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Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CELECOXIB CO-CRYSTALS

Abstract: The present invention relates to formulations comprising co-crystals of celecoxib, where such co-crystals can be prone to conversion to one or more thermodynamically stable forms when contacted with aqueous media. The present invention provides compositions comprising a co-crystal of celecoxib and a form conversion inhibitor. Such compositions are capable of delaying or preventing crystallization of poorly soluble forms in aqueous media.
PHARMACEUTICAL COMPOSITIONS COMPRISING CELECOXIB CO-CRYSTALS

BACKGROUND OF THE INVENTION

[001] Many crystalline forms of active pharmaceutical ingredients (APIs) are prone to conversion to more thermodynamically stable forms upon oral administration. Often, such stable forms can lead to decreased bioavailability or slower dissolution in vivo. Uncontrolled form conversion can cause significant setbacks in the pharmaceutical development process or result in attenuated performance in vivo.

[002] Celecoxib, also known as 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, is an API known to exist in many forms. Commercially available celecoxib is known as celecoxib Form III (G. W. Lu et ah, Journal of Pharmaceutical Sciences, 2005, 95, pp. 305-317). Celecoxib form III has significantly lower aqueous solubility than other celecoxib crystalline forms known in the art. Celecoxib form III is reported to yield slower dissolution or lower bioavailability than other more soluble crystalline forms of celecoxib (See e.g., US20050025791). It would be desirable to develop a pharmaceutical formulation which results in a more soluble form in aqueous media and does not rapidly convert to Form III.

[003] The present invention provides compositions which enable the formulation and administration of celecoxib resulting in the formation of a form of celecoxib with higher solubility than that of commercially available celecoxib.

SUMMARY OF THE INVENTION

[004] In one aspect, the present invention provides a composition comprising a co-crystal of celecoxib and one or more form conversion inhibitors able to delay crystallization of a poorly soluble form of celecoxib in aqueous media.

[005] In a first embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor. In a further embodiment, said composition further comprises SDS (sodium dodecylsulfate).

[006] In another embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor, such as PVP (polyvinylpyrrolidone), HPC (hydroxypropyl cellulose), or HPMC.
(hydroxypropylmethylcellulose) or the like, or any combination thereof. In a further embodiment, said composition further comprises SDS (sodium dodecylsulfate).

[007] In another embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor, wherein said form conversion inhibitor is present in an amount from about 50 percent mass to about 500 percent mass, relative to the mass of celecoxib. In a further embodiment, said composition further comprises SDS in an amount from about 1 percent mass to about 12 percent mass, relative to the mass of celecoxib.

DETAILED DESCRIPTION OF THE INVENTION

[008] The present invention relates to novel formulations comprising co-crystals of celecoxib, where such co-crystals can be prone to conversion to one or more thermodynamically stable forms when contacted with aqueous media. Such conversion may take place following oral administration.

[009] In one aspect, the present invention provides a composition comprising a co-crystal of celecoxib and one or more form conversion inhibitors able to delay crystallization of a poorly soluble form of celecoxib in aqueous media.

[010] In a first embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor. In a further embodiment, said composition further comprises SDS (sodium dodecylsulfate).

[011] According to the present invention, the instant pharmaceutical compositions can act to delay or prevent form conversion to poorly soluble forms upon contact with aqueous media. Such delay or prevention of form conversion occurs with compositions comprising a co-crystal of celecoxib.

[012] In another embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor, such as PVP (polyvinylpyrrolidone), HPC (hydroxypropyl cellulose), or HPMC (hydroxypropylmethylcellulose) or the like, or any combination thereof. In a further embodiment, said composition further comprises SDS (sodium dodecylsulfate).

[013] In another embodiment, the present invention provides a composition comprising a co-crystal of celecoxib and a form conversion inhibitor, wherein said form conversion inhibitor is present in an amount from about 50 percent mass to about 500 percent mass, relative to the mass of celecoxib. In a further embodiment, said
composition further comprises SDS in an amount from about 1 percent mass to about 12 percent mass, relative to the mass of celecoxib.

[0014] According to the present invention, when considering the mass percent of the form conversion inhibitor or the SDS, the mass of celecoxib is measured according to the mass of the free acid only, and is not dependant upon a particular co-crystal of celecoxib. Therefore, where a co-crystal of celecoxib is used in a composition, only the mass of the celecoxib (and not that of the co-crystal former (e.g., nicotinamide)) is considered in determining the mass percent of the form conversion inhibitor or the SDS.

[0015] In a specific embodiment, the present invention provides a pharmaceutical composition comprising:

(a) a co-crystal of celecoxib; and

(b) a form conversion inhibitor, selected from the group consisting of: PVP, HPC, HPMC, and any combination thereof, wherein said inhibitor is present in an amount from about 50 percent to about 500 percent by mass, relative to the mass of celecoxib.

[0016] In another specific embodiment, said co-crystal of celecoxib is a celecoxib nicotinamide co-crystal. In another specific embodiment, said form conversion inhibitor is PVP (i.e., povidone). In another specific embodiment, said form conversion inhibitor is HPC. In another specific embodiment, said form conversion inhibitor is HPMC. In another specific embodiment, said pharmaceutical composition further comprises between about 1 percent and about 12 percent SDS by mass, relative to the mass of celecoxib.

[0017] Pharmaceutical compositions of the present invention can include combinations of two or more form conversion inhibitors. For example, compositions can comprise PVP and HPC, or PVP and HPMC. For the purpose of calculating percent mass of form conversion inhibitors where two or more inhibitors are present, the present invention includes all inhibitors as a sum for such determinations.

[0018] The pharmaceutical compositions of the present invention comprise a form conversion inhibitor. In another embodiment, the pharmaceutical compositions of the present invention comprise from about 50 percent to about 500 percent form conversion inhibitor by mass, relative to the mass of celecoxib. For example, about 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425,
450, 475, or about 500 percent form conversion inhibitor by mass, or any intermediate amount, relative to the mass of celecoxib. In another embodiment, the pharmaceutical compositions of the present invention comprise from about 50 percent to about 500 percent, from about 75 percent to about 400 percent, from about 100 percent to about 300 percent, from about 100 percent to about 250 percent, from about 100 percent to about 200 percent, from about 50 percent to about 200 percent, or from about 200 percent to about 400 percent form conversion inhibitor by mass, relative to the mass of celecoxib.

[0019] The pharmaceutical compositions of the present invention can further comprise SDS (sodium dodecylsulfate). In another embodiment, the pharmaceutical compositions of the present invention further comprise from about 1 percent to about 12 percent SDS by mass, relative to the mass of celecoxib. For example, about 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, or about 12.00, percent SDS by mass, or any intermediate amount, relative to the mass of celecoxib. In another embodiment, the pharmaceutical compositions of the present invention comprise from about 1 percent to about 12 percent, from about 1 percent to about 10 percent, from about 2 percent to about 12 percent, from about 3 percent to about 7 percent, from about 2 percent to about 6 percent, from about 5 percent to about 12 percent, or from about 1 percent to about 5 percent SDS by mass, relative to the mass of celecoxib.

[0020] In another embodiment, the present invention provides a medicament comprising a co-crystal of celecoxib and a form conversion inhibitor. In another embodiment, said medicament further comprises SDS.

[0021] Pharmaceutical compositions and medicaments of the present invention can further comprise one or more additional excipients such as, but not limited to, a binder, a diluent, a carrier, a disintegrant, a wetting agent, a surfactant, a lubricant, an anti-adherent, a glidant, or an effervescent agent. See e.g., Handbook of Pharmaceutical Excipients, Fourth Edition, Edited by R. C. Rowe, P. J. Sheskey, and P. J. Weller, 2003.

[0022] In another embodiment, a method of treating a mammal suffering from one or more conditions such as, but not limited to, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, pain, ankylosing spondylitis, and familial adenomatous polyposis is provided, comprising administering to said mammal a pharmaceutical composition of the present invention. In another embodiment, said mammal is a human.
Pharmaceutical dosage forms can be administered in several ways including, but not limited to, oral administration. Oral pharmaceutical compositions and dosage forms are exemplary dosage forms. Optionally, the oral dosage form is a solid dosage form, such as a tablet, a caplet, a hard gelatin capsule, a starch capsule, or a soft elastic gelatin capsule. Liquid dosage forms may also be provided by the present invention, including such non-limiting examples as a suspension, solution, syrup, or emulsion.

Typical daily dosage forms of the invention comprise celecoxib, in an amount of from about 50.0 mg to about 500.0 mg, from about 100.0 mg to 400.0 mg, or from about 200.0 mg to about 400.0 mg. The dosage amounts described herein are expressed in amounts of celecoxib free acid and do not include the weight of a counterion, co-crystal former (e.g., nicotinamide), or any water or solvent molecules.

In another embodiment of the invention, a pharmaceutical composition is administered orally as needed in an amount of from about 50.0 mg to about 500.0 mg, from about 100.0 mg to about 400.0 mg, or from about 200.0 mg to about 400.0 mg celecoxib. For example, about 50.0 mg, about 100.0 mg, about 200.0 mg, or about 400.0 mg. The dosage amounts can be administered in single or divided doses. In another embodiment, a daily dose of a celecoxib pharmaceutical composition comprises up to about 500.0 mg celecoxib.

Although the invention has been described with respect to various embodiments, it should be realized this invention is also capable of a wide variety of further and other embodiments within the spirit and scope of the appended claims.

EXEMPLIFICATION

Example 1
Celecoxib : Nicotinamide Co-crystal

The celecoxib : nicotinamide co-crystal was crystallized by cooling a hot solution containing celecoxib free acid (1.91 g, 5.01 mmol) and nicotinamide (0.644 g, 5.27 mmol) in chloroform (18 g) to room temperature. The slurry was allowed to stand for 10 minutes at room temperature and was then filtered by suction. The crystalline solid was rinsed with 3 mL of cold chloroform, initially dried on the filter paper for 10
minutes, then transferred to a vacuum oven and dried at 50 °C under house vacuum for 30 minutes. Dried aggregates were gently broken up with a mortar and pestle and the solids were shaken periodically in an 850 µm sieve until all aggregates were small enough to pass through. The sieved solids were transferred to a clean vial and stored at room temperature without protection from ambient light. The resulting crystals appear as thin, birefringent needles under crossed-polars. The crystals have a sharp melting point at 130 °C, observed as an endothermic peak in the DSC. The material loses less than 0.25 % weight on heating to 100 °C in the TGA. The co-crystal is non-hygroscopic, undergoing less than 0.1 % change in weight when cycled between 5 and 90 % relative humidity at 25 °C.

Example 2
Formulations for Dissolution Studies of Celecoxib:Nicotinamide Co-crystal

Components were gently ground with celecoxib:nicotinamide co-crystal (as described in Example 1) to ensure complete mixing. For the series of mixtures containing solid SDS (ICN Biomedicals, Inc.), a blend of 400 mg PVP-K30 (Spectrum) and 100 mg of SDS were thoroughly ground together to distribute the SDS evenly on the PVP. This 4:1 PVP:SDS blend was used as is to prepare a formulation containing 11 percent SDS, and the blend was further diluted with PVP and ground in the amounts shown in Table 1 to use in preparation of the celecoxib:nicotinamide-PVP mixtures containing 3.5 and 1 percent SDS. The amounts of celecoxib described in Table 1 represent the mass of celecoxib free acid only, and not that of the co-crystal mass.

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<tr>
<th>Formulation</th>
<th>Amounts of each component weighed to ± 2 mg</th>
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<tr>
<td>1:1 Co-crystal:PVP</td>
<td>200 mg of celecoxib + 200 mg of PVP-K30</td>
</tr>
<tr>
<td>11 % SDS + 1:1 Co-crystal:PVP</td>
<td>200 mg of celecoxib + 250 mg of 4:1 PVP-K30:SDS</td>
</tr>
<tr>
<td>3.5 % SDS + 1:1 Co-crystal:PVP</td>
<td>200 mg of celecoxib + 75 mg of 4:1 PVP-K30:SDS + 140 mg of PVP-K30</td>
</tr>
<tr>
<td>1 % SDS + 1:1 Co-crystal:PVP</td>
<td>200 mg of celecoxib + 25 mg of 4:1 PVP-K30:SDS + 180 mg of PVP-K30</td>
</tr>
</tbody>
</table>

*= CelecoxifrNicotinamide co-crystal as described in Example 1

Example 3
In Vitro Dissolution Study of Celecoxib:Nicotinamide Co-crystal in HCl
A 1:1 mixture of celecoxib:nicotinamide co-crystal with PVP-K30 was prepared and the fate of the co-crystal suspended in 0.01 N HCl with and without added surfactants was monitored by PXRD for 60 minutes. In the absence of any surfactant, the formulation is slow to wet and floats on the surface. Isolation of the materials from the PVP blend has shown that the form conversion inhibitor can protect the co-crystal for up to an hour in the absence of a surfactant. Addition of SDS to the dissolution medium at a low concentration of 0.05 % mass promotes rapid wetting of the mixture and the co-crystal is lost within 5 minutes. However, the isolated solids appear to be predominantly amorphous by PXRD, as opposed to aggregates of celecoxib form III, a poorly soluble polymorph of the free acid, that formed with the neat co-crystal. While the addition of SDS promoted dissolution of the co-crystal, the composition impeded formation of a poorly soluble form, celecoxib form III, in favor of a more soluble form. Amorphous celecoxib has been shown to increase plasma concentrations of celecoxib in dogs relative to celecoxib form III (e.g., US2001042221).

Example 4

Dissolution of Co-crystal-PVP compositions with SDS

Table 1 describes three compositions of 1:1 celecoxib:nicotinamide co-crystal:PVP with SDS. These compositions were analyzed for form conversion in surfactant-free 0.01 N HCl at 37 degrees C. All three compositions were analyzed for a week at 37 degrees C and yielded no conversion to celecoxib Form III. In addition, some aliquots were seeded with celecoxib form III overnight and still no conversion to form III was detected using PXRD.
What is claimed is:

1. A pharmaceutical composition comprising:
   (a) a celecoxib nicotinamide co-crystal; and
   (b) a form conversion inhibitor, selected from the group consisting of: PVP, HPC, HPMC, and any combination thereof, wherein said inhibitor is present in an amount from about 50 percent to about 500 percent by mass, relative to the mass of celecoxib.

2. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is PVP.

3. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is present in an amount from about 50 percent to about 400 percent by mass, relative to the mass of celecoxib.

4. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is present in an amount from about 50 percent to about 200 percent by mass, relative to the mass of celecoxib.

5. The pharmaceutical composition of claim 1, further comprising SDS.

6. The pharmaceutical composition of claim 5, wherein said SDS is present in an amount from about 1 percent to about 12 percent by mass, relative to the mass of celecoxib.

7. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is PVP, and further wherein said PVP is present in an amount of about 100 percent by mass relative to the mass of celecoxib.

8. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is PVP, further wherein said PVP is present in an amount of about 100 percent by mass relative to the mass of celecoxib, and further wherein SDS is present in an amount of about 12 percent by mass relative to the mass of celecoxib.
9. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is PVP, further wherein said PVP is present in an amount of about 100 percent by mass relative to the mass of celecoxib, and further wherein SDS is present in an amount of about 3.5 percent by mass relative to the mass of celecoxib.

10. The pharmaceutical composition of claim 1, wherein said form conversion inhibitor is PVP, further wherein said PVP is present in an amount of about 100 percent by mass relative to the mass of celecoxib, and further wherein SDS is present in an amount of about 1 percent by mass relative to the mass of celecoxib.
INTERNATIONAL SEARCH REPORT

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USPC - 514/343

According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/343

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/406, 514/256, 514/304, 514/337, 514/355

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST DB=PGPB,USPT,USOC,EPAB,JPAB
Google Scholar/Patents co-crystal celecoxib conversion inhibitor

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>Y</td>
<td>US 2006/0134198 A1 (TAWA et al) 22 June 2006 (22 06 2006) para [0293], [0152J, [0038]; [0039], [0041], [0251]-[0251]</td>
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Further documents are listed in the continuation of Box C

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