US 20040186105A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0186105 A1**

Allenspach et al. (43) **Pub. Date: Sep. 23, 2004**

(54) **PHARMACEUTICAL COMPOSITION EXHIBITING CONSISTENT DRUG RELEASE PROFILE**

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(21) Appl. No.: **10/647,501**

(22) Filed: **Aug. 25, 2003**

Related U.S. Application Data

(60) Provisional application No. 60/407,212, filed on Aug. 30, 2002. Provisional application No. 60/479,584, filed on Jun. 18, 2003.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/50**; A61K 31/415; A61K 31/365; A61K 31/18

(52) **U.S. Cl.** **514/247**; 514/406; 514/471; 514/602

(57) **ABSTRACT**

An orally deliverable pharmaceutical composition comprises a drug of low water solubility and a pregelatinized starch having low viscosity and/or exhibiting a multimodal particle size distribution. A process for preparing such a composition comprises a step of selecting a pregelatinized starch having low viscosity and/or exhibiting a multimodal particle size profile, and a step of admixing the selected pregelatinized starch with a drug of low water solubility.

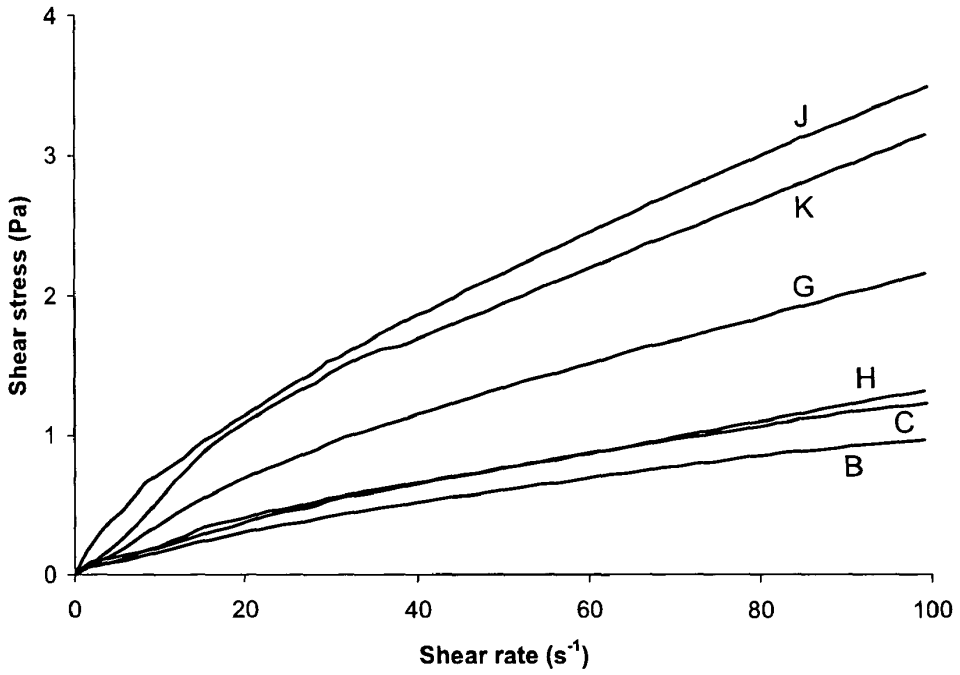

Fig. 1

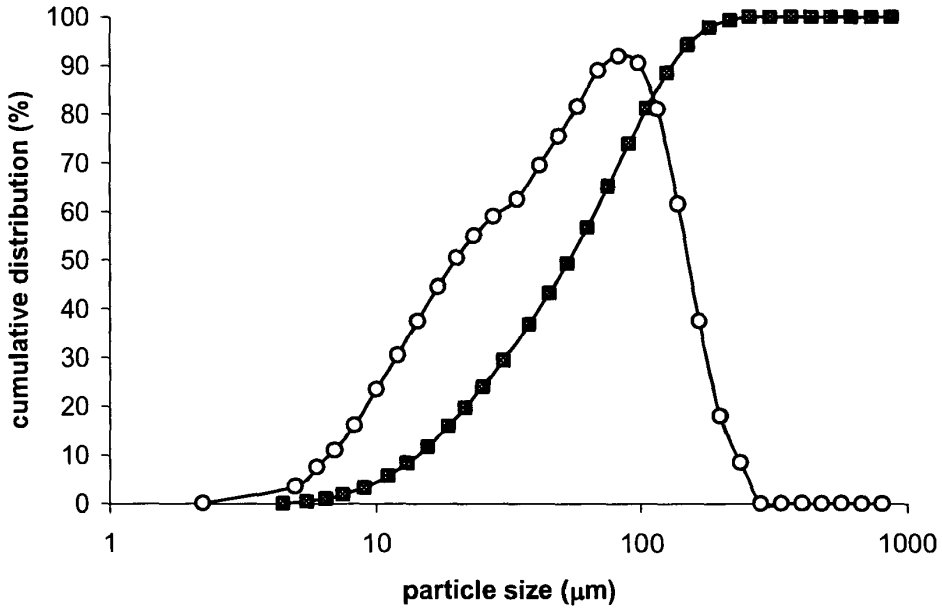

Fig. 2

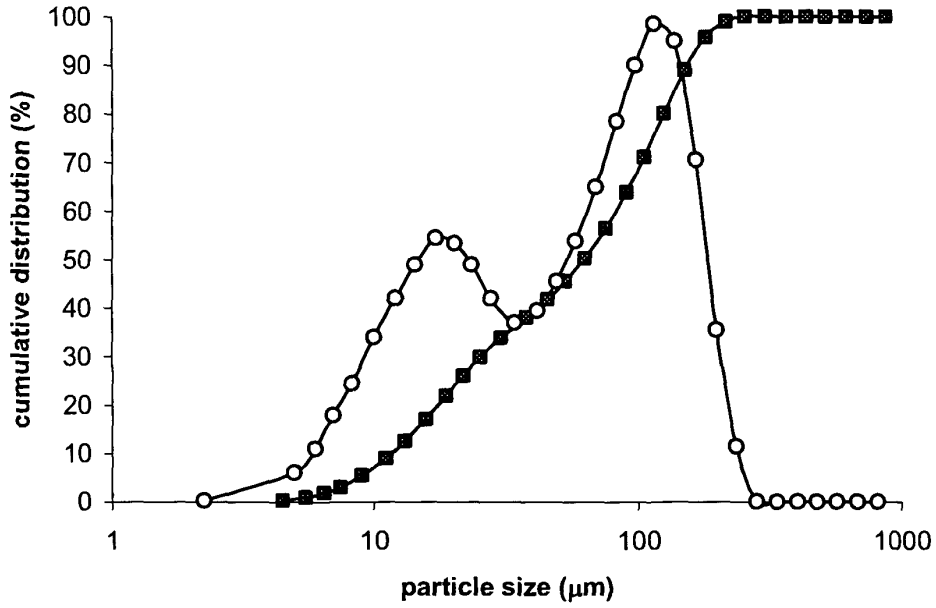

Fig. 3

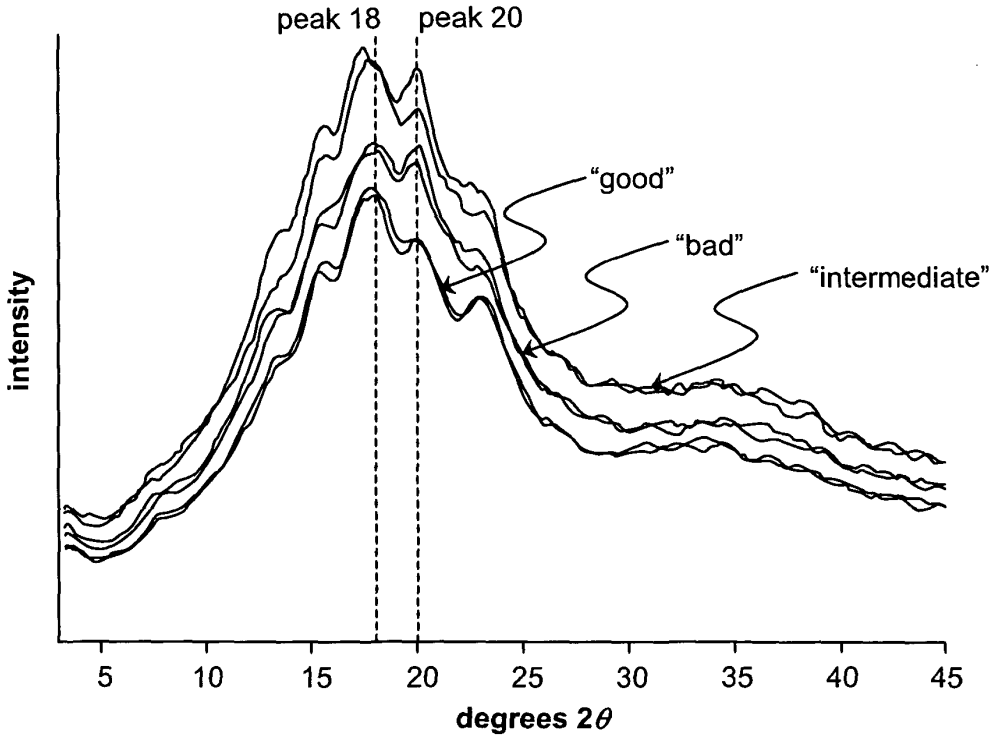

Fig. 4

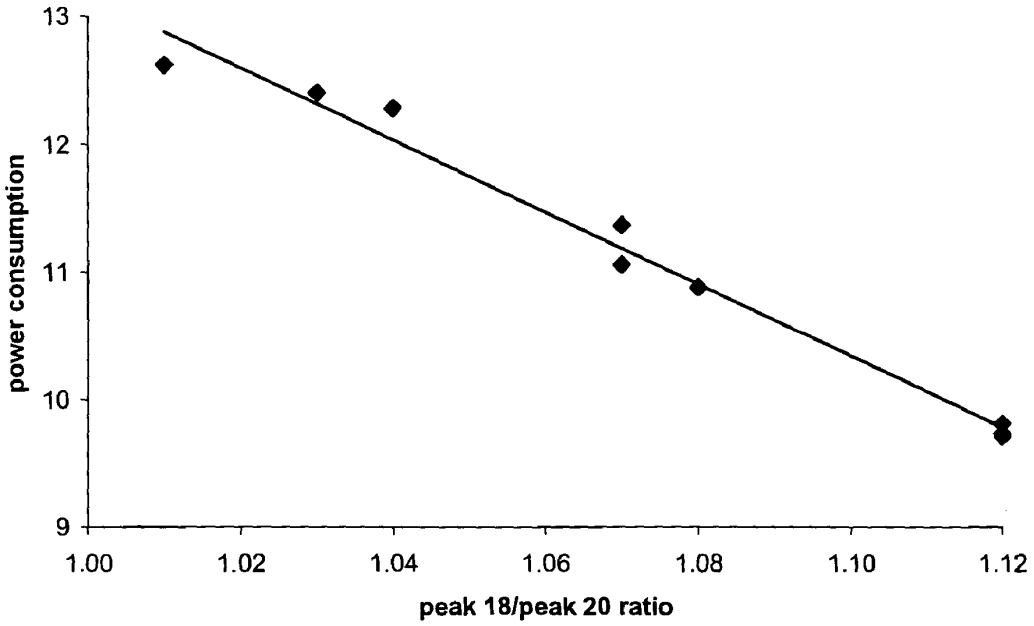

Fig. 5

PHARMACEUTICAL COMPOSITION EXHIBITING CONSISTENT DRUG RELEASE PROFILE

RELEASE PROFILE

[0001] This application claims priority of U.S. provisional application Serial No. 60/407,212 filed on Aug. 30, 2002 and U.S. provisional application Serial No. 60/479,584 filed on Jun. 18, 2003.

FIELD OF THE INVENTION

[0002] The present invention relates to orally deliverable pharmaceutical compositions containing a drug, for example a selective cyclooxygenase-2 (COX-2) inhibitory drug of low water solubility, as an active ingredient, to processes for preparing such compositions, to methods of treatment of COX-2 mediated disorders comprising orally administering such compositions to a subject, and to use of such compositions in manufacture of medicaments.

BACKGROUND OF THE INVENTION

[0003] During the process of seeking approval for and registering a pharmaceutical product with the Food and Drug Administration (FDA) in the U.S. and corresponding regulatory authorities in other countries, a particular candidate drug product, for example a tablet, must be shown to meet certain pre-established in vivo bioavailability and in vitro dissolution rate criteria. As a quality control measure, once such a drug product has received FDA or similar regulatory approval, samples drawn from batches of manufactured product must meet the dissolution rate criteria established during the regulatory approval process.

[0004] Typically, a drug manufacturer performs in-process or bulk finished product dissolution testing on a manufactured drug product to ensure that each batch of product meets established dissolution criteria; any drug product not meeting such criteria cannot be released to market and thus represents potentially wasted raw materials, labor, energy and resources. Therefore, from regulatory, production efficiency, financial and human resource perspectives, it is desirable that lot-to-lot, batch-to-batch and/or inter-tablet dissolution rate differences, and/or any other dissolution rate differences potentially present in a given manufacturing campaign, are negligible or small enough so as not to result in failure of product to meet pre-established dissolution rate criteria.

[0005] Furthermore, it is desirable also from safety and efficacy standpoints that lot-to-lot, batch-to-batch and/or inter-tablet dissolution rate differences are minimal. Where substantial variability in drug dissolution exists, some tablets can dissolve very quickly while others dissolve more slowly. Those tablets exhibiting increased dissolution rate can provide more rapid in vivo release, which in turn can lead to higher blood levels of the drug shortly after administration, with potentially increased risk for undesirable side-effects. Conversely, those tablets exhibiting decreased dissolution rate can provide less rapid in vivo release, which in turn can lead to lower blood levels of the drug shortly after administration, with potentially increased risk for reduced therapeutic response.

[0006] The compound 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide, also referred to herein as valdecoxib, was disclosed in U.S. Pat. No. 5,633,272 to Talley et al. together with processes for preparing this and related compounds. Valdecoxib has the structure:

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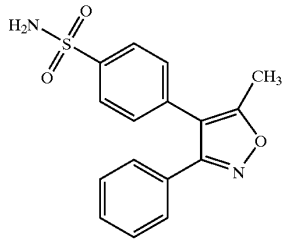

[0007] The compounds reported in above-cited U.S. Pat. No. 5,633,272, including valdecoxib, are disclosed therein as useful anti-inflammatory, analgesic and antipyretic drugs having a high degree of selectivity for inhibition of cyclooxygenase-2 (COX-2) over cyclooxygenase-1 (COX-1). Above-cited U.S. Pat. No. 5,633,272 also contains general references to formulations for the administration of such compounds, including orally deliverable dosage forms such as tablets and capsules.

[0008] European Patent Application No. 0 863 134 discloses orally deliverable compositions comprising a selective COX-2 inhibitory drug, specifically 2-(3,5-difluorophenyl)-3-(4-methyl-sulfonyl)phenyl)-2-cyclopenten-1-one, in combination with excipient ingredients including microcrystalline cellulose, lactose monohydrate, hydroxypropylcellulose, croscarmellose sodium and magnesium stearate.

[0009] International Patent Publication No. WO 00/32189 discloses orally deliverable compositions comprising a selective COX-2 inhibitory drug, specifically celecoxib, in combination with excipient ingredients selected from extensive lists of suitable diluents, disintegrants, binding agents, wetting agents, lubricants, etc.

[0010] International Patent Publication No. WO 01/41762 describes orally deliverable pharmaceutical compositions containing, inter alia, valdecoxib and pregelatinized starch (e.g., National Starch 1500). Pregelatinized starch is a commonly used excipient in pharmaceutical dosage forms and is generally employed as a diluent, disintegrant, and/or binder.

[0011] We have now discovered that pharmaceutical dosage forms (e.g., tablets) comprising a drug of low water solubility (e.g., valdecoxib) and pharmaceutical grade pregelatinized starch can exhibit the undesirable attribute of drug dissolution rate variability. As indicated above, drug dissolution rate variability is particularly undesirable as it can lead to side effects, lack of therapeutic response in some patients, and/or production inefficiencies.

[0012] If orally deliverable pharmaceutical dosage forms comprising a drug of low water solubility (e.g., valdecoxib) and pregelatinized starch could be prepared exhibiting the desirable attribute of improved dissolution rate uniformity, a significant advance in the safety, efficacy and production efficiency of many pharmaceutical dosage forms would be realized.

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