02 ± 0.42</td>
</tr>
<tr>
<td>120</td>
<td>7.87 ± 0.25</td>
<td>10.39 ± 0.18</td>
<td>12.51 ± 1.09</td>
<td>12.65 ± 0.15</td>
<td>12.97 ± 0.52</td>
</tr>
<tr>
<td>180</td>
<td>10.89 ± 0.0</td>
<td>11.67 ± 0.17</td>
<td>12.01 ± 0.13</td>
<td>12.05 ± 0.12</td>
<td>12.96 ± 0.2</td>
</tr>
<tr>
<td>240</td>
<td>10.88 ± 1.17</td>
<td>12.02 ± 0.52</td>
<td>11.71 ± 1.09</td>
<td>10.88 ± 0.57</td>
<td>11.84 ± 0.31</td>
</tr>
<tr>
<td>300</td>
<td>10.97 ± 1.32</td>
<td>12.4 ± 0</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>360</td>
<td>11.26 ± 0</td>
<td>12.29 ± 0.08</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>420</td>
<td>11 ± 0.64</td>
<td>12.29 ± 0</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>480</td>
<td>11.04 ± 0.06</td>
<td>12.16 ± 0</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation (n=3)

**Preparation of piroxicam capsules**

Six different formulas (Table 1) of piroxicam capsules were prepared using starch, lactose or combination of lactose: starch (2:1) by weight \(^{(20)}\) with or without the addition 60 mg SSG (the minimum amount among the superdisintegrants that cause the highest solubility) since the presence of any of the above additives have no adverse effect on the solubility of the drug.

**Dissolution studies**

**Effect of gelatin shell**

The dissolution of drug from hard gelatin capsule was faster than that from pure powdered drug as shown in figure (1). Pure powdered drug added to dissolution medium remains as agglomerate floats on the surface of the dissolution medium. The enhancement effect of gelatin may be due to its hydrophilic nature that increases wetting and dissolution of the drug. This result can be supported by that obtained by Chono S. *et al*\(^{(21)}\) who found that gelatin enhances the dissolution of poorly soluble drugs and their absorption from G.I.T.

![Figure 1: Effect of gelatin shell on the dissolution of piroxicam in 0.1 N HCl at 37°C](image-url)
**Effect of type of diluents**

Dissolution profiles of powdered drug, encapsulated drug, and formula (F1, F2 and F3) which contain starch, lactose and lactose: starch (2:1) by weight respectively are shown in figure (2). It is evident that all additives increase the dissolution of the drug. In addition the dissolution profiles of these formulas are not similar. Dissolution profiles comparison (table 3) between F1 and F2 yield $f_2$ 39.75, while dissolution profiles comparison between F2 and F3 yield $f_2$ 48.9. The higher effect was obtained with F2 mainly for the first 20 minutes which is in agreement with the result obtained by Ampolsuk C. et al (22) who stated that deposition of hydrophobic drug in a molecular subdivision on excess powdered lactose (due to frictionally prepared triturate) is an effective method of increasing surface of the drug and hence, its dissolution. Since lactose is soluble in simulated gastric fluid, its presence in the dissolution medium would physically separate drug particles, preventing their agglomeration and enhancing their dissolution. On the other hand, the less enhancing effect of F1 and F3 at the first 20 minutes may be due to the presence of starch which has less solubility in the dissolution medium.

**Effect of addition of SSG**

Trying to further enhance the release of piroxicam from the prepared capsules, SSG was added in combination with the used diluents to prepare F4, F5 and F6. The dissolution profiles shown in figures 3a and 3c are non similar with $f_2$ 39.17 and 47.47 respectively which indicate that SSG enhances the release of the drug when it is present in combination with starch (F4) or with lactose: starch (2:1) (F6). On the other hand, combination of SSG with lactose (F5) gives similar dissolution profiles as shown in figure 3b with $f_2$ 59.57, so no further improvement in dissolution. These results indicate that the presence of the SSG in the dissolution medium kept the drug particles in dispersed condition i.e. it prevents the agglomeration of drug particles and promote its wetting and dissolution (23). This action is most effective when it is combined with insoluble or slightly soluble diluents (24), since the water soluble diluents may increase the viscosity of the penetrating fluid which tends to reduce the effectiveness of SSG while the insoluble diluents produce rapid disintegration with adequate of disintegrant (25).

**Figure 2:** Effect of type of diluents on the dissolution of piroxicam in 0.1 N HCl at 37°C

**Figure 3a:** Effect of combination of SSG with starch on the dissolution of piroxicam in 0.1 N HCl at 37°C

**Figure 3b:** Effect of combination of SSG with lactose on the dissolution of piroxicam in 0.1 N HCl at 37°C

**Figure 3c:** Effect of combination of SSG with lactose: starch (2:1) on the dissolution of piroxicam in 0.1 N HCl at 37°C
Comparison of the prepared capsules with the marketed capsule

All the prepared capsules of F1, F2, F4, and F6 met the USP specification for the release of the drug in simulated gastric fluid (not less than 75% of the drug is dissolved in 45 minutes)(16). The prepared capsules from F4 and F6 which showed fastest dissolution were compared with the marketed Feldene (R) Pfizer capsules (figure 4). Similar release profiles were obtained between F4 and Feldene (R) Pfizer capsules yield f2 74.6, and that between F6 and Feldene (R) Pfizer capsules yield f2 80.37. In addition, to similar dissolution profiles these preparations contain simple, safe (26), available materials that enhance the solubility and the dissolution of the drug. This gives superiority of using these diluents on sodium lauryl sulfate (a solubilizing agent) that is used in Pfizer product (27) for preparation of piroxicam capsules.

Figure 4: Comparison of the release profile of the prepared capsules with the marketed Feldene (R) Pfizer capsules in 0.1 N HCl at 37°C

Table 3: Values for the similarity factor f2 for the release profiles in 0.1 N HCl

<table>
<thead>
<tr>
<th>Formula no.</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>Felden Cap. Pfizer (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>39.7504</td>
<td>54.85394</td>
<td>39.17509</td>
<td>49.29237</td>
<td>40.85396</td>
<td>39.12536</td>
</tr>
<tr>
<td>F2</td>
<td>48.90846</td>
<td>60.2949</td>
<td>59.57132</td>
<td>68.30451</td>
<td>74.60086</td>
<td>61.21903</td>
</tr>
<tr>
<td>F3</td>
<td>43.99996</td>
<td>66.79376</td>
<td>47.47173</td>
<td>51.63288</td>
<td>73.76971</td>
<td>44.28989</td>
</tr>
<tr>
<td>F4</td>
<td>51.63288</td>
<td>73.76971</td>
<td>47.47173</td>
<td>56.26644</td>
<td>74.60086</td>
<td>51.46837</td>
</tr>
<tr>
<td>F5</td>
<td>56.26644</td>
<td>74.60086</td>
<td>73.76971</td>
<td>80.37825</td>
<td>80.37825</td>
<td>80.37825</td>
</tr>
</tbody>
</table>

Conclusion

The results of this study indicate that the simple physical dry mixing of the piroxicam with starch or with lactose:starch (2:1) by weight in presence of SSG can enhance its solubility as well as its dissolution characteristics to be similar to that of Felden (R) Pfizer. This physical dry mixing of hydrophobic drug with suitable type and amount of additives may be considered as a useful, simple method for preparation of a required solid dosage form. Further work may be required to study the stability of the prepared capsules to investigate its expiration date.

References

16. USP. 30 NF 25 2007
24. Product Sheet
27. Feldene (R) Pfizer capsules material safety data sheet