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(54) **Title**: POSACONAZOLE PHARMACEUTICAL COMPOSITION AND PREPARATION METHOD, APPLICATION AND PHARMACEUTICAL PREPARATION THEREOF

(54) **发明名称** : 泊沙康唑药物组合物及其制备方法、应用和药物制剂

(57) **Abstract**: The present invention relates to pharmaceutical compositions, comprising posaconazole and carrier material, the carrier material comprising: a vinylpyrrolidone-vinyl acetate copolymer or a polymer comprising glycol units. The present invention further relates to a method of preparing the pharmaceutical composition, method of using the pharmaceutical composition to treat and/or prevent mammalian fungal infection and related diseases, and pharmaceutical preparation comprising the pharmaceutical composition.

(57) **摘要**: 本发明涉及药物组合物，其包含泊沙康唑和载体材料，其中所述载体材料包含：乙烯基吡咯烷酮 -醋酸乙烯酯共聚物或含乙二醇单元的聚合物。本发明还涉及所述药物组合物的制备方法、使用所述药物组合物治疗和/或预防哺乳动物真菌感染和相关疾病的方法以及包含所述药物组合物的药物制剂。

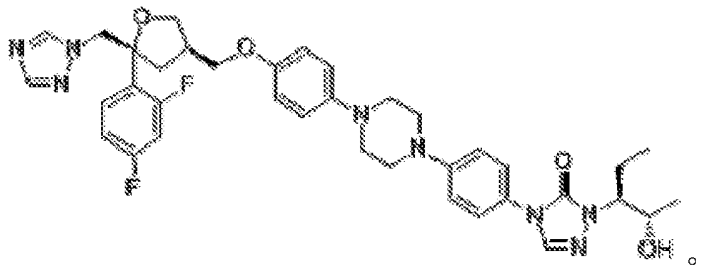
泊沙康唑药物组合物及其制备方法、应用和药物制剂

技术领域

本发明涉及药物组合物及其制备方法、应用和药物制剂。具体而言，本发明涉及包含泊沙康唑作为活性成分的药物组合物、制备所述药物组合物的方法、使用所述药物组合物治疗和/或预防哺乳动物真菌感染和相关疾病的方法以及包含所述药物组合物的药物制剂。

背景技术

泊沙康唑(Posaconazole)是伊曲康唑的衍生物，属于第二代三唑类抗真菌药物，其化学名称为 4-[4-[4-[4-[[(3R,5R)-5-(2,4-二氟苯基)-5-(1,2,4-三唑-1-基甲基)氧杂戊环-3-基]甲氧基]苯基]哌嗪-1-基]苯基]-2-[(2S,3S)-2-羟基戊-3-基]-1,2,4-三唑-3-酮，结构式如下：



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美国专利 US 5,703,079 和 US 5,661,151 分别公开了泊沙康唑及其合成方法，在此将其全部内容援引加入本文。

泊沙康唑克服了第一代三唑类药物抗菌谱窄、生物利用度低和耐药性等问题，具有抗菌谱广的特性。与氟康唑和伊曲康唑相比，泊沙康唑能更有效地预防侵袭性曲霉菌属感染病，可降低侵袭性真菌感染相关的病死率。

含结晶形式的泊沙康唑(40 mg/ml)的混悬剂已作为 Noxafil®被批准用于治疗侵入性真菌感染，例如治疗口咽念珠菌病，包括耐受其他唑类抗真菌剂治疗的感染，和用作预防性治疗由于严重免疫缺失而非常可能发生这些感染的患者，如具有移植物抗宿主病(GVHD)的造血干细胞移植(HSCT)受体或具有来自化疗的长期嗜中性白血球减少症的血液恶性肿瘤患者中的真菌感染。

然而，适用于制备口服固体剂型的包含泊沙康唑的药物组合物的供给迄今仍受制于泊沙康唑游离碱化合物的弱碱性和低水溶性。泊沙康唑的pKa 为 3.6 (哌嗪)和 4.6 (三唑)，其在低 pH 下微溶。例如在胃环境中(pH 大约为 1.2)，泊沙康唑游离碱具有大约 0.8 mg/ml 的溶解度。但当 pH 高于 4 时，泊沙康唑几乎不溶(溶解度小于大约 1 μg/ml)。因此，当溶解在胃液中的泊沙康唑经胃排空到达肠环境(通常 pH 不低于大约 6.4)时，已溶解的泊沙康唑会结晶析出，从而减少了药物的吸收，影响其生物利用度。

US2011123627A 公开了一种使得药物在通过胃环境时基本不可溶但一旦进入小肠环境就容易释放的包含肠溶性载体材料羟丙基甲基纤维素醋酸琥珀酸酯(HPMCAS)聚合物的泊沙康唑药物组合物。与现有的已上市的泊沙康唑口服混悬剂相比，该药物组合物提高了泊沙康唑在体内的最大血浆药物浓度及生物利用度。但该药物组合物限制了泊沙康唑在胃中的释放，使得药物在体内的血浆药物浓度达峰时间(T_{max})滞后。另外，使用 HPMCAS 作为载体材料经热熔挤出工艺制备的泊沙康唑药物组合物硬度较高，研磨困难。且该药物组合物可压性差，给后续工艺例如压片带来困难。

发明内容

本发明的目的是提供克服现有技术的上述缺陷的泊沙康唑药物组合物。

在第一方面，本发明提供药物组合物，其包含泊沙康唑和载体材料，其中所述载体材料包含：乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物。所述药物组合物可用于预防和/或治疗哺乳动物真菌感染和相关疾病。

在第二方面，本发明提供本发明第一方面的药物组合物在制备用于预防和/或治疗哺乳动物真菌感染和相关疾病的药物中的应用。

在第三方面，本发明提供预防和/或治疗哺乳动物真菌感染和相关疾病的方法，其包括给予所述哺乳动物有效量的本发明第一方面的药物组合物。

在第四方面，本发明提供制备本发明第一方面的药物组合物的方法，其包括：

将热熔挤出机预热至 120℃-180℃；

向所述热熔挤出机中进料已混匀的计量比的泊沙康唑、载体材料及任

选存在的药学上可接受的药用辅料的混合物，或者向所述热熔挤出机中直接进料计量比的泊沙康唑、载体材料及任选存在的药学上可接受的药用辅料；

挤出；和

将所得挤出物冷却、粉碎并过筛，任选地与药学上可接受的药用辅料混合，由此得到所述药物组合物。

在第五方面，本发明提供包含本发明第一方面的药物组合物的药物制剂，其是散剂、颗粒剂、丸剂、胶囊剂或片剂的形式。

附图说明

结合以下附图，本发明的目的和特征将变得更为清楚：

图1显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物中VA64含量对Tg值的影响，其中VA64/(VA64+HPMCAS)%为0%、25%、37.5%、50%和100%时所对应的Tg值分别为组合物2-1、组合物2-2、组合物2-3、组合物2-4和组合物1-3或相应的空白组合物的Tg值。

图2显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物的X-RD图谱，自下至上依次为原料药、组合物1-3、组合物2-3和组合物2-4的X-RD图谱。

图3显示泊沙康唑-Kollidon® VA64/HPMCAS混合载体制成的药物组合物(组合物2-3)及原料药的模拟体内空腹条件的溶出曲线，其中pH在30 min时从1.2转换到6.8。

图4显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物(其中泊沙康唑和载体材料重量比为1:3)中的VA64含量对泊沙康唑在pH 1.2和pH 6.8的溶出介质中的溶出度的影响，其中VA64/(VA64+HPMCAS)%为0%、25%、37.5%、50%和100%时所对应的溶出度分别为组合物2-1、组合物2-2、组合物2-3、组合物2-4和组合物1-3的溶出度。

图5为泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物(组合物2-1和组合物2-2)在给予空腹条件下的人体受试者后的泊沙康唑平均血药浓度-时间曲线，其中组合物2-1和组合物2-2中VA64/(VA64+HPMCAS)%分别为0%和25%。

具体实施方式

除非另有定义，本文使用的所有技术和科学术语具有与本发明所属领域技术人员通常理解的相同的含义。若存在矛盾，则以本文提供的定义为准。

当以范围、优选范围或者优选的数值上限以及优选的数值下限的形式表述某个量、浓度或其它值或参数的时候，应当理解相当于具体揭示了通过将任意一对范围上限或优选数值与任意范围下限或优选数值结合起来的任何范围，而不考虑该范围是否具体揭示。除非另外指出，本文所列出的数值范围旨在包括范围的端点，和该范围之内的所有整数和分数。

术语“约”、“大约”当与数值变量并用时，通常指该变量的数值和该变量的所有数值在实验误差内(例如对于平均值 95%的置信区间内)或在指定数值的±10%内，或更宽范围内。

术语“计量比”是将各种物质按一定重量进行配比。例如在本发明中，将药物(泊沙康唑)与载体材料及任选存在的药学上可接受的药用辅料按一定重量的比例进行配比。

术语“药学上可接受”的物质指如下物质，其在正常的医学判断范围内适用于与患者的组织接触而不会有不适当毒性、刺激性、过敏反应等，具有合理的利弊比，且能有效用于其目的用途。

术语“药物组合物”指一种或多种活性成分与载体材料和任选存在的一种或多种药学上可接受的药用辅料组成的物质。在本发明中可将其简称为组合物。例如药物组合物 1-1 可简称为组合物 1-1。

术语“空白组合物”是指相对于药物组合物而言，其不含活性成分(即泊沙康唑)而仅含载体材料和任选存在的其它药学上可接受的药用辅料。

术语“药剂产品”、“药物剂型”、“剂型”、“药物制剂”等指被施予需要治疗的患者的药物组合物，其通常可以为下述形式：散剂、颗粒剂、丸剂、胶囊剂、片剂、溶液剂、混悬剂或贴剂等。

术语“溶解在或以分子水平分散在载体材料中”指药物分散在所述载体材料中，形成单相药物组合物。在本发明中，该术语即指泊沙康唑分散在所述载体材料中，形成单相药物组合物(也称为固体溶液、分散体或固体分散体)。所得泊沙康唑药物组合物的 Tg 值不同于载体材料和泊沙康唑原料

药的 Tg 值。术语“溶解在”、“以分子水平分散”、“分散体”、“固体溶液”、“固体分散体”在本文中视方便使用，以描述在制备的各阶段中和在各温度下的本发明的药物组合物。

术语“生物利用度”指药物或其他物质在施用后能够为靶组织所利用的程度。

术语“血浆药物浓度达峰时间(T_{max})”指施用后达到血浆药物浓度峰值(C_{max})的时间。

术语“血浆药物浓度峰值(C_{max})”指施用药物后达到的最大血浆药物浓度。

术语“$AUC_{0-\infty}$”指施用药物后时间由 0 至无穷的血浆药物浓度对时间曲线的曲线下面积；而术语“AUC_{0-t}”指施用药物后时间由 0 至 t 的血浆药物浓度对时间曲线的曲线下面积。

除非另有说明，本文中所有的百分比、份数、比值等均是按重量计。

本发明提供了一种泊沙康唑药物组合物，与现有技术相比，本发明的药物组合物改善了泊沙康唑在人体内的吸收行为，增加了该药物的吸收和生物利用度。此外，本发明的药物组合物通过简单且易操作的热熔挤出法制备，与现有技术相比，改善了工艺，降低了能耗，提高了生产能力。

具体地，本发明的发明人发现，一定比例的乙烯基吡咯烷酮-醋酸乙烯酯共聚物作为载体材料和泊沙康唑经过本发明的热熔挤出工艺的处理即可制备成泊沙康唑溶解在或以分子水平分散在所述载体材料中的药物组合物。本发明的发明人更出人意料地发现，泊沙康唑分散在乙烯基吡咯烷酮-醋酸乙烯酯共聚物中的药物组合物可提高泊沙康唑在胃肠道的溶解度；可改善溶解在胃环境中的泊沙康唑随胃排空进入肠道时由于 pH 变化而溶解度急剧下降导致的析出沉淀或结晶的问题，从而增加泊沙康唑在体内的吸收，提高生物利用度。另一方面，所述药物组合物还能改变泊沙康唑在体内的吸收表现，在不延迟其 T_{max} 的情况下，增加 C_{max} 和 AUC。同时，所述药物组合物还具有更好的生产工艺特性，比如容易研磨、较好的可压性等。

另外，本发明的发明人还进一步出人意料地发现，在所述药物组合物中使用一定比例的乙烯基吡咯烷酮-醋酸乙烯酯共聚物和肠溶聚合物例如 HPMCAS 的组合作为混合载体材料，不仅能进一步提高泊沙康唑在胃肠道的溶解度，而且还能进一步改善溶解在胃环境中的泊沙康唑随胃排空进入

肠道时由于 pH 变化而溶解度急剧下降导致的析出沉淀或结晶的问题，从而进一步增加泊沙康唑的吸收和生物利用度。

再者，本发明的发明人又出人意料地发现，向所述药物组合物中加入聚乙二醇 1000 维生素 E 琥珀酸酯(TPGS)后，可进一步提高泊沙康唑在胃肠道的溶解度，而且还能进一步改善溶解在胃环境中的泊沙康唑随胃排空进入肠道时由于 pH 变化而溶解度急剧下降导致的析出沉淀或结晶的问题，从而进一步增加泊沙康唑的吸收和生物利用度。此外，采用本发明的热熔挤出工艺制备所述药物组合物时，加入 TPGS 使药物组合物的玻璃化转换温度(Tg)降低，挤出机扭矩显著降低，能耗减少，生产能力提高。

具体地，本发明提供药物组合物，其包含泊沙康唑和载体材料，其中所述载体材料包含：乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物。

在本发明的一个实施方案中，泊沙康唑溶解在或以分子水平分散在所述载体材料中。

所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物可例如通过在 2-丙醇中使 N-乙烯基吡咯烷酮与乙酸乙烯酯进行自由基聚合而得到。所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物也可以是例如 US5426163A 中公开的乙烯基吡咯烷酮与醋酸乙烯酯的重量比为 15:85-40:60 的共聚物。本发明中适用作载体材料的乙烯基吡咯烷酮-醋酸乙烯酯共聚物中的乙烯基吡咯烷酮单元与醋酸乙烯酯单元的重量比为约 1:9-约 9:1，优选为约 4:6-约 6:4。所述共聚物的 K 值为约 25-约 70。K 值又称为 Fikentscher K 值，是本领域中常用的对包含乙烯基吡咯烷酮单元的聚合物或其混合物分子量的度量，并且可以如 H. Fikentscher 在 Cellulose-Chemie, 1932, 13:58-64/71-74 中所述的方法以 1 重量%水溶液进行测定。在一个实施方案中，本发明中使用的乙烯基吡咯烷酮-醋酸乙烯酯共聚物也可为例如 BASF 公司的市售产品 Kollidon® VA64 和/或 International Specialty Products 公司的市售产品 Plasdone® S630 (两者都是乙烯基吡咯烷酮与醋酸乙烯酯的重量比为 6:4 的共聚物)，但不限于此。在本发明的一个优选实施方案中，所述载体材料是 Kollidon® VA64 (以下简称 VA64)。

本发明中适用作载体材料的含乙二醇单元的聚合物可以例如是聚乙二醇/乙烯基己内酰胺/醋酸乙烯酯共聚物，其可为例如BASF公司的市售产品

Soluplus®。在本发明的一个优选实施方案中，所述载体材料是Soluplus®。

在本发明的另一个实施方案中，所述载体材料还包含肠溶聚合物，所述肠溶聚合物为乙酸邻苯二甲酸纤维素、乙酸偏苯三酸纤维素、乙酸琥珀酸纤维素、邻苯二甲酸甲基纤维素、邻苯二甲酸乙基羟甲基纤维素、邻苯二甲酸羟丙基甲基纤维素、羟丙基甲基纤维素醋酸琥珀酸酯(HPMCAS)、乙酸马来酸羟丙基甲基纤维素、偏苯三酸羟丙基甲基纤维素、羧甲基乙基纤维素、聚丁酸乙烯邻苯二甲酸酯、聚乙酸乙烯醇邻苯二甲酸酯、甲基丙烯酸/丙烯酸乙酯共聚物(其中甲基丙烯酸与丙烯酸乙酯的优选重量比为1:99-99:1)及甲基丙烯酸/甲基丙烯酸甲酯共聚物(其中甲基丙烯酸与甲基丙烯酸甲酯的优选重量比为 1:99-99:1)中的一种或多种，优选选自邻苯二甲酸羟丙基甲基纤维素、HPMCAS、乙酸马来酸羟丙基甲基纤维素以及偏苯三酸羟丙基甲基纤维素，更优选为 HPMCAS。

HPMCAS 是一种纤维素衍生物，具有(1)两种类型的醚取代基：甲基和2-羟丙基和(2)两种类型的酯取代基：乙酰基和琥珀酰基。在科学文献中称为 O-(2-羟丙基)-O-甲基-纤维素醋酸琥珀酸酯。在一些实施方案中，所述 HPMCAS 优选为下列中的至少一种或多种：基于 HPMCAS 的重量，(i)具有平均 5-9 重量%乙酰基含量和平均 14-18 重量%琥珀酰基含量的 HPMCAS，(ii)具有平均 7-11 重量%乙酰基含量和平均 10-14 重量%琥珀酰基含量的 HPMCAS，(iii)具有平均 10-14 重量%乙酰基含量和平均 4-8 重量%琥珀酰基含量的 HPMCAS，其中(ii)是更优选的。所述 HPMCAS 可为例如 Shin-Etsu 公司的市售产品 AQOAT® AS-L、AQOAT® AS-M 和 AQOAT® AS-H，以及 Ashland 公司的市售产品 AquaSolve™ L、AquaSolve™ LM、AquaSolve™ LH 和 AquaSolve AS™ L、AquaSolve AS™ M、AquaSolve AS™ H，但不限于此。在本发明的一个优选实施方案中，所述 HPMCAS 优选 AQOAT® AS-M。

在本发明的又一个实施方案中，泊沙康唑与载体材料的重量比可以为约 1:1-约 1:10，优选约 1:1-约 1:5，更优选约 1:3。

在本发明的又一个实施方案中，乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物以相对于所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物和肠溶聚合物例如 HPMCAS 的总重量的 10 重量%-100 重量%的量存在，优选 25 重量%-100 重量%，更优选 25 重量%-50

重量%，甚至更优选 20 重量%-40 重量%，最优选 25 重量%-37.5 重量%，并且所述范围中各子范围也包括在内，例如由以下数值中的任意两个所组成的范围：25、25.5、26、26.5、27、27.5、28、28.5、29、29.5、30、30.5、31、31.5、32、32.5、33、33.5、34、34.5、35、35.5、36、36.5、37、37.5、38、38.5、39、39.5、40、40.5、41、41.5、42、42.5、43、43.5、44、44.5、45、45.5、46、46.5、47、47.5、48、48.5、49、49.5 和 50。

在本发明的又一个实施方案中，所述药物组合物还包含聚乙二醇 1000 维生素 E 琥珀酸酯(D-α-tocopherol polyethylene glycol 1000 succinate, TPGS, Vitamin E TPGS, Tocophersolan)。

本发明中适用的 TPGS 是维生素 E 的水溶性衍生物，由维生素 E 琥珀酸酯(VES)的羧基与聚乙二醇 1000 (PEG 1000)酯化而成，相对分子量约为 1513，已载入美国药典。TPGS 在本发明的药物组合物和药物制剂中作为增溶剂起作用，并且还可以通过影响肠道粘膜细胞里的药物转运糖蛋白而减少药物的外排，从而有助于口服生物利用度的提高。本发明中可使用的 TPGS 的实例为 BASF 公司的市售产品 Kolliphor™ TPGS，但不限于此。在本发明的一个优选实施方案中，所述 TPGS 是 Kolliphor™ TPGS。

本发明中采用的 TPGS 的量没有特殊限制，可以根据实际情况进行调整。通常，TPGS 以相对于泊沙康唑、所述载体材料和 TPGS 的总重量的约 1-12 重量%的量存在。

本发明的药物组合物还可包含药学上可接受的药用辅料，所述药用辅料包括但不限于表面活性剂、pH 调节剂、稀释剂、崩解剂、粘合剂和润滑剂中的一种或多种。

另一方面，本发明还提供制备本发明的药物组合物的方法，其包括但不限于热熔挤出法和喷雾干燥法。例如，热熔挤出法的具体步骤如下：

将热熔挤出机预热至约 120℃-约 180℃；

向所述热熔挤出机中进料已混匀的计量比的泊沙康唑、载体材料及任选存在的药学上可接受的药用辅料的混合物(或进料已混匀的计量比的泊沙康唑、载体材料、TPGS 及任选存在的药学上可接受的药用辅料的混合物)，或者向所述热熔挤出机中直接进料计量比的泊沙康唑、载体材料及任选存在的药学上可接受的药用辅料(或直接进料计量比的泊沙康唑、载体材料、TPGS 及任选存在的药学上可接受的药用辅料)；

挤出；和

将所得挤出物冷却、粉碎并过筛，任选地与药学上可接受的药用辅料混合，由此得到所述药物组合物。

对于本发明的制备方法中所述的冷却方式没有特别限制，其可包括风冷、水冷、机械冷却等。

对于适用于本发明的挤出机的类型没有特别限制，其包括但不限于单螺杆或双螺杆型热熔挤出机。在本发明的一个实施方案中，用于制备本发明的药物组合物的挤出机是双螺杆型挤出机。在该情况下，对于螺杆转动的类型没有特别限制，其包括但不限于同向双螺杆、异向双螺杆和双锥型螺杆转动模式。在本发明的一个优选实施方案中，用于制备本发明的药物组合物的挤出机优选是同向双螺杆型挤出机。

热熔挤出机设定的温度为约 120℃-约 180℃，螺杆转速为约 50-约 500 rpm。螺杆长度和直径的比例(L/D)可选取约 15-约 40。如果热熔挤出机温度过低，L/D 过短，螺杆转速过慢，则热熔过程中热能和机械能提供不足，进而泊沙康唑、载体材料或聚乙二醇 1000 维生素 E 琥珀酸酯达不到熔融状态，或者泊沙康唑不能溶解在熔融的载体材料中。因此泊沙康唑与载体材料虽然充分混合，但不能得到泊沙康唑溶解在或以分子水平分散在所述载体材料中的单相固体分散体(固体溶液)。如果热熔挤出机温度过高，L/D 过长，螺杆转速过快，则热熔过程中热能和机械能提供过量，即使得到的是泊沙康唑溶解在或以分子水平分散在所述载体材料中的单相固体分散体(固体溶液)，也会造成泊沙康唑和/或载体材料和/或 TPGS 不必要的降解。

另外，本发明还提供包含本发明的药物组合物的药物制剂。即本发明的药物组合物可根据需要进一步与药学上可接受的药用辅料组合以制成各种剂型。在本发明的一个实施方案中，所述药物制剂可以是散剂、颗粒剂、丸剂、胶囊剂或片剂的形式。

所述药学上可接受的药用辅料包括但不限于表面活性剂、pH 调节剂、稀释剂、崩解剂、粘合剂和润滑剂中的一种或多种。

应强调的是，该列举的药学上可接受的药用辅料只是阐述性的、代表性的而不是绝无遗漏的。因此，本发明并不限于下文所列举的药学上可接受的辅料。

本发明中采用的表面活性剂可以是阴离子型、阳离子型、两性离子型

或非离子型的表面活性剂，优选为两性离子型或非离子型的表面活性剂。本发明中采用的表面活性剂也可以是两种或更多种表面活性剂的混合物。表面活性剂的选择可以是由本发明的药物组合物中所使用的特定化合物而定。适用于本发明的药物组合物的表面活性剂如下文所列。

可以适用于本发明的合适的表面活性剂为以下中的一种或多种：聚氧乙烯蓖麻油衍生物，例如聚氧乙烯甘油三蓖麻醇酸酯或聚氧乙烯醚 35 蓖麻油(Cremophor EL，BASF)或聚氧乙烯甘油羟基硬脂酸酯如聚乙二醇 40 氢化蓖麻油(Cremophor RH40)或聚乙二醇 60 氢化蓖麻油(Cremophor RH 60)；环氧乙烷和环氧丙烷的嵌段共聚物，又名聚氧乙烯聚氧丙烯嵌段共聚物或聚氧乙烯聚丙二醇，比如 Poloxamer 124、Poloxamer 188、Poloxamer 237、Poloxamer 388、Poloxamer 407(BASF)；聚氧乙烯(20)失水山梨醇的单脂肪酸酯，如聚氧乙烯(20)失水山梨醇单油酸酯(Tween 80)、聚氧乙烯(20)失水山梨醇单硬脂酸酯(Tween 60)、聚氧乙烯(20)失水山梨醇单棕榈酸酯(Tween 40)、聚氧乙烯(20)失水山梨醇单月桂酸酯(Tween 20)；聚乙二醇脂肪酸酯，例如 PEG-200 单月桂酸酯、PEG-200 双月桂酸酯、PEG-300 双月桂酸酯、PEG-400 双月桂酸酯、PEG-300 双硬脂酸酯、PET-300 二油酸酯；亚烷基二醇脂肪酸单酯，例如丙二醇单月桂酸酯(Lauroglycol)；失水山梨醇脂肪酸单酯，例如失水山梨醇单月桂酸酯(Span 20)、失水山梨醇单油酸酯、失水山梨醇单棕榈酸酯(Span 40)或失水山梨醇硬脂酸酯。

本发明适用的表面活性剂优选是聚氧乙烯蓖麻油衍生物、环氧乙烷和环氧丙烷的嵌段共聚物，尤其优选 Cremophor RH40 和/或 Poloxamer 188。

可以适用于本发明的合适的 pH 调节剂为柠檬酸、乙酸、反丁烯二酸、顺丁烯二酸、酒石酸、苹果酸、琥珀酸、富马酸、草酸、丙二酸、苯甲酸和苦杏仁酸和抗坏血酸中的一种或多种，优选柠檬酸。

可以适用于本发明的合适的稀释剂可以是微晶纤维素、淀粉、预胶化淀粉、乳糖、甘露醇和磷酸氢钙中的一种或多种。

可以适用于本发明的合适的崩解剂可以是低取代纤维素、羧甲基纤维素、羧甲基纤维素钠、交联羧甲基纤维素钠、羧甲基纤维素钙、羧甲基淀粉钠、交联聚乙烯基吡咯烷酮(即交联聚维酮)、具有 5-16 重量%的羟丙氧基的低取代的羟丙基纤维素(L-HPC)和羟甲基淀粉中的一种或多种。

可以适用于本发明的合适的粘合剂可以是羧甲基纤维素钠、羟丙基纤

维素、甲基纤维素、乙基纤维素和羟丙甲纤维素的一种或多种。

可以适用于本发明的合适的润滑剂可以是硬脂酸镁、二氧化硅、滑石粉、硬脂酸和氢化植物油中的一种或多种。

实施例

各实施例中进行物理化学性质评价所用的测定方法如下：

1. 玻璃化转换温度(Tg)：精密称取大约3 mg的待测物(泊沙康唑原料药(以下简称原料药)、载药组合物(即本发明的药物组合物)或空白组合物)进行差示扫描量热分析(mDSC，TA Q2000差示扫描量热仪)，扫描温度范围为40-180℃。

2. 粉末X-衍射(X-RD)：取待测物(原料药、载药组合物或空白组合物)适量，在Cu靶、电压45 kv、电流45 mA的条件下记录粉末X-衍射图谱(BRUKER制造的D8ADVANCE型X射线衍射仪)。

3. 表观溶解度：称取过量的泊沙康唑药物组合物放入容器中，加入约相当于容器体积2/3的pH 6.8磷酸盐缓冲液后，将容器置于37℃的摇床中震荡3 h。将容器内容物用0.45 μm滤膜过滤后，收集滤液，用适量的甲醇稀释，经涡旋混合后以HPLC分析方法测定泊沙康唑浓度，HPLC分析方法如下。

色谱柱	C_{18}柱 (3 μm，4.6×75 mm)
流动相	0.1%磷酸/乙腈 = 50 : 50
流速	1.5 ml/min
样品盘	室温
检测波长	254 nm
进样量	10 μl
单针分析时间	约 2 min

4. 溶出度：

溶出方法	USP II法 (浆法)
溶出介质	pH 1.2/6.8的介质：900 ml。 pH 1.2→6.8的介质，将pH 1.2的溶出介质800 ml在30 min取样后立即加入配制好的缓冲液100 ml，使整体溶出介质的pH值为6.8。
转速	100 rpm
温度	37.5℃
测试剂量	100 mg (泊沙康唑)/杯

溶出样品分析方法：与上述表观溶解度测定中所述HPLC分析方法相

同。

实施例1 泊沙康唑-Kollidon® VA64药物组合物

1. 制备：泊沙康唑-Kollidon® VA64药物组合物的组成及各组分用量如表1-1所示。

制备方法：按表1-1中所示的用量将泊沙康唑和载体材料和/或TPGS直接或者在混合机中混合均匀后进料至同向双螺杆挤出机(印度Steer公司Omicron 12)的加料斗内，将同向双螺杆挤出机的温度控制在约120℃-约180℃之间，进行挤出，螺杆转速为约50-约500 rpm。将所得挤出物冷却、粉碎、过筛，得到固体粉末。然后按表1-1中所示的用量将其他药用辅料与该固体粉末混合均匀，即得到泊沙康唑-Kollidon® VA64药物组合物。

表1-1 泊沙康唑-Kollidon® VA64药物组合物的组成及各组分用量(重量%)

	功能	组合物1-1	组合物1-2	组合物1-3	组合物1-4
泊沙康唑	活性成分	13.6	12.4	11.3	4.5
Kollidon® VA64	载体材料	13.6	37.3	33.9	22.7
Kolliphor® TPGS	增溶剂	/	/	4.5	/
微晶纤维素	稀释剂	54.4	31.1	31.1	54.4
交联聚维酮	崩解剂	16.3	18.6	18.6	16.3
二氧化硅	润滑剂	1.4	0.4	0.4	1.4
硬脂酸镁	润滑剂	0.7	0.2	0.2	0.7

2. 物理化学性质评价

2.1. 玻璃化转换温度(Tg)测定

经测定，泊沙康唑原料药(晶体型)的熔融温度为约170℃，组合物1-2的Tg值为97.6℃，组合物1-3的Tg值为71.8℃；与组合物1-2对应的空白组合物的Tg值为106.3℃，与组合物1-3对应的空白组合物的Tg值为81.4℃。与这两个空白组合物的Tg值相比，组合物1-2和1-3的Tg值发生明显的偏移，但与泊沙康唑的Tg值(68℃)明显不同，且泊沙康唑的熔融峰消失。上述结果清楚地表明，在本发明的各药物组合物中，泊沙康唑是溶解在或以分子水平分散在载体材料中的。

2.2. 表观溶解度测定

表1-2 泊沙康唑-Kollidon® VA64药物组合物在pH 6.8磷酸盐缓冲液中的表

观溶解度

	原料药	组合物1-1	组合物1-2	组合物1-3	组合物1-4
表观溶解度(μg/ml)	<1	10.6	14.3	44.3	15.9
表观溶解度比(组合物/原料药)	1	>10	>14	>44	>15

由表1-2可知，使用热熔挤出法制备的本发明的各药物组合物对泊沙康唑都具有明显的增溶作用，说明Kollidon® VA64对泊沙康唑的增溶效果较好。将药物组合物内的载体材料(Kollidon® VA64)和原料药的重量比从1:1调整到5:1时，表观溶解度从10.6 μg/ml增加到15.9 μg/ml，表明载体材料与原料药的重量比对泊沙康唑溶解度的影响不大。但是，在组合物1-2的基础上少量加入Kolliphor® TPGS (组合物1-3)就使表观溶解度从14.3 μg/ml增加到44.3 μg/ml，表明包含TPGS的药物组合物能大幅度提高泊沙康唑的溶解度。

2.3. 模拟体内条件的溶出度测定

据报道，人体胃环境的pH值约为1.2，肠环境的pH值约为6.8。对本发明的各药物组合物进行模拟体内条件的溶出度测定，结果如表1-3所示。

表1-3 泊沙康唑-Kollidon® VA64药物组合物在pH 1.2→6.8的介质转换中的溶出度

	溶出度(%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
原料药	89.0	87.0	98.7	7.1	5.6	5.6
组合物1-1	36.4	72.3	87.8	92.1	66.3	64.8
组合物1-2	82.3	86.8	91.1	93.3	95.6	97.9
组合物1-3	90.1	91.2	93.3	94.4	93.0	95.8
组合物1-4	70.7	102.5	84.4	50.1	60.1	82.2

由表1-3可知，原料药在经过pH 1.2到6.8转换后溶出度大幅度降低，从98.7%减小到5.6%，表明泊沙康唑在体内经胃排空到达肠道时会从生理液中沉淀或结晶出来，从而降低其体内生物利用度。和原料药相比，本发明的药物组合物(特别是组合物1-2和组合物1-3)在pH 1.2到6.8转换后3 h内的溶出度下降不明显，并且所有本发明的药物组合物在30 min之后各个时间点的溶出度均在50%以上，最高达到97.9%，显著高于原料药的溶出度，表明

它们均能够显著提高泊沙康唑在体内的吸收。特别地，组合物1-2和组合物1-3在30 min之后各个时间点的溶出度均在93%以上，表明它们可更好地提高泊沙康唑在体内的吸收。

实施例2 泊沙康唑-Kollidon® VA64/HPMCAS药物组合物(混合载体药物组合物)

1. 制备：泊沙康唑-Kollidon® VA64/HPMCAS药物组合物的组成及各组分用量如表2-1所示。

制备方法：按表2-1中所示的用量将泊沙康唑和载体材料(VA64和/或HPMCAS (具体为AQOAT® AS-M))和/或TPGS直接或者在混合机中混合均匀后进料至同向双螺杆挤出机(印度Steer公司Omicron 12)的加料斗内，将同向双螺杆挤出机的温度控制在约120℃-约180℃之间，进行挤出，螺杆转速为约50-约500 rpm。将所得挤出物冷却、粉碎、过筛，得到固体粉末。然后按表2-1中所示的用量将其他药用辅料与该固体粉末混合均匀，即得到泊沙康唑-Kollidon® VA64/HPMCAS药物组合物。

组合物2-1为根据US2011123627A制备的对比组合物，其载体材料仅含AQOAT® AS-M一种物质。

表2-1 泊沙康唑-Kollidon®VA64/HPMCAS药物组合物的组成及各组分用量(重量%)

	功能	组合物2-1	组合物2-2	组合物2-3	组合物2-4	组合物2-5	组合物2-6
泊沙康唑	活性成分	17.4	15.6	12.5	12.5	14.5	7.9
AQOAT® AS-M	载体材料	52.2	35.2	23.5	18.8	18.2	19.7
Kollidon® VA64	载体材料	/	11.7	14.1	18.8	10.9	11.8
Kolliphor® TPGS	增溶剂	/	6.3	5.0	5.0	4.3	3.9
微晶纤维素	稀释剂	12.3	15.5	29.5	29.5	34.3	37.3
羟丙基纤维素	粘合剂	13.0	9.4	/	/	/	/
交联羧甲基纤维素钠	崩解剂	4.3	5.5	13.8	13.8	15.9	17.3

二氧化硅	润滑剂	0.5	0.5	1.0	1.0	1.2	1.3
硬脂酸镁	润滑剂	0.3	0.3	0.6	0.6	0.7	0.8

2. 物理化学性质评价

2.1. 玻璃化转换温度(Tg)测定

测定结果如图1所示。图1显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物中VA64含量对Tg值的影响，其中VA64/(VA64+HPMCAS)%为0%、25%、37.5%、50%和100%时所对应的Tg值分别为组合物2-1、组合物2-2、组合物2-3、组合物2-4和组合物1-3或相应的空白组合物的Tg值。从图1可以看出，随组合物中VA64含量的增加，Tg值呈下降趋势；含药组合物的Tg值比与它们各自对应的空白组合物的Tg值降低约10-20℃，发生明显的偏移，但与泊沙康唑的Tg值(68℃)明显不同。

图2显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物的X-RD图谱，自下至上依次为原料药、组合物1-3、组合物2-3和组合物2-4的X-RD图谱。从图2可以看出，单一载体材料制成的组合物1-3和混合载体材料制成的组合物2-3和组合物2-4的X-RD图谱中未见泊沙康唑的衍射峰，表明在本发明的药物组合物中，泊沙康唑是溶解在或以分子水平分散在载体材料中的。

2.2. 表观溶解度测定

表2-2 泊沙康唑-Kollidon®VA64/HPMCAS药物组合物在pH 6.8磷酸盐缓冲液中的表观溶解度

	原料药	组合物2-1	组合物2-2	组合物2-3	组合物2-4	组合物2-5	组合物2-6
表观溶解度(μg/ml)	<1	90.1	92.6	93.7	68.3	119.8	116.3
表观溶解度比(组合物/原料药)	1	>90	>92	>93	>68	>119	>116

由表2-2可知，使用热熔挤出法制备的本发明的各混合载体药物组合物对泊沙康唑都具有明显的增溶作用。当保持原料药和载体材料的重量比不变(例如1:3)时，将VA64/(VA64+HPMCAS)%从100% (组合物1-3)调整到50% (组合物2-4)使表观溶解度从44.3 μg/ml增加到68.3 μg/ml，将VA64/(VA64+HPMCAS)%从50%继续调整到37.5% (组合物2-3)使表观溶解度从68.3 μg/ml继续增加到93.7 μg/ml，但是进一步将

VA64/(VA64+HPMCAS)%降低至0% (组合物2-1)则使表观溶解度稍微降低至90.1 μg/ml，表明混合载体材料制成的药物组合物在一定范围内对泊沙康唑的溶解度有有利影响。由表2-2可知，组合物2-5对泊沙康唑的溶解度提高最明显。

另一方面，当保持载体材料中VA64/(VA64+HPMCAS)%不变(例如37.5%)时，将原料药和载体材料的重量比从1:2 (组合物2-5)调整到1:3 (组合物2-3)和1:4 (组合物2-6)使药物组合物的表观溶解度分别比原料药提高至少119、93和116倍，且均高于对比组合物(组合物2-1)的表观溶解度，表明混合载体材料中VA64/(VA64+HPMCAS)%为37.5%的几个组合物对泊沙康唑的增溶效果最为显著。

2.3. 模拟体内条件的溶出度测定

表2-3 泊沙康唑-Kollidon®VA64/HPMCAS药物组合物在pH 1.2→6.8的介质转换中的溶出度

	溶出度(%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
原料药	89.0	87.0	98.7	7.1	5.6	5.6
组合物2-1	2.0	4.2	5.6	95.2	92.9	92.0
组合物2-2	62.3	70.5	77.6	103.0	99.6	103.1
组合物2-3	72.6	79.7	85.2	93.0	95.4	94.2
组合物2-4	84.7	87.1	91.0	95.9	94.7	96.4
组合物2-5	63.4	65.4	71.4	83.1	83.0	84.1
组合物2-6	85.0	87.6	100.1	101.0	95.7	100.3

组合物2-3及原料药的溶出曲线如图3所示。由表2-3和图3可知，原料药在经过pH 1.2到6.8转换后溶出度大幅度降低，从98.7%减小到5.6%，表明泊沙康唑在体内经胃排空到达肠道时会从生理液中沉淀或结晶出来，从而降低其体内生物利用度。和原料药相比，本发明的药物组合物在pH 1.2到6.8转换后的3 h内的溶出度下降不明显，其中组合物2-2到组合物2-6在30 min之后各个时间点的溶出度均在83%以上，表明它们能够显著提高泊沙康唑在体内的吸收。在pH 1.2的条件下，混合载体材料制成的组合物2-2到组合物2-6的溶出度比单一载体材料制成的组合物2-1均有显著提高，表明组合物2-2到组合物2-6在胃中的吸收会好于组合物2-1；在pH 6.8的条件下，混合载

体材料制成的组合物2-2到组合物2-6的溶出度与单一载体材料制成的组合物2-1接近，表明组合物2-2到组合物2-6在肠道的吸收会与组合物2-1相当；因而混合载体材料制成的组合物2-2到组合物2-6在体内总的吸收要好于组合物2-1。

图4显示泊沙康唑-Kollidon® VA64和/或HPMCAS载体制成的药物组合物(泊沙康唑和载体材料重量比为1:3)中的VA64含量对泊沙康唑在pH 1.2和pH 6.8的溶出介质中的溶出度的影响，其中VA64/(VA64+HPMCAS)%为0%、25%、37.5%、50%和100%时所对应的溶出度分别为组合物2-1、组合物2-2、组合物2-3、组合物2-4和组合物1-3的溶出度。从图4可以看出，在pH 1.2的溶出条件下，当VA64/(VA64+HPMCAS)%在25.0%以上时，各药物组合物的溶出度均在75%以上，与VA64/(VA64+HPMCAS)%为0%的组合物2-1相比有着极为显著的提高；在pH 6.8的溶出条件下，当VA64/(VA64+HPMCAS)%提高到50.0%以上时，各药物组合物的溶出度均下降到50%以下。

以上结果表明，VA64/(VA64+HPMCAS)%分别为25.0%和37.5%的混合载体材料制成的组合物2-2和组合物2-3在两种pH溶出介质中的溶出度的综合表现明显优于不含VA64的组合物2-1和仅含VA64的组合物1-3。

实施例3 泊沙康唑-Soluplus®药物组合物

1. 制备：泊沙康唑-Soluplus®药物组合物的组成及各组分用量如表3-1所示。

表3-1 泊沙康唑-Soluplus®药物组合物的组成及各组分用量(重量%)

	功能	组合物3-1	组合物3-2	组合物3-3
泊沙康唑	活性成分	14.3	7.2	4.8
Soluplus®	载体材料	14.3	21.7	24.2
微晶纤维素	稀释剂	57.2	58.1	58.0
交联羧甲基纤维素钠	崩解剂	12.1	10.9	10.9
二氧化硅	润滑剂	1.4	1.4	1.4
硬脂酸镁	润滑剂	0.7	0.7	0.7

制备方法：按表3-1中所示的用量将泊沙康唑和载体材料直接或者在混合机中混合均匀后进料至同向双螺杆挤出机(印度Steer公司Omicron 12)的

加料斗内，将同向螺杆挤出机的温度控制在120℃-约180℃之间，进行挤出，螺杆转速为约50-约500 rpm。将所得挤出物冷却、粉碎、过筛，得到固体粉末。然后按表3-1中所示的用量将其他药用辅料与该固体粉末混合均匀，即得到泊沙康唑-Soluplus®药物组合物。

2. 物理化学性质评价

2.1. 表观溶解度测定

表3-2 泊沙康唑-Soluplus®药物组合物在pH 6.8磷酸盐缓冲液中的表观溶解度

	原料药	组合物3-1	组合物3-2	组合物3-3
表观溶解度 (μg/ml)	<1	40.9	87.7	159.0
表观溶解度比 (组合物/原料药)	1	>40	>87	>159

由表3-2可知，各泊沙康唑-Soluplus®药物组合物均能显著提高泊沙康唑的溶解度，而且随着载体材料的重量比增加，增溶效果越来越明显。当载体材料和原料药的重量比为5:1时(组合物3-3)，泊沙康唑的溶解度能提高至少159倍。

2.2. 模拟体内条件的溶出度测定

表3-3 泊沙康唑-Soluplus®药物组合物在pH 1.2→6.8的介质转换中的溶出度

	溶出度(%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
原料药	89.0	87.0	98.7	7.1	5.6	5.6
组合物3-1	55.6	68.1	88.7	71.3	65.2	54.0
组合物3-2	67.8	71.5	101.3	67.9	45.2	32.9
组合物3-3	58.8	92.2	102.3	52.4	28.9	25.6

由表3-3可知，与原料药相比，各泊沙康唑-Soluplus®药物组合物均能明显提高泊沙康唑的模拟体内条件的溶出度。

实施例4 泊沙康唑-Soluplus®/HPMCAS药物组合物(混合载体药物组合物)

1. 制备：泊沙康唑-Soluplus®/HPMCAS药物组合物的组合及个组分用

量如表4-1所示。

表4-1 泊沙康唑-Soluplus®/HPMCAS药物组合物的组成及各组分用量(重量%)

	功能	组合物4-1	组合物4-2	组合物4-3
泊沙康唑	活性成分	13.2	13.2	13.2
Soluplus®	载体材料	29.6	19.8	10.0
AQOAT® AS-M	载体材料	10.0	19.8	29.6
微晶纤维素	稀释剂	31.2	31.2	31.2
交联羧甲基纤维素钠	崩解剂	14.5	14.5	14.5
二氧化硅	润滑剂	1.1	1.1	1.1
硬脂酸镁	润滑剂	0.7	0.7	0.7

制备方法：按表4-1中所示的用量将泊沙康唑和混合载体材料(Soluplus®和HPMCAS(具体为AQOAT® AS-M))直接或者在混合机中混合均匀后进料至同向双螺杆挤出机(印度Steer公司Omicron 12)的加料斗内，将同向双螺杆挤出机的温度控制在120℃-约120℃-约180℃之间，进行挤出，螺杆转速为约50-约500 rpm。将所得挤出物冷却、粉碎、过筛，得到固体粉末。然后按表4-1中所示的用量将其他药用辅料和该固体粉末混合均匀，即得到泊沙康唑-Soluplus®/HPMCAS药物组合物。

2. 物理化学性质评价

2.1. 表观溶解度测定

表4-2 泊沙康唑-Soluplus®/HPMCAS药物组合物在pH 6.8磷酸盐缓冲液中的表观溶解度

	原料药	组合物4-1	组合物4-2	组合物4-3
表观溶解度(μg/ml)	<1	84.0	22.4	20.4
表观溶解度比(组合物/原料药)	1	>84	>22	>20

由表4-2可知，各泊沙康唑-Soluplus®/HPMCAS药物组合物均能显著提高泊沙康唑的溶解度，其中组合物4-1所致的提高最为明显。

2.2. 模拟体内条件的溶出度测定

表4-3 泊沙康唑-Soluplus®/HPMCAS药物组合物在pH 1.2→6.8的介质转换中的溶出度

	溶出度(%)

	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
原料药	89.0	87.0	98.7	7.1	5.6	5.6
组合物4-1	87.6	93.8	84.9	74.3	55.6	52.8
组合物4-2	36.2	45.8	62.8	51.5	42.9	49.8
组合物4-3	10.2	12.5	25.8	33.6	20.9	25.4

由表4-3可知，与原料药相比，各泊沙康唑-Soluplus®/HPMCAS药物组合物均能明显提高泊沙康唑的模拟体内条件的溶出度。

实施例5 泊沙康唑-Kollidon® VA64/HPMCAS药物组合物(混合载体药物组合物)的制备方法评价

1. 热熔挤出工艺

表5-1 热熔挤出工艺参数

组合物	投料器转速 (RPM)	螺杆转速 (RPM)	物料熔融温度 (℃)	每千克能耗 (kW·h)	扭矩百分比
1-3	30	160	125	12	51%
2-1	60	200	137	6	59%
2-2	30	200	136	7	34%
2-3	25	160	136	4	12%
2-4	25	150	136	4	12%

具体的工艺见实施例1-4中各药物组合物的制备。如表5-1所示，与单一载体材料制成的组合物1-3和2-1相比，混合载体材料制成的组合物的每千克能耗更低，所产生的扭矩百分比也更低，表明使用混合载体材料制备药物组合物能显著降低热熔挤出工艺的能耗和仪器扭矩，大幅度提升其可操作性。

2. 粉碎工艺

表5-2 挤出物粉碎工艺参数

组合物	挤出物重量 (g)	粉碎时间 (s)	过60目筛颗粒重量 (g)	过筛效率* w/w(%)
1-3	20.0	30	16.5	82.5
2-1	20.3	30	1.6	7.9
2-2	20.5	30	6.8	33.2
2-3	22.8	30	11.6	50.9

2-4	20.0	30	10.7	53.5

注：*指过筛后颗粒占过筛前总颗粒的重量百分比。

将各药物组合物的制备中所得的挤出物用剪刀切割成约 2 cm 的条状物，用小型咖啡研磨机(意大利德龙 KG40 型)粉碎 30 s。将粉碎后的颗粒过 60 目筛，称量过晒后所得粉末重量，计算过筛效率。如表 5-2 所示，与单一载体材料 HPMCAS 制成的组合物 2-1 的过筛效率(7.9%)相比，包含 VA64 的混合载体材料或 VA64 单一载体材料制成的药物组合物的过筛效率更高，表明其粉碎工艺的可操作性更强。

3. 压片工艺

表5-3 片剂处方组成(重量%)及压片工艺参数

	组合物1-3	组合物2-1	组合物2-2	组合物2-3	组合物2-4
固体粉末*	55.0	55.0	55.0	55.0	55.0
微晶纤维素	29.6	29.6	29.6	29.6	29.6
交联羧甲基纤维素钠	13.8	13.8	13.8	13.8	13.8
二氧化硅	1.0	1.0	1.0	1.0	1.0
硬脂酸镁	0.6	0.6	0.6	0.6	0.6
压片压力 (cm)	13.8	13.8	13.8	13.8	13.8
物料填充量 (mg)	800	800	800	800	800
片剂硬度 (kg)	38.5	1.9	8.7	15.5	21.0
崩解时间 (min)	21.9	0.3	0.6	2.0	3.3

注：*指实施例 1-4 中在组合物的制备中与药物辅料混合前的固体粉末。

按表 5-3 中所示的用量将过 60 目筛的固体粉末和其他辅料混合均匀，用单冲压片机(上海天凡药机制造厂 DP-5 型)在相同的压力和物料填充量下压片以考察不同处方的可压性(硬度测定仪：天大天发科技有限公司 YD-35 型)和崩解性能(崩解仪：天大天发科技有限公司 ZB-1 型)，结果如表 5-3 所示。由表 5-3 可见，随着载体材料中 VA64 含量的降低，片剂硬度降低，崩解时间缩短。

实施例6 泊沙康唑-Kollidon® VA64/HPMCAS药物组合物(混合载体药物组合物)的体内药代动力学研究

研究采用空腹条件下的开放、随机、二周期、双交叉自身对照的药代动力学对比试验在人体中进行。

1. 方法

受试者为9名年龄20-45周岁的健康男性，体重指数(BMI)为19-25。全部受试者均充分理解试验内容并已自愿签署知情同意书。

受试者在第一天18:00入住临床试验病房并在20:00开始禁食。第二天07:00采集血样(给药前的空白血样)，08:00在医生指导下空腹下用240 mL水送服含100 mg泊沙康唑的组合物2-1或组合物2-2 (具体组成见实施例2)。在给药后1、2、3、4、5、6、8、12、24、48、72小时采集血样(共12次，每次3 mL)。采集的血样立即移至肝素抗凝管中，摇匀，4000 rpm离心5 min取血浆，一式两份，-20℃保存供血药浓度测定用。在第九天，采用与第二天相同的方法进行交叉给药，并随后进行相同的血样采集过程。在整个试验期间观察受试者生命体征及不良事件以保证其安全。

采用LC-MS/MS方法测定各血浆样品中的泊沙康唑浓度(血药浓度)，经药代动力学统计软件DAS 3.2.5计算，完成生物统计分析，得到组合物2-1和组合物2-2的药代动力学参数，计算各参数的算数平均值比(组合物2-2/组合物2-1)并考察组合物2-2的AUC和C_{max}的90%置信区间分布。将组合物2-2和组合物2-1的C_{max}、AUC_{0-72h}、$AUC_{0-\infty}$ 经对数转换后进行方差分析，并进行双向单侧t检验。

2. 结果

试验结果如表6-1和图5所示。结果表明：泊沙康唑的C_{max}、AUC_{0-72h}、$AUC_{0-\infty}$在组合物2-1和组合物2-2之间均有显著性差异，以样本量(n=9)计算得出组合物2-2的C_{max}的90%置信区间为(106%~ 147%)，AUC_{0-72h}的90%置信区间为(115.8%~147.1%)，$AUC_{0-\infty}$的90%置信区间为(117.9%~ 146.7%)。

表 6-1 泊沙康唑药代动力学参数

药代动力学参数(算数平均值，n=9)	组合物 2-1	组合物 2-2
C_{max} ($ng\cdot ml^{-1}$)	432.8	533.2
AUC_{0-72h} ($ng\cdot h\cdot ml^{-1}$)	11793	15214
$AUC_{0-\infty}$ ($ng\cdot h\cdot ml^{-1}$)	13251	17276

从图 5 和表 6-1 可知，与使用单一载体材料 HPMCAS 的组合物(组合

物 2-1)相比，使用 Kollidon® VA64/HPMCAS 混合载体材料的组合物(组合物 2-2)中的泊沙康唑在体内的吸收速度更快，血药浓度更高，相应地生物利用度也更高。C_{max}的算数平均值比(组合物2-2/组合物2-1)为1.23；AUC_{0-72h}的算数平均值比(组合物 2-2/组合物 2-1)为 1.29；$AUC_{0-\infty}$的算数平均值比(组合物 2-2/组合物 2-1)为 1.30。这些数据表明：在保证 pH 6.8 溶出水平与对比组合物 2-1 一致的前提下，提高泊沙康唑在酸性条件下的溶出度或溶解度会增加药物在体内胃中的吸收，从而提高药物在体内的吸收速率和利用，使得组合物 2-2 的体内生物利用度整体上得到提高。

权 利 要 求 书

1、药物组合物，其包含泊沙康唑和载体材料，其中所述载体材料包含：乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物。

2、权利要求 1 的药物组合物，其中所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物中的乙烯基吡咯烷酮单元与醋酸乙烯酯单元的重量比为 1:9-9:1，优选为 4:6-6:4。

3、权利要求1或2的药物组合物，其中所述含乙二醇单元的聚合物为聚乙二醇/乙烯基己内酰胺/醋酸乙烯酯共聚物。

4、权利要求 1-3 中任一项的药物组合物，其中所述载体材料还包含肠溶聚合物，所述肠溶聚合物为选自乙酸邻苯二甲酸纤维素、乙酸偏苯三酸纤维素、乙酸琥珀酸纤维素、邻苯二甲酸甲基纤维素、邻苯二甲酸乙基羟甲基纤维素、邻苯二甲酸羟丙基甲基纤维素、羟丙基甲基纤维素醋酸琥珀酸酯、乙酸马来酸羟丙基甲基纤维素、偏苯三酸羟丙基甲基纤维素、羧甲基乙基纤维素、聚丁酸乙烯邻苯二甲酸酯、聚乙酸乙烯醇邻苯二甲酸酯、甲基丙烯酸/丙烯酸乙酯共聚物及甲基丙烯酸/甲基丙烯酸甲酯共聚物中的一种或多种。

5、权利要求 4 的药物组合物，其中所述肠溶聚合物为羟丙基甲基纤维素醋酸琥珀酸酯。

6、权利要求 1-5 中任一项的药物组合物，其中泊沙康唑与所述载体材料的重量比为 1:1-1:5，优选为 1:3。

7、权利要求 4 或 5 的药物组合物，其中所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物以相对于所述乙烯基吡咯烷酮-醋酸乙烯酯共聚物或含乙二醇单元的聚合物和所述肠溶聚合物的总重量的 10 重量%-100 重量%的量存在，优选 25 重量%-100 重量%，更优选 25 重量%-50 重

量%，甚至更优选 20 重量%-40 重量%，并且最优选 25 重量%-37.5 重量%。

8、权利要求 1-7 中任一项的药物组合物，其还包含作为增溶剂的聚乙二醇 1000 维生素 E 琥珀酸酯。

9、权利要求 8 的药物组合物，其中所述聚乙二醇 1000 维生素 E 琥珀酸酯以相对于泊沙康唑、所述载体材料和聚乙二醇 1000 维生素 E 琥珀酸酯的总重量的 1-12 重量%的量存在。

10、权利要求 8 或 9 的药物组合物，其还包含药学上可接受的药用辅料，所述药用辅料为选自表面活性剂、pH 调节剂、稀释剂、崩解剂、粘合剂、润滑剂中的一种或多种。

11、权利要求 1-10 中任一项的药物组合物，其中泊沙康唑溶解在或以分子水平分散在所述载体材料中。

12、预防和/或治疗哺乳动物真菌感染和相关疾病的方法，其包括给予所述哺乳动物有效量的权利要求 1-11 中任一项的药物组合物。

13、制备权利要求 1-11 中任一项的药物组合物的方法，其包括：

将热熔挤出机预热至 120℃-180℃；

向所述热熔挤出机中进料已混匀的计量比的泊沙康唑、载体材料及任选存在的药学上可接受的药用辅料的混合物，或者向所述热熔挤出机中直接进料计量比的泊沙康唑、载体材料及任选存在的药学上可接受的药用辅料；

挤出；和

将所得挤出物冷却、粉碎并过筛，任选地与药学上可接受的药用辅料混合，由此得到所述药物组合物。

14、包含权利要求 1-11 中任一项的药物组合物的药物制剂，其是散剂、颗粒剂、丸剂、胶囊剂或片剂的形式。

说 明 书 附 图

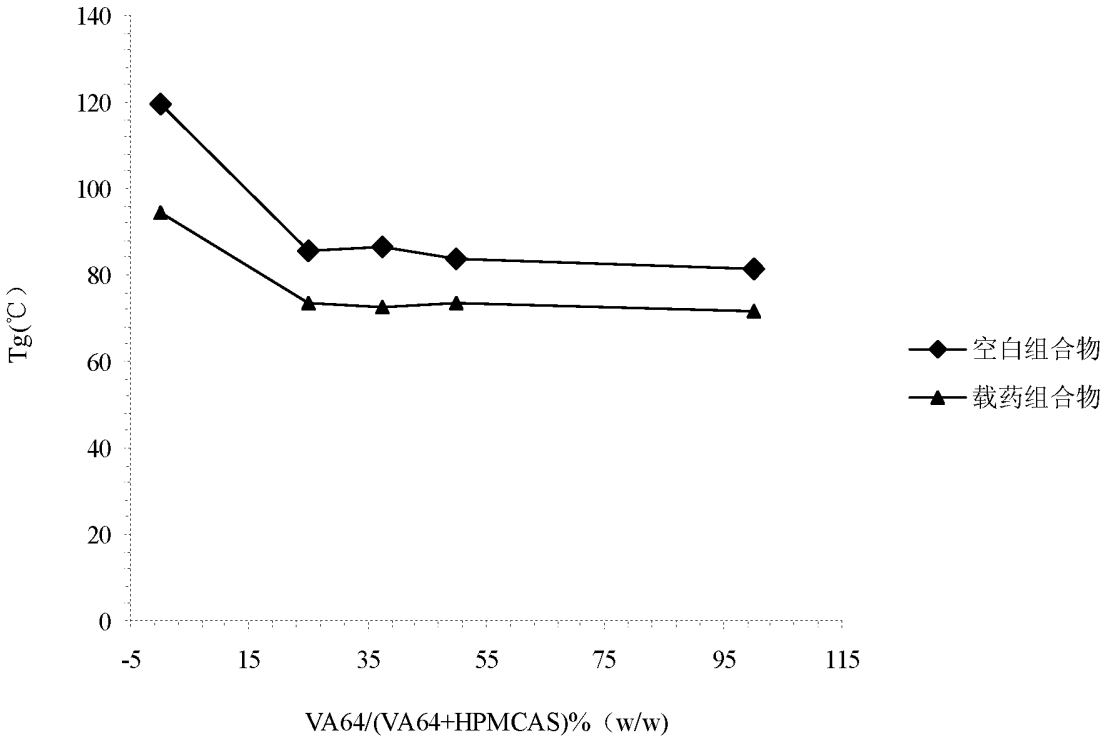
140
120
100
80
60
40
20
0
Tg(℃)
-5
15
35
55
75
95
115
VA64/(VA64+HPMCAS)%（w/w)
空白组合物
载药组合物

图 1

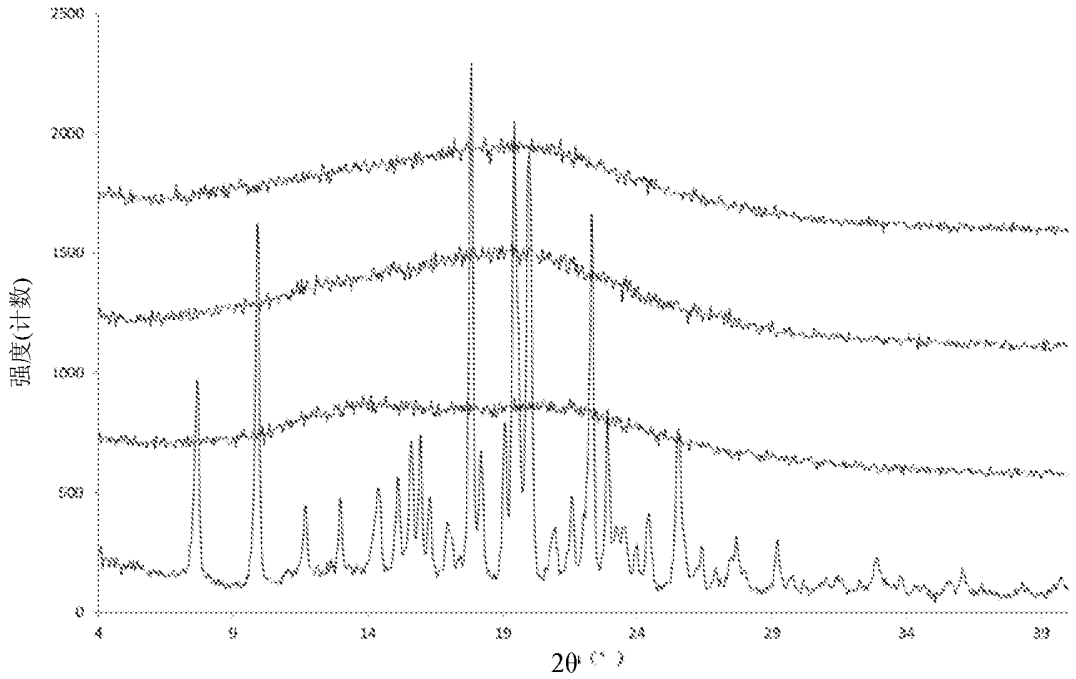
2500
2000
1500
1000
500
0
强度(计数)
4
9
14
19
24
29
34
39
2θ(°)

图 2

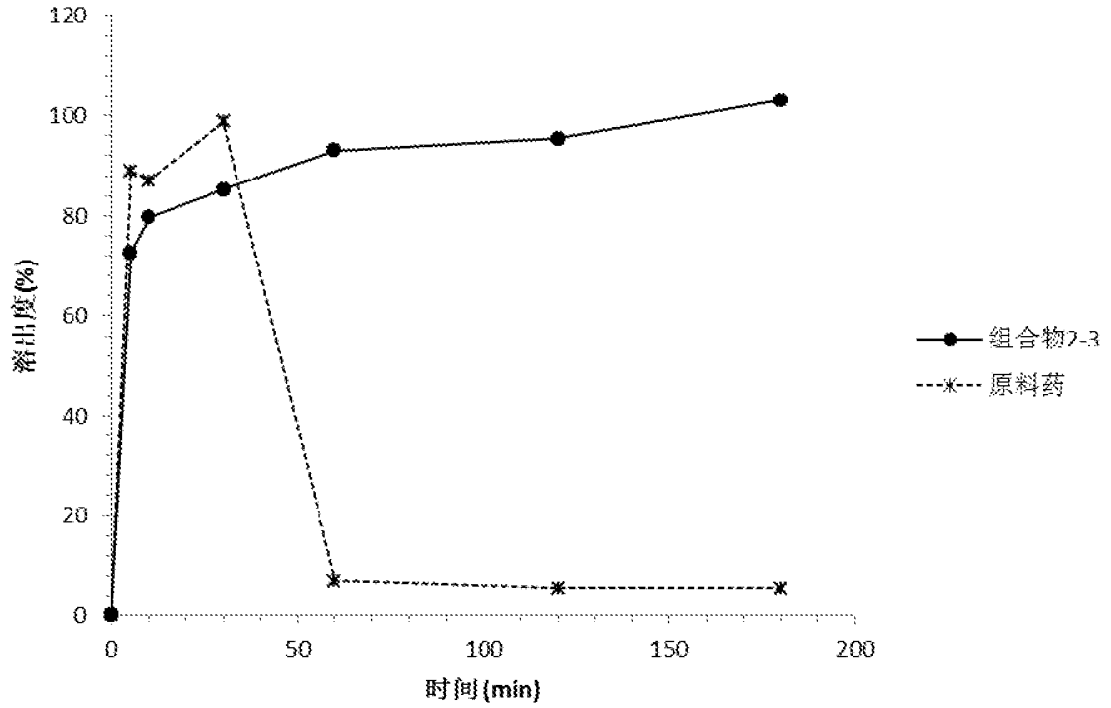
120
100
80
60
40
20
0
溶出度(%)
0
50
100
150
200
时间(min)
组合物2-3
原料药

图 3

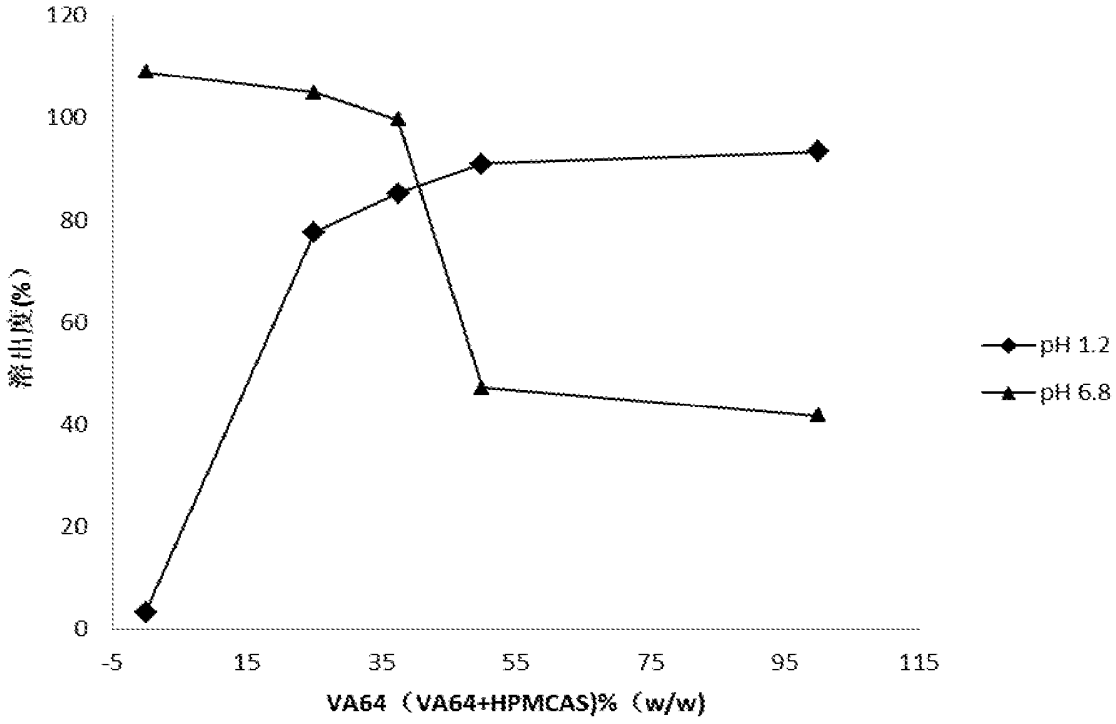
120
100
80
60
40
20
0
溶出度(%)
-5
15
35
55
75
95
115
VA64（VA64+HPMCAS)%（w/w)
pH 1.2
pH 6.8

图 4

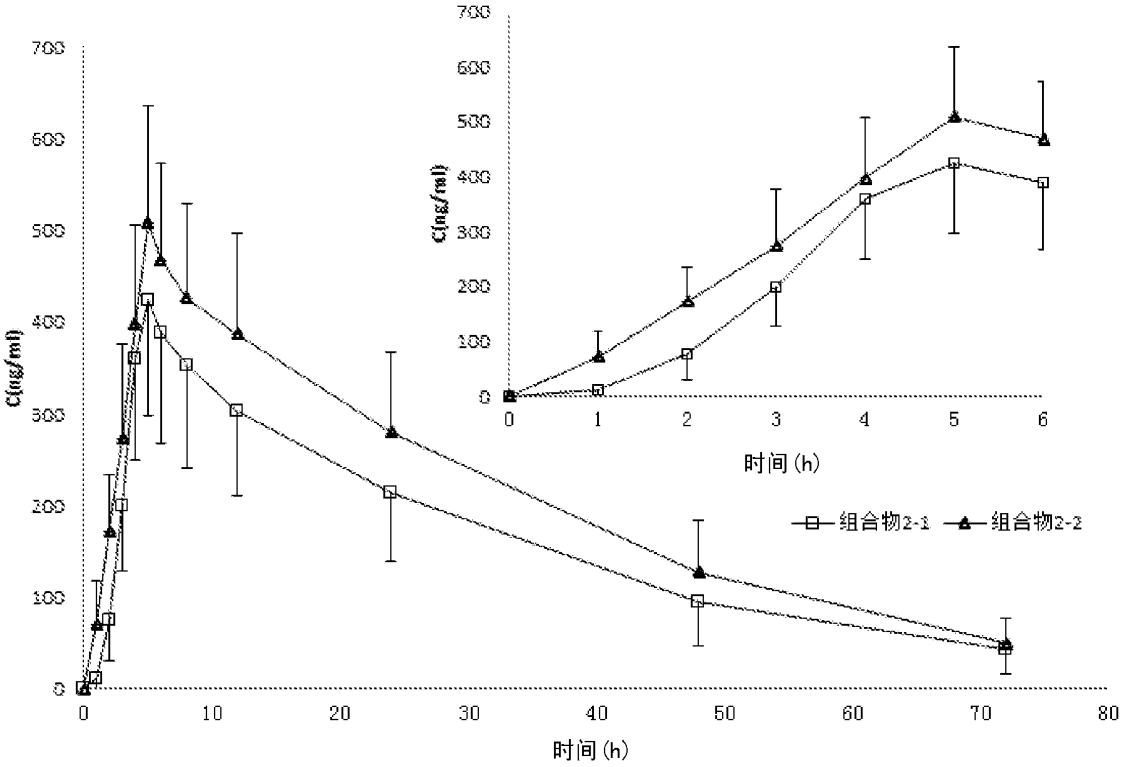

图5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/076299

A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/32 (2006.01) i; A61K 47/34 (2006.01) i; A61K 31/496 (2006.01) i; A61P 31/10 (2006.01) i
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)

A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNKI, DWPI, SIPOABS, CA, MEDLINE, EMBASE: posaconazole, PVP/VA, PVP-VA, Kollidon VA64, N-VinylPyrrolidone/Vinyl Acetate Copolymers, Poly(N-VinylPyrrolidone)/Vinyl Acetate, PCA-PVA-PEG, soluplus, Ethylene oxide-vinyl acetate-N-vinylcaprolactam graft copolymer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101495096 A (ELAN PHARMA INT LTD) 29 July 2009 (29.07.2009) , see claims 1, 6 and 11	1, 4-11, 13, 14
A	CN 101495096 A (ELAN PHARMA INT LTD) 29 July 2009 (29.07.2009) , see claims 1, and 11	2, 3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 July 2015	15 July 2015
Name and mailing address of the ISA State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No. (86-10) 62019451	Authorized officer LIU, Qiming Telephone No. (86-10) 62412173

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/076299

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:12
because they relate to subject matter not required to be searched by this Authority, namely:
the subject-matter of claim 12 is directed to a therapeutical method of disease.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/076299

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 101495096 A	29 July 2009	MX 2008015275 A	06 February 2009
		US 2007281011 A1	06 December 2007
		CA 2653504 A1	13 December 2007
		EP 2040675 A1	01 April 2009
		BR PI0712130 A2	17 January 2012
		AR 063940 A1	04 March 2009
		EP 2343053 A1	13 July 2011
		WO 2007143390 A1	13 December 2007
		TW 200811145 A	01 March 2008
		ZA 200809971 A	26 August 2009
		KR 20090015994 A	12 February 2009
		NZ 573555 A	28 September 2012
		AU 2007256983 A1	13 December 2007
		IL 195524 D0	01 September 2009
		SG 170047 A1	29 April 2011
		JP 2009538927 A	12 November 2009

国际检索报告

国际申请号 PCT/CN2015/076299

A. 主题的分类

A61K 47/32(2006.01)i; A61K 47/34(2006.01)i; A61K 31/496(2006.01)i; A61P 31/10(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

A61K; A61P

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称，和使用的检索词（如使用）)

CNABS, CNKI, DWPI, SIPOABS, CA, MEDLINE, EMBASE: 泊沙康唑，乙烯基吡咯烷酮-醋酸乙烯酯共聚物，聚乙烯基吡咯烷酮/醋酸乙烯酯共聚物，聚(醋酸乙烯聚合物-共-乙烯吡咯烷酮)，共聚（醋酸乙烯酯乙烯基吡咯烷酮），乙二醇，聚合物，聚乙二醇/乙烯基己内酰胺/醋酸乙烯酯共聚物，posaconazole, PVP/VA, PVP-VA, Kollidon VA64, N-VinylPyrrolidone/Vinyl Acetate Copolymers, Poly(N-VinylPyrrolidone)/Vinyl Acetate, PCA-PVA-PEG, soluplus, Ethylene oxide-vinyl acetate-N-vinylcaprolactam graft copolymer

C. 相关文件

类 型*	引用文件，必要时，指明相关段落	相关的权利要求
X	CN 101495096 A (伊兰制药国际有限公司) 2009年 7月 29日 (2009-07-29) 参见权利要求1、6和11	1、4-11、13、14
A	CN 101495096 A (伊兰制药国际有限公司) 2009年 7月 29日 (2009-07-29) 参见权利要求1-11	2、3

☐ 其余文件在C栏的续页中列出。

☑ 见同族专利附件。

* 引用文件的具体类型：

"A" 认为不特别相关的表示了现有技术一般状态的文件

"E" 在国际申请日的当天或之后公布的在先申请或专利

"L" 可能对优先权要求构成怀疑的文件，或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件（如具体说明的）

"O" 涉及口头公开、使用、展览或其他方式公开的文件

"P" 公布日先于国际申请日但迟于所要求的优先权日的文件

"T" 在申请日或优先权日之后公布，与申请不相抵触，但为了理解发明之理论或原理的在后文件

"X" 特别相关的文件，单独考虑该文件，认定要求保护的发明不是新颖的或不具有创造性

"Y" 特别相关的文件，当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时，要求保护的发明不具有创造性

"&" 同族专利的文件

国际检索实际完成的日期	国际检索报告邮寄日期
2015年 7月 8日	2015年 7月 15日

ISA/CN的名称和邮寄地址	受权官员
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国际检索报告

国际申请号
PCT/CN2015/076299

第II栏　　某些权利要求被认为是不能检索的意见(续第1页第2项)

根据条约第17条(2)(a)，对某些权利要求未做国际检索报告的理由如下:

1. ☑ 权利要求： 12
因为它们涉及不要求本单位进行检索的主题，即：

[1] 权利要求12涉及疾病的治疗方法。

2. ☐ 权利要求：
因为它们涉及国际申请中不符合规定的要求的部分，以致不能进行任何有意义的国际检索， 具体地说：

3. ☐ 权利要求：
因为它们是从属权利要求，并且没有按照细则6.4(a)第2句和第3句的要求撰写。

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2015/076299

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(54) POSACONAZOLE PHARMACEUTICAL COMPOSITION AND PREPARATION METHOD, APPLICATION AND PHARMACEUTICAL PREPARATION THEREOF

(57) The present invention relates to a pharmaceutical composition comprising posaconazole and a carrier material, wherein the carrier material comprises a vinylpyrrolidone-vinyl acetate copolymer or a polymer containing ethylene glycol units. The present invention also relates to a method for the preparation of the pharmaceutical composition, a method for the prevention and/or treatment of fungal infections and related diseases in a mammal using the pharmaceutical composition, and a pharmaceutical formulation comprising the pharmaceutical composition.

EP 3 130 354 A1

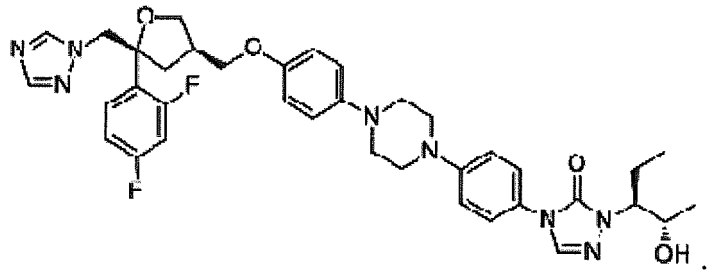
Description

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical compositions and preparation methods, uses and pharmaceutical formulations thereof. In particular, the present invention relates to pharmaceutical compositions comprising posaconazole as an active ingredient, methods for the preparation of the pharmaceutical compositions, methods for the prevention and/or treatment of fungal infections and related diseases in mammals using the pharmaceutical compositions, and pharmaceutical formulations comprising the pharmaceutical compositions.

BACKGROUND OF THE INVENTION

[0002] Posaconazole is a derivative of itraconazole, and belongs to the second-generation triazole antifungal agents. It has the chemical name of 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)-5-(1,2,4-triazole-1-ylmethyl)oxolan-3-yl]methoxy]phenyl]piperazin-1-yl] phenyl]-2-[(2S,3S)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one, and has the structural formula



[0003] US 5,703,079 and US 5,661,151, the disclosures of which in their entireties are hereby incorporated by reference into this application, disclose posaconazole and its synthetic method, respectively.

[0004] Posaconazole overcomes the problems of the first-generation triazole antifungal agents, i.e. narrow antibacterial spectrum, low bioavailability, drug resistance, etc., and has the characteristic of broad antibacterial spectrum. Posaconazole can prevent invasive aspergillosis more effectively by comparison with fluconazole and itraconazole, and can reduce the mortality rate in relation to invasive fungal infections.

[0005] A suspension containing posaconazole (40 mg/ml) in a crystalline form, Noxafil®, has been approved for the treatment of invasive fungal infections such as oropharyngeal candidiasis, including infections resistant to treatments with other azole antifungal agents, and for the prophylactic treatment of fungal infections in patients greatly susceptible to such infections due to severe immunodeficiency, such as hematopoietic stem cell transplantation (HSCT) receptors suffering from graft versus-host diseases (GVHD), or patients suffering from hematological malignances and having permanent leucopenia resulting from chemotherapy.

[0006] However, provision of pharmaceutical compositions comprising posaconazole suitable for the preparation of oral solid dosage forms has heretofore been hampered by the weak basicity and low solubility of posaconazole in free base form. Posaconazole has pKa values of 3.6 (piperazine) and 4.6 (triazole), and is slightly soluble at low pH. For example, in the environment of the stomach (pH = ~ 1.2), posaconazole in free base form has a solubility of about 0.8 mg/ml. However, when pH is higher than 4, posaconazole is practically insoluble (solubility < ~ 1 μg/ml). Therefore, when posaconazole dissolved in gastric fluid reaches the environment of the intestinal tract (typically, pH is or is higher than about 6.4) upon gastric emptying, the dissolved posaconazole crystallizes out, and thus the absorption of posaconazole is reduced and the bioavailability thereof is influenced.

[0007] US2011123627A discloses a posaconazole pharmaceutical composition comprising an enteric carrier material, the polymer hydroxypropylmethyl cellulose acetate succinate (HPMCAS), such that posaconazole is essentially insoluble when passing through stomach, but can be easily released upon entry into small intestine. This pharmaceutical composition improves the maximum plasma drug concentration and bioavailability of posaconazole *in vivo* by comparison with commercially available posaconazole oral suspensions. This pharmaceutical composition, however, limits the release of posaconazole in stomach, resulting in a delayed peak time (T_{max}) of plasma drug concentration *in vivo.* In addition, a posaconazole pharmaceutical composition prepared by hot melt extrusion using HPMCAS as a carrier material has high hardness, leading to difficulties in grinding. Also, the pharmaceutical composition has poor compressibility, bringing difficulties in subsequent processing such as tableting.

SUMMARY OF THE INVENTION

[0008] The object of the invention is to provide posaconazole pharmaceutical compositions that overcome the above-mentioned defects in the prior art.

[0009] In a first aspect of the present invention, there is provided a pharmaceutical composition comprising posaconazole and a carrier material, wherein the carrier material comprises a vinylpyrrolidone-vinyl acetate copolymer or a polymer containing ethylene glycol units. The pharmaceutical composition can be used for the prevention and/or treatment of fungal infections and related diseases in a mammal.

[0010] In a second aspect of the present invention, there is provided use of a pharmaceutical composition according to the first aspect of the invention in the manufacture of a medicament for the prevention and/or treatment of fungal infections and related diseases in a mammal.

[0011] In a third aspect of the present invention, there is provided a method for the prevention and/or treatment of fungal infections and related diseases in a mammal, comprising administering an effective amount of a pharmaceutical composition according to the first aspect of the invention to the mammal.

[0012] In a fourth aspect of the present invention, there is provided a method for the preparation of a pharmaceutical composition according to the first aspect of the invention, comprising: preheating a hot melt extruder to 120°C-180°C; feeding a homogeneously-mixed stoichiometric mixture of posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients into the hot melt extruder, or stoichiometrically feeding posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients into the hot melt extruder directly; extruding; and

cooling, pulverizing and sieving the extrudate, optionally mixing it with one or more pharmaceutically acceptable excipients, thereby obtaining the pharmaceutical composition.

[0013] In a fifth aspect of the present invention, there is provided a pharmaceutical formulation in the form of a powder, a granule, a pill, a capsule or a tablet, comprising the pharmaceutical composition according to the first aspect of the invention.

DESCRIPTION OF DRAWINGS

[0014] The object and characteristics of the present invention will become more apparent with reference to the drawings, in which

Figure 1 shows the effect of VA64 content on Tg value in a pharmaceutical composition prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s), wherein Tg values corresponding to VA64/(VA64+HPMCAS)% of 0%, 25%, 37.5%, 50% and 100% are those of Composition 2-1, Composition 2-2, Composition 2-3, Composition 2-4, and Composition 1-3 or the corresponding blank compositions, respectively.

Figure 2 shows X-RD spectrums of pharmaceutical compositions prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s), which are, from bottom to top, the X-RD spectrums of API, Composition 1-3, Composition 2-3, and Composition 2-4, respectively.

Figure 3 shows dissolution profiles of a pharmaceutical composition (Composition 2-3) prepared with posaconazole - Kollidon® VA64/HPMCAS mixed carriers, and of API, under a simulated *in vivo* fasted condition with a pH conversion of from 1.2 to 6.8 at the time of 30 min.

Figure 4 shows the effect of VA64 content in a pharmaceutical composition (wherein the weight ratio of posaconazole to the carrier material is 1:3) prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s) on the dissolution of posaconazole in dissolution mediums of pH 1.2 and pH 6.8, wherein the dissolution values corresponding to VA64/(VA64+HPMCAS)% of 0%, 25%, 37.5%, 50% and 100% are those of Composition 2-1, Composition 2-2, Composition 2-3, Composition 2-4 and Composition 1-3, respectively.

Figure 5 shows the average plasma drug concentration - time curves of posaconazole obtained after administering pharmaceutical compositions prepared with posaconazole - Kollidon® VA64 and/or an HPMCAS carrier(s) (Composition 2-1 and Composition 2-2) to fasted human subjects, wherein VA64/(VA64+HPMCAS)% in Composition 2-1 and Composition 2-2 is 0% and 25%, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Unless defined otherwise, all the technical and scientific terms used herein have the same meanings as com-

monly known by a person skilled in the art. In case of confliction, the definitions provided herein will prevail.

[0016] When a certain value, concentration, or the like, or a parameter is expressed in the form of a range, a preferred range, or a preferred upper limit and a preferred lower limit, it shall be appreciated that it equals to disclosure of any range obtained by combining any of the upper limits or preferred values with any of the lower limits or preferred values, regardless whether the range is specifically disclosed or not. Unless indicated otherwise, it is intended that a numerical range recited herein encompasses the end points, as well as all the integers and fractions within the range.

[0017] The terms "about" and "approximate", when used along with a numerical variable, generally means the value of the variable and all the values of the variable within an experimental error (e.g. 95% confidence interval for the mean) or within a specified value ± 10% or within a broader range.

[0018] The term "stoichiometric" means that substances are used in a certain weight ratio. For example, in the present invention, the API (posaconazole), the carrier material and the optional pharmaceutically acceptable excipient(s) are used in a certain weight ratio.

[0019] The term "pharmaceutically acceptable" substances means those, which, according to a common medical judgment, are suitable to be in contact with a tissue of a patient without any inappropriate toxicity, irritation, allergic response, etc., have a reasonable balance between advantages and disadvantages, and can be applied to its target use effectively.

[0020] The term "pharmaceutical composition" means substances composed of one or more active ingredients, carriers and optionally one or more pharmaceutically acceptable excipients. In the present invention, it can be simply referred to as "composition". For example, Pharmaceutical Composition 1-1 can be simply referred to as Composition 1-1.

[0021] The term "blank composition" is relative to a pharmaceutical composition, and means that it comprises no active ingredient (i.e. posaconazole) and only comprises a carrier material and optionally one or more other pharmaceutically acceptable excipients.

[0022] The terms "pharmaceutical product", "pharmaceutical dosage form", "dosage form", "pharmaceutical formulation", etc., refer to a pharmaceutical composition administered to a patient in need of treatment, which is typically in the form of a powder, a granule, a pill, a capsule, a tablet, a solution, a suspension, or a patch, etc.

[0023] The term "dissolved in or dispersed at a molecular level in a (the) carrier material" means that a drug is dispersed in a (the) carrier material to form a single-phase pharmaceutical composition. In the present invention, this term means that posaconazole is dispersed in the carrier material to form a single-phase pharmaceutical composition (also referred to as a solid solution, a suspension, or a solid suspension). The Tg value of the resulting posaconazole pharmaceutical composition is different from those of the carrier material and the API posaconazole. The terms "dissolved in", "dispersed at a molecular level", "dispersion", "solid solution" and "solid dispersion" are used herein as appropriate to describe a pharmaceutical composition according to the invention in various stages during preparation and at various temperatures.

[0024] The term "bioavailability" indicates the extent to which a drug or another substance is utilized by a target tissue after administration.

[0025] The term "peak time of plasma drug concentration (T_{max})" means the time when peak plasma drug concentration (C_{max}) is attained after drug administration.

[0026] The term "peak plasma drug concentration (C_{max})" means the maximum plasma drug concentration attained after drug administration.

[0027] The term "$AUC_{0-\infty}$" means the area under a plasma drug concentration - time curve from the time point of 0 to infinity after drug administration, and the term "AUC_{0-t}" means the area under a plasma drug concentration - time curve from the time point of 0 to t after drug administration.

[0028] Unless specified otherwise, all the percentages, portions and ratios in the present invention are on weight basis.

[0029] The present invention provides a posaconazole pharmaceutical composition. The pharmaceutical composition according to the invention improves the absorption behavior of posaconazole in human body, and increases the absorption and bioavailability of the drug by comparison with the prior art. Further, the pharmaceutical composition according to the invention is prepared by a hot melt extrusion process, which is simple and easy to operate, and improves technique, decreases energy consumption, and increases productivity by comparison with the prior art.

[0030] Specifically, the inventors have found that a pharmaceutical composition wherein posaconazole is dissolved or dispersed at a molecular level in a carrier material can be prepared by processing a vinylpyrrolidone-vinyl acetate copolymer of a certain ratio, as a carrier material, and posaconazole with a hot melt extrusion process according to the invention. The inventors have found surprisingly that a pharmaceutical composition wherein posaconazole is dispersed in a vinylpyrrolidone-vinyl acetate copolymer can increase the solubility of posaconazole in gastrointestinal tract, and can ameliorate the problem of precipitation or crystallization due to the significant decrease of solubility resulting from the pH change upon entry of posaconazole dissolved in stomach into intestinal tract through gastric emptying, thereby increasing the absorption of posaconazole *in vivo* and the bioavailability thereof. In another aspect, the pharmaceutical composition can also alter the absorption behavior of posaconazole *in vivo*, increasing C_{max} and AUC without prolonging T_{max}. Meanwhile, the pharmaceutical composition also has better properties in terms of production process, such as good grindability and compressibility.

[0031] In addition, the inventors have also found surprisingly that by using a vinylpyrrolidone-vinyl acetate copolymer of a certain ratio and an enteric polymer such as HPMCAS in combination as a mixed carrier material, not only the solubility of posaconazole in gastrointestinal tract is further increased, but also the problem of precipitation or crystallization due to the significant decrease of solubility resulting from the pH change upon entry of posaconazole dissolved in stomach into intestinal tract through gastric emptying is ameliorated, thereby further increasing the absorption of posaconazole and the bioavailability thereof.

[0032] Also, the inventors have found surprisingly that by adding D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) into the pharmaceutical composition, not only the solubility of posaconazole in gastrointestinal tract is further increased, but also the problem of precipitation or crystallization due to the significant decrease of solubility resulting from the pH change upon entry of posaconazole dissolved in stomach into intestinal tract through gastric emptying is ameliorated, thereby further increasing the absorption of posaconazole and the bioavailability thereof. In addition, when preparing the pharmaceutical composition using the hot melt extrusion process according to the invention, the addition of TPGS lowers the glass transition temperature (Tg) of the pharmaceutical composition, significantly decreasing the torque of the extruder, reducing energy consumption, and increasing productivity.

[0033] In particular, the present invention provides a pharmaceutical composition comprising posaconazole and a carrier material, wherein the carrier material comprises a vinylpyrrolidone-vinyl acetate copolymer or a polymer containing ethylene glycol units.

[0034] In an embodiment of the invention, posaconazole is dissolved in or dispersed at a molecular level in the carrier material.

[0035] The vinylpyrrolidone-vinyl acetate copolymer can be prepared by, e.g., free-radical polymerization of N-vinylpyrrolidone and vinyl acetate in 2-propanol. The vinylpyrrolidone-vinyl acetate copolymer can also be a copolymer of vinylpyrrolidone and vinyl acetate in a weight ratio of 15:85 to 40:60 disclosed in e.g. US 5,426,163A.

[0036] The weight ratio of vinylpyrrolidone units to vinyl acetate units in the vinylpyrrolidone-vinyl acetate copolymer useful as a carrier material in the present invention is in the range of about 1:9 to about 9:1, preferably about 4:6 to about 6:4. The K value of the copolymer is in the range of about 25 to about 70. K value, also referred to as Fikentscher K value, is a measure of molecular weight of a polymer comprising vinylpyrrolidone units or of mixtures of such polymers commonly known in the art, and can be determined using a 1 wt.% aqueous solution according to the method described in H. Fikentscher, Cellulose-Chemie, 1932, 13:58-64/71-74. In an embodiment, the vinylpyrrolidone-vinyl acetate copolymer used in the present invention can also be, but is not limited to, e.g., Kollidon® VA64 commercially available from BASF, and/or Plasdone® S630 commercially available from International Specialty Products (both are copolymers of vinylpyrrolidone and vinyl acetate in a weight ratio of 6:4). In a preferred embodiment of the invention, the carrier material is Kollidon® VA64 (hereinafter simply referred to as VA64).

[0037] A polymer containing ethylene glycol units useful as a carrier material in the present invention can be, e.g., a polyethylene glycol/N-vinylcaprolactam/vinyl acetate copolymer, and can be, e.g., Soluplus® commercially available from BASF. In a preferred embodiment of the invention, the carrier material is Soluplus®.

[0038] In another embodiment of the invention, the carrier material further comprises one or more enteric polymers selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, methyl cellulose phthalate, ethylhydroxymethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate (HPMCAS), hydroxypropylmethyl cellulose acetate maleate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl cellulose, polyvinyl butyrate phthalate, polyvinyl acetate phthalate, a methacrylic acid/ethyl acrylate copolymer (wherein the preferred weight ratio of methacrylic acid to ethyl acrylate is in the range of 1:99 to 99:1) and a methacrylic acid/methyl methacrylate copolymer (wherein the preferred weight ratio of methacrylic acid to methyl methacrylate is in the range of 1:99 to 99:1), preferably selected from the group consisting of hydroxypropylmethylcellulose phthalate, HPMCAS, hydroxypropylmethyl cellulose acetate maleate and hydroxypropylmethylcellulose trimellitate, and more preferably is HPMCAS.

[0039] HPMCAS is a cellulose derivative, and has (1) two types of ether substituents: methyl and 2-hydroxypropyl, and (2) two types of ester substituents: acetyl and succinyl. In scientific literatures, it is referred to as O-(2-hydroxypropyl)-O-methyl-cellulose acetate succinate. In some embodiments, the HPMCAS is preferably at least one or more of: (i) an HPMCAS having an average acetyl content of 5-9 wt.% and an average succinyl content of 14-18 wt.%, based on the weight of the HPMCAS; (ii) an HPMCAS having an average acetyl content of 7-11 wt.% and an average succinyl content of 10-14 wt.%, based on the weight of the HPMCAS; and (iii) an HPMCAS having an average acetyl content of 10-14 wt.% and an average succinyl content of 4-8 wt.%, based on the weight of the HPMCAS, with (ii) being preferred. The HPMCAS can be, e.g., but is not limited to, AQOAT® AS-L, AQOAT AS-M and AQOAT® AS-H commercially available from Shin-Etsu, and AquaSolve™ L, AquaSolve™ LM, AquaSolve™ LH and AquaSolve AS™ L, AquaSolve AS™ M, AquaSolve AS™ H commercially available from Ashland. In a preferred embodiment of the invention, the HPMCAS is preferably AQOAT® AS-M.

[0040] In another embodiment of the invention, the weight ratio of posaconazole to the carrier material can be in the range of about 1:1 to about 1:10, preferably about 1:1 to about 1:5, and more preferably about 1:3.

[0041] In a further embodiment of the invention, the vinylpyrrolidone-vinyl acetate copolymer or the polymer containing ethylene glycol units is present in an amount of 10 wt.% to 100 wt.%, preferably 25 wt.% to 100 wt.%, more preferably 25 wt.% to 50 wt.%, even more preferably 20 wt.% to 40 wt.%, and most preferably 25 wt.% to 37.5 wt.%, based on the total weight of the vinylpyrrolidone-vinyl acetate copolymer or the polymer containing ethylene glycol units and the enteric polymer such as HPMCAS, and each of the sub-ranges within the above ranges, e.g. any range defined by any two of the following values: 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5 and 50.

[0042] In a further embodiment of the invention, the pharmaceutical composition further comprises D-α-tocopherol polyethylene glycol 1000 succinate (TPGS, Vitamin E TPGS, Tocophersolan).

[0043] The TPGS useful in the present invention is a soluble derivative of vitamin E formed by esterification of a carboxyl group in D-α-tocopherol succinate (VES) and polyethylene glycol 1000 (PEG 1000), has a relative molecular weight of about 1513, and has been recorded in U.S. pharmacopeia. TPGS acts as a solubilizing agent in the pharmaceutical composition and pharmaceutical formulation of the present invention, and can reduce drug efflux by the effect thereof on drug transport glycoproteins in intestinal mucous cells, thus contributing to the improvement of oral bioavailability. Exemplary TPGS useful in the present invention is, but is not limited to, Kolliphor™ TPGS commercially available from BASF. In a preferred embodiment of the invention, the TPGS is Kolliphor™ TPGS.

[0044] The amount of TPGS used in the present invention is not particularly limited, and can be adjusted according to actual practice. Typically, TPGS is present in an amount of about 1-12 wt.%, based on the total weight of posaconazole, the carrier material and TPGS.

[0045] The pharmaceutical composition according to the invention can further comprise one or more pharmaceutically acceptable excipients, including but not limited to, one or more of a surfactant, a pH modifier, a diluent, a disintegrant, a binder, and a lubricant.

[0046] In another aspect, the present invention also provides a method for the preparation of a pharmaceutical composition of the present invention, including but not limited to, a hot melt extrusion process and a spray drying process. For example, the specific steps of a hot melt extrusion process are:

preheating a hot melt extruder to 120°C-180°C;

feeding a homogeneously-mixed stoichiometric mixture of posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients (or a homogeneously-mixed stoichiometric mixture of posaconazole, a carrier material, TPGS, and optionally one or more pharmaceutically acceptable excipients) into the hot melt extruder, or stoichiometrically feeding posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients (or posaconazole, a carrier material, TPGS, and optionally one or more pharmaceutically acceptable excipients) into the hot melt extruder directly;

extruding; and

cooling, pulverizing and sieving the extrudate, optionally mixing it with one or more pharmaceutically acceptable excipients, thereby obtaining the pharmaceutical composition.

[0047] The cooling process in the preparation method of the present invention is not particularly limited, and can include air cooling, water cooling, mechanical cooling, etc.

[0048] The extruder useful in the present invention is not particularly limited, and includes but is not limited to a single-screw type hot melt extruder or a twin-screw type hot melt extruder. In an embodiment of the invention, the extruder for the preparation of the pharmaceutical composition according to the invention is a twin-screw type extruder. In this case, the rotation type of the screw is not particularly limited, and includes but is not limited to co-rotating twin-screw type, counter-rotating twin-screw type, and conical twin-screw type. In a preferred embodiment of the invention, the extruder for the preparation of the pharmaceutical composition according to the invention is preferably a co-rotating twin-screw extruder.

[0049] The temperature of the hot melt extruder is set in the range of about 120°C to about 180°C, and the rotation speed of the screw is set in the range of about 50 to about 500 rpm. The length to diameter ratio (L/D) of the screw can be about 15 to about 40. If the temperature of the hot melt extruder is too low, the L/D is too short, or the rotation speed is too slow, insufficient provision of heat energy and mechanical energy during the hot-melt process will occur, and in turn posaconazole, the carrier material or D-α-tocopherol polyethylene glycol 1000 succinate cannot get a molten state, or posaconazole cannot be dissolved in the molten carrier material, thus no single-phase solid dispersion wherein posaconazole is dissolved in or dispersed at a molecular level in the carrier material (a solid solution) can be obtained even though posaconazole is well mixed with the carrier material. If the temperature of the hot melt extruder is too high,

the L/D is too long, or the rotation speed is too fast, excess provision of heat energy and mechanical energy during the hot-melt process will occur, and unnecessary degradation of posaconazole and/or the carrier material and/or TPGS will occur even though a single-phase solid dispersion wherein posaconazole is dissolved in or dispersed at a molecular level in the carrier material (a solid solution) is obtained.

[0050] In addition, the present invention provides a pharmaceutical formulation comprising a pharmaceutical composition of the present invention. In other words, a pharmaceutical composition of the present invention can be further combined with one or more pharmaceutically acceptable excipients as required to form various dosage forms. In an embodiment of the invention, the pharmaceutical formulation can be in the form of a powder, a granule, a pill, a capsule, or a tablet.

[0051] The pharmaceutically acceptable excipients include, but are not limited to, one or more of a surfactant, a pH modifier, a diluent, a disintegrant, a binder, and a lubricant.

[0052] It should be noted that the pharmaceutically acceptable excipients listed above are only illustrative and representative, and are in no way exhaustive. Therefore, the present invention is not limited by the pharmaceutically acceptable excipients illustrated hereinafter.

[0053] The surfactant used in the present invention can be an anionic, cationic, zwitterionic or nonionic surfactant, preferably a zwitterionic or nonionic surfactant. The surfactant used in the present invention can also be a mixture of two or more surfactants. The selection of the surfactant can depend on the special compound used in the pharmaceutical composition of the present invention. Surfactants useful for the pharmaceutical composition of the present invention are listed below.

[0054] A surfactant useful in the present invention is one or more of a polyoxyethylene castor oil derivative, such as polyoxyethylene glyceryl triricinoleate or polyoxyl 35 castor oil (Cremophor EL, BASF), or polyoxyethylene glyceryl hydroxyl stearate such as polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40) or polyethylene glycol 60 hydrogenated castor oil (Cremophor RH 60); a block copolymer of ethylene oxide and propylene oxide, also referred to as a polyoxyethylene polyoxypropylene block copolymer or polyoxyethylene polypropylene glycol, such as Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 388, Poloxamer 407 (BASF); fatty acid monoester of polyoxyethylene(20)sorbitan, such as polyoxyethylene(20)sorbitan monooleate (Tween 80), polyoxyethylene(20)sorbitan monostearate (Tween 60), polyoxyethylene(20)sorbitan monopalmitate (Tween 40), polyoxyethylene(20)sorbitan monolaurate (Tween 20); a fatty acid ester of polyethylene glycol, such as PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; a fatty acid monoester of alkylene glycol, such as propylene glycol monolaurate (Lauroglycol); a fatty acid monoester of sorbitan, such as sorbitan monolaurate (Span 20), sorbitan monooleate, sorbitan monopalmitate (Span 40), or sorbitan stearate.

[0055] Preferably, the surfactant useful in the present invention is a polyoxyethylene castor oil derivative, a block copolymer of ethylene oxide and propylene oxide, particularly Cremophor RH40 and/or Poloxamer 188.

[0056] A suitable pH modifier useful in the present invention is one or more of citric acid, acetic acid, fumaric acid, maleic acid, tartaric acid, malic acid, succinic acid, fumaric acid, oxalic acid, malonic acid, benzoic acid, mandelic acid, and ascorbic acid, preferably citric acid.

[0057] A suitable diluent useful in the present invention can be one or more of microcrystalline cellulose, starch, pregelatinized starch, lactose, mannitol, and calcium hydrogen phosphate.

[0058] A suitable disintegrant useful in the present invention can be one or more of low-substituted cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, crosslinked sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, crosslinked polyvinylpyrrolidone (i.e. crospovidone), low-substituted hydroxypropylcellulose having 5-16 wt.% of hydroxypropoxy groups (L-HPC), and hydroxymethyl starch.

[0059] A suitable binder useful in the present invention can be one or more of sodium carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, ethyl cellulose, and hydroxypropylmethyl cellulose.

[0060] A suitable lubricant useful in the present invention can be one or more of magnesium stearate, silicon dioxide, talc, stearic acid, and hydrogenated vegetable oil.

EXAMPLES

[0061] The assays for the evaluation of physical and chemical properties in each example are as follows:

1. Glass transition temperature (Tg):

Precisely weighting about 3 mg test substance (the API posaconazole, hereinafter simply referred to as API; a drug-loaded composition (i.e. a pharmaceutical composition according to the invention); or a blank composition) and performing differential scanning calorimetry (mDSC, TA Q2000 differential scanning calorimeter) in a scanning temperature range of 40 to 180°C.

2. Powdery X-ray diffraction (X-RD):

Taking an appropriate amount of test substance (API, a drug-loaded composition, or a blank composition), and recording the X-ray diffraction spectrum under the conditions of Cu target, voltage = 45 kv, and current = 45 mA (X-ray diffractometer, model D8ADVANCE, manufactured by BRUKER).

3. Apparent solubility:

Weighting an excess amount of posaconazole pharmaceutical composition into a container, adding phosphate buffer solution (pH 6.8, about 2/3 of the volume of the container), and then placing the container in a shaking table at 37°C, and shaking for 3 h. Filtering the content with a 0.45 μm filter membrane, collecting the filtrate, diluting it with an appropriate amount of methanol, vortex mixing, and then determining the concentration of posaconazole via the following HPLC method:

Column	C_{18} column (3 μm, 4.6×75 mm)
Mobile phase	0.1 % phosphoric acid/acetonitrile = 50 : 50
Flow rate	1.5 ml/min
Sample plate	Room temperature
Detection wavelength	254 nm
Injection volume	10 μl
Analysis period for an injection	about 2 min

4. Dissolution rate:

Dissolution method	USP II method (paddle method)
Dissolution medium	Medium of pH 1.2/6.8: 900 ml. Medium of pH 1.2→6.8: after sampling at 30 min, adding 100 ml of buffer
	solution immediately into 800 ml of the dissolution medium of pH 1.2, such that the pH value of the overall dissolution medium reaches 6.8.
Rotary speed	100 rpm
Temperature	37.5°C
Test dosage	100 mg (posaconazole)/cup

Analytical method for dissolution samples: the same as the HPLC method in the above assay of apparent solubility.

Example 1. Posaconazole - Kollidon® VA64 pharmaceutical compositions

1. Preparation:

[0062] The composition of the posaconazole - Kollidon® VA64 pharmaceutical compositions and the amount of each component are shown in Table 1-1.

Preparation process:

[0063] Posaconazole and a carrier material and/or TPGS in the amounts shown in Table 1-1 were fed into the loading hopper of a co-rotating twin-screw extruder (Omicron 12, Steer, India) directly or after homogeneously mixed in a mixer. The temperature of the co-rotating twin-screw extruder was kept in the range of about 120°C to about 180°C, and extrusion was carried out at a screw rotary speed of about 50 to about 500 rpm. The resulting extrudate was cooled, pulverized and sieved to obtain solid powders. Then, other pharmaceutical excipients in the amounts shown in Table 1-1 and the solid powders were homogeneously mixed, offering the posaconazole - Kollidon® VA64 pharmaceutical

composition.

Table 1-1. Composition of posaconazole - Kollidon® VA64 pharmaceutical compositions and amount of each component (wt.%)

	Function	Composition 1-1	Composition 1-2	Composition 1-3	Composition 1-4
Posaconazole	Active ingredient	13.6	12.4	11.3	4.5
Kollidon® VA64	Carrier	13.6	37.3	33.9	22.7
Kolliphor® TPGS	Solubilizing agent	/	/	4.5	/
Microcrystalline cellulose	Diluent	54.4	31.1	31.1	54.4
Crospovidone	Disintegrant	16.3	18.6	18.6	16.3
Silicon dioxide	Lubricant	1.4	0.4	0.4	1.4
Magnesium stearate	Lubricant	0.7	0.2	0.2	0.7

2. Evaluation of physical and chemical properties

2.1. Determination of glass transition temperature (Tg)

[0064] It was determined that the melting temperature of the API posaconazole (crystalline form) was about 170°C, the Tg value of Composition 1-2 was 97.6°C, the Tg value of Composition 1-3 was 71.8°C, the Tg value of the blank composition corresponding to Composition 1-2 was 106.3°C, and the Tg value of the blank composition corresponding to Composition 1-3 was 81.4°C. There were significant shifts in the Tg values of Compositions 1-2 and 1-3 by comparison with the Tg values of the two blank compositions, but they both were significantly different from the Tg value of posaconazole (68°C), and the melting peak of posaconazole disappeared. The above results clearly show that in each of the pharmaceutical compositions of the present invention, posaconazole is dissolved in or dispersed at a molecular level in the carrier material.

2.2. Determination of apparent solubility

[0065] Table 1-2. Apparent solubility of posaconazole - Kollidon® VA64 pharmaceutical compositions in a phosphate buffer solution, pH 6.8

	API	Composition 1-1	Composition 1-2	Composition 1-3	Composition 1-4
Apparent solubility (μg/ml)	<1	10.6	14.3	44.3	15.9
Apparent solubility ratio (composition/API)	1	>10	>14	>44	>15

[0066] It can be seen from Table 1-2 that each of the pharmaceutical compositions of the present invention prepared using a hot melt extrusion process has a significant solubilizing effect on posaconazole, demonstrating that Kollidon® VA64 has a good solubilizing effect on posaconazole. When the weight ratio of the carrier material (Kollidon® VA64) to API in the pharmaceutical composition was adjusted from 1:1 to 5:1, the apparent solubility increased from 10.6 μg/ml to 15.9 μg/ml, demonstrating that the weight ratio of the carrier material to API does not have significant influence on the solubility of posaconazole. However, addition of a small amount of Kolliphor® TPGS in Composition 1-2 led to an increase of apparent solubility from 14.3 μg/ml to 44.3 μg/ml (Composition 1-3), demonstrating that a pharmaceutical composition comprising TPGS can increase the solubility of posaconazole significantly.

2.3. Determination of dissolution under a stimulated *in vivo* condition

[0067] It was reported that the pH value in human stomach was about 1.2, and that in human intestine was about 6.8. The dissolution of each of the pharmaceutical compositions of the present invention was determined under a stimulated

in vivo condition, and the results are shown in Table 1-3.

Table 1-3. Dissolution of posaconazole - Kollidon® VA64 pharmaceutical compositions in a medium conversion of pH 1.2→6.8

	Dissolution (%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
API	89.0	87.0	98.7	7.1	5.6	5.6
Composition 1-1	36.4	72.3	87.8	92.1	66.3	64.8
Composition 1-2	82.3	86.8	91.1	93.3	95.6	97.9
Composition 1-3	90.1	91.2	93.3	94.4	93.0	95.8
Composition 1-4	70.7	102.5	84.4	50.1	60.1	82.2

[0068] It can be seen from Table 1-3 that the dissolution of API significantly decreases from 98.7% to 5.6% upon the conversion of pH 1.2 to pH 6.8, demonstrating that posaconazole precipitates or crystallizes out from physiological fluids upon entry into intestinal tract through gastric emptying, decreasing the *in vivo* bioavailability thereof. The dissolution decrease of the pharmaceutical compositions of the present invention (especially Composition 1-2 and Composition 1-3) is not significant within 3 h from the conversion of pH 1.2 to pH 6.8 by comparison with API. Further, at each time point after 30 min, the dissolution of each of the pharmaceutical compositions of the present invention is above 50%, and up to 97.9%, significantly higher than the dissolution of API, demonstrating that they all can improve the absorption of posaconazole *in vivo* significantly. In particular, at each time point after 30 min, the dissolution of both Composition 1-2 and Composition 1-3 is above 93%, demonstrating that they can improve the absorption of posaconazole *in vivo* better.

Example 2. Posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions (pharmaceutical compositions having mixed carriers)

1. Preparation:

[0069] The composition of the posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions and the amount of each component are shown in Table 2-1.

Preparation process:

[0070] Posaconazole and a carrier material (VA64 and/or HPMCAS (in particular, AQOAT® AS-M)) and/or TPGS in the amounts shown in Table 2-1 were fed into the loading hopper of a co-rotating twin-screw extruder (Omicron 12, Steer, India) directly or after homogeneously mixed in a mixer. The temperature of the co-rotating twin-screw extruder was kept in the range of about 120°C to about 180°C, and extrusion was carried out at a screw rotation speed of about 50 to about 500 rpm. The resulting extrudate was cooled, pulverized and sieved to obtain solid powders. Then, other pharmaceutical excipients in the amounts shown in Table 2-1 and the solid powders were homogeneously mixed, offering the posaconazole - Kollidon® VA64/HPMCAS pharmaceutical composition.

[0071] Composition 2-1 was a comparative composition prepared according to US2011123627A, comprising only AQOAT® AS-M in its carrier material.

Table 2-1. Composition of posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions and amount of each component (wt.%)

	Function	Composition 2-1	Composition 2-2	Composition 2-3	Composition 2-4	Composition 2-5	Composition 2-6
Posaconazole	Active ingredient	17.4	15.6	12.5	12.5	14.5	7.9
AQOAT® AS-M	Carrier	52.2	35.2	23.5	18.8	18.2	19.7
Kollidon® VA64	Carrier	/	11.7	14.1	18.8	10.9	11.8
Kolliphor® TPGS	Solubilizing agent	/	6.3	5.0	5.0	4.3	3.9
Microcrystalline cellulose	Diluent	12.3	15.5	29.5	29.5	34.3	37.3
Hydroxypropyl cellulose	Binder	13.0	9.4	/	/	/	/
Crosslinked sodium carboxymethyl cellulose	Disintegrant	4.3	5.5	13.8	13.8	15.9	17.3
Silicon dioxide	Lubricant	0.5	0.5	1.0	1.0	1.2	1.3
Magnesium stearate	Lubricant	0.3	0.3	0.6	0.6	0.7	0.8

2. Evaluation of physical and chemical properties

2.1. Determination of glass transition temperature (Tg)

[0072] The determination results are as shown in Figure 1. Figure 1 shows the effect of VA64 content on Tg value in a pharmaceutical composition prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s), wherein Tg values corresponding to VA64/(VA64+HPMCAS)% of 0%, 25%, 37.5%, 50% and 100% are those of Composition 2-1, Composition 2-2, Composition 2-3, Composition 2-4, and Composition 1-3 or the corresponding blank compositions, respectively. It can be seen from Figure 1 that with the increase of VA64 content in the compositions, the Tg values tend to decrease, and the Tg values of drug-loaded compositions have significant shifts by comparison with the Tg values of the corresponding blank compositions, decreasing by about 10-20°C, though significantly differ from the Tg value of posaconazole (68°C).

[0073] Figure 2 shows X-RD spectrums of pharmaceutical compositions prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s), which are, from bottom to top, the X-RD spectrums of API, Composition 1-3, Composition 2-3, and Composition 2-4, respectively. It can be seen from Figure 2 that no diffraction peak of posaconazole exists in the X-RD spectrums of Composition 1-3 prepared with a single carrier material and Compositions 2-3 and 2-4 prepared with a mixed carrier material, demonstrating that in the pharmaceutical composition of the present invention, posaconazole is dissolved in or dispersed at a molecular level in the carrier material.

2.2. Determination of apparent solubility

[0074]

Table 2-2. Apparent solubility of posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions in a phosphate buffer solution, pH 6.8

	API	Composition 2-1	Composition 2-2	Composition 2-3	Composition 2-4	Composition 2-5	Composition 2-6
Apparent solubility (μg/ml)	<1	90.1	92.6	93.7	68.3	119.8	116.3
Apparent solubility ratio (composition/API)	1	>90	>92	>93	>68	>119	>116

[0075] It can be seen from Table 2-2 that each of the pharmaceutical compositions of the present invention having mixed carriers and prepared using a hot melt extrusion process has a significant solubilizing effect on posaconazole. When the weight ratio of API to the carrier material was kept constant (e.g., 1:3), adjusting VA64/(VA64+HPMCAS)% from 100% (Composition 1-3) to 50% (Composition 2-4) led to an increase of the apparent solubility from 44.3 μg/ml to 68.3 μg/ml, and further adjusting VA64/(VA64+HPMCAS)% from 50% to 37.5% (Composition 2-3) led to a further increase of the apparent solubility from 68.3 μg/ml to 93.7 μg/ml, but further decreasing VA64/(VA64+HPMCAS)% to 0% (Composition 2-1) led to a slight decrease of the apparent solubility to 90.1 μg/ml, demonstrating that pharmaceutical compositions prepared with a mixed carrier material had an advantageous effect on the solubility of posaconazole in a certain range. As shown in Table 2-2, Composition 2-5 increases the solubility of posaconazole most significantly.

[0076] On the other hand, when VA64/(VA64+HPMCAS)% in the carrier material was kept constant (e.g., 37.5%), adjusting the weight ratio of API to the carrier material from 1:2 (Composition 2-5) to 1:3 (Composition 2-3) and 1:4 (Composition 2-6) led to increase of the apparent solubility of the pharmaceutical composition of at least 119, 93, and 116 times of that of API, respectively, and they were all higher than the apparent solubility of the comparative composition (Composition 2-1), demonstrating that the compositions having VA64/(VA64+HPMCAS)% of 37.5% in the mixed carrier material had the most significant solubilizing effects on posaconazole.

2.3 Determination of dissolution under a stimulated *in vivo* condition

[0077]

Table 2-3. Dissolution of posaconazole - Kollidon® VA64/HPMCAS pharmaceutical composition in a medium conversion of pH 1.2→6.8

	Dissolution (%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
API	89.0	87.0	98.7	7.1	5.6	5.6
Composition 2-1	2.0	4.2	5.6	95.2	92.9	92.0
Composition 2-2	62.3	70.5	77.6	103.0	99.6	103.1
Composition 2-3	72.6	79.7	85.2	93.0	95.4	94.2
Composition 2-4	84.7	87.1	91.0	95.9	94.7	96.4
Composition 2-5	63.4	65.4	71.4	83.1	83.0	84.1
Composition 2-6	85.0	87.6	100.1	101.0	95.7	100.3

[0078] The dissolution profiles of Composition 2-3 and API are shown in Figure 3. It can be seen from Table 2-3 and Figure 3 that the dissolution of API significantly decreases from 98.7% to 5.6% upon the conversion of pH 1.2 to pH 6.8, demonstrating that posaconazole precipitates or crystallizes out from physiological fluids upon entry into intestinal tract through gastric emptying, decreasing the *in vivo* bioavailability thereof. The dissolution decrease of the pharmaceutical compositions of the present invention is not significant within 3 h from the conversion of pH 1.2 to pH 6.8 by comparison with API, and at each time point after 30 min, the dissolution of Compositions 2-2 to 2-6 are above 83%, demonstrating that they can improve the absorption of posaconazole *in vivo* significantly. At pH 1.2, the dissolution of Compositions 2-2 to 2-6 prepared with a mixed carrier material is significantly improved by comparison with Composition 2-1 prepared with a single carrier material, demonstrating that the absorption of Compositions 2-2 to 2-6 in stomach will be better than that of Composition 2-1. At pH 6.8, the dissolution of Compositions 2-2 to 2-6 prepared with a mixed carrier material is close to that of Composition 2-1 prepared with a single carrier material, demonstrating that the absorption of Compositions 2-2 to 2-6 in intestinal tract will be comparable to that of Composition 2-1. Therefore, the overall absorption of Compositions 2-2 to 2-6 prepared with a mixed carrier material *in vivo* will be better than that of Composition 2-1.

[0079] Figure 4 shows the effect of VA64 content in a pharmaceutical composition (wherein the weight ratio of posaconazole to the carrier material is 1:3) prepared with posaconazole - Kollidon® VA64 and/or HPMCAS carrier(s) on the dissolution of posaconazole in dissolution mediums at pH 1.2 and pH 6.8, wherein dissolution corresponding to VA64/(VA64+HPMCAS)% of 0%, 25%, 37.5%, 50% and 100% is that of Composition 2-1, Composition 2-2, Composition 2-3, Composition 2-4, and Composition 1-3, respectively. It can be seen from Figure 4 that under a dissolution condition of pH 1.2, the dissolution of each of the pharmaceutical compositions is above 75% when VA64/(VA64+HPMCAS)% is above 25.0%, significantly higher than that of Composition 2-1 wherein VA64/(VA64+HPMCAS)% is 0%, and under a

dissolution condition of pH 6.8, the dissolution of each of the pharmaceutical compositions decreases to lower than 50% when VA64/(VA64+HPMCAS)% increases to higher than 50.0%.

[0080] The above results show that the overall dissolution of Composition 2-2 and Composition 2-3 prepared with mixed carrier materials having VA64/(VA64+HPMCAS)% of 25.0% and 37.5%, respectively in the dissolution mediums at the two pH values is significantly better than that of Composition 2-1 comprising no VA64 and Composition 1-3 comprising VA64 solely.

Example 3. Posaconazole - Soluplus® pharmaceutical compositions

1. Preparation:

[0081] The composition of posaconazole - Soluplus® pharmaceutical compositions and the amount of each component are shown in Table 3-1.

Table 3-1. Composition of posaconazole - Soluplus® pharmaceutical compositions and amount of each component (wt.%)

	Function	Composition 3-1	Composition 3-2	Composition 3-3
Posaconazole	Active ingredient	14.3	7.2	4.8
Soluplus®	Carrier	14.3	21.7	24.2
Microcrystalline cellulose	Diluent	57.2	58.1	58.0
Crosslinked sodium carboxymethyl cellulose	Disintegrant	12.1	10.9	10.9
Silicon dioxide	Lubricant	1.4	1.4	1.4
Magnesium stearate	Lucricant	0.7	0.7	0.7

Preparation process:

[0082] Posaconazole and a carrier material in the amounts shown in Table 3-1 were fed into the loading hopper of a co-rotating twin-screw extruder (Omicron 12, Steer, India) directly or after homogeneously mixed in a mixer. The temperature of the co-rotating twin-screw extruder was kept in the range of about 120°C to about 180°C, and extrusion was carried out at a screw rotation speed of about 50 to about 500 rpm. The resulting extrudate was cooled, pulverized and sieved to obtain solid powders. Then, other pharmaceutical excipients in the amounts shown in Table 3-1 and the solid powders were homogeneously mixed, offering the posaconazole - Soluplus® pharmaceutical composition.

2. Evaluation of physical and chemical properties

2.1. Determination of apparent solubility

[0083]

Table 3-2. Apparent solubility of posaconazole - Soluplus® pharmaceutical compositions in a phosphate buffer solution, pH 6.8

	API	Composition 3-1	Composition 3-2	Composition 3-3
Apparent solubility (μg/ml)	<1	40.9	87.7	159.0
Apparent solubility ratio (composition/API)	1	>40	>87	>159

[0084] It can be seen from Table 3-2 that each of the posaconazole - Soluplus® pharmaceutical compositions can improve the solubility of posaconazole significantly, and with the increase of the weight proportion of the carrier material, the solubilizing effect becomes more and more apparent. When the weight ratio of the carrier material to API is 5:1

(Composition 3-3), the solubility of posaconazole can be increased by at least 159 times.

2.2. Determination of dissolution under a stimulated *in vivo* condition

[0085]

Table 3-3. Dissolution of posaconazole - Soluplus® pharmaceutical compositions in a medium conversion of pH 1.2→6.8

	Dissolution (%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
API	89.0	87.0	98.7	7.1	5.6	5.6
Composition 3-1	55.6	68.1	88.7	71.3	65.2	54.0
Composition 3-2	67.8	71.5	101.3	67.9	45.2	32.9
Composition 3-3	58.8	92.2	102.3	52.4	28.9	25.6

[0086] It can be seen from Table 3-3 that each of the posaconazole - Soluplus® pharmaceutical compositions can significantly increase the dissolution of posaconazole under a stimulated *in vivo* condition by comparison with API.

Example 4. Posaconazole - Soluplus®/HPMCAS pharmaceutical composition (pharmaceutical composition having mixed carriers)

1. Preparation:

[0087] The composition of the posaconazole - Soluplus®/HPMCAS pharmaceutical compositions and the amount of each component are shown in Table 4-1.

Table 4-1. Composition of posaconazole - Soluplus®/HPMCAS pharmaceutical compositions and amount of each component (wt.%)

	Fuction	Composition 4-1	Composition 4-2	Composition 4-3
Posaconazole	Active ingredient	13.2	13.2	13.2
Soluplus®	Carrier	29.6	19.8	10.0
AQOAT® AS-M	Carrier	10.0	19.8	29.6
Microcrystalline cellulose	Diluent	31.2	31.2	31.2
Crosslinked sodium carboxymethyl cellulose	Disintegrant	14.5	14.5	14.5
Silicon dioxide	Lubricant	1.1	1.1	1.1
Magnesium stearate	Lubricant	0.7	0.7	0.7

Preparation process:

[0088] Posaconazole and a mixed carrier material (Soluplus® and HPMCAS (in particular, AQOAT® AS-M)) in the amounts shown in Table 4-1 were fed into the loading hopper of a co-rotating twin-screw extruder (Omicron 12, Steer, India) directly or after homogeneously mixed in a mixer. The temperature of the co-rotating twin-screw extruder was kept in the range of about 120°C to about 180°C, and extrusion was carried out at a screw rotation speed of about 50 to about 500 rpm. The resulting extrudate was cooled, pulverized and sieved to obtain solid powders. Then, other pharmaceutical excipients in the amounts shown in Table 4-1 and the solid powders were homogeneously mixed, offering the posaconazole - Soluplus®/HPMCAS pharmaceutical composition.

2. Evaluation of physical and chemical properties

2.1. Determination of apparent solubility

[0089]

Table 4-2. Apparent solubility of posaconazole - Soluplus®/HPMCAS pharmaceutical compositions in a phosphate buffer solution, pH 6.8

	API	Composition 4-1	Composition 4-2	Composition 4-3
Apparent solubility (μg/ml)	<1	84.0	22.4	20.4
Apparent solubility ratio (composition/API)	1	>84	>22	>20

[0090] It can be seen from Table 4-2 that each of the posaconazole - Soluplus®/HPMCAS pharmaceutical compositions can improve the solubility of posaconazole significantly, and the increase by Composition 4-1 is most significant.

2.2. Determination of dissolution under a stimulated *in vivo* condition

[0091]

Table 4-3. Dissolution of posaconazole - Soluplus®/HPMCAS pharmaceutical compositions in a medium conversion of pH 1.2→6.8

	Dissolution (%)					
	pH 1.2			pH 6.8		
	5 min	10 min	30 min	60 min	120 min	180 min
API	89.0	87.0	98.7	7.1	5.6	5.6
Composition 4-1	87.6	93.8	84.9	74.3	55.6	52.8
Composition 4-2	36.2	45.8	62.8	51.5	42.9	49.8
Composition 4-3	10.2	12.5	25.8	33.6	20.9	25.4

[0092] It can be seen from Table 4-3 that each of the posaconazole - Soluplus®/HPMCAS pharmaceutical compositions can significantly increase the dissolution under a stimulated *in vivo* condition by comparison with API.

Example 5. Evaluation of preparation methods of posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions (pharmaceutical compositions having mixed carriers)

1. Hot melt extrusion process

[0093]

Table 5-1. Parameters of hot melt extrusion process

Composition	Rotation speed of material feeder (RPM)	Rotation speed of screw (RPM)	Melting temperature of material (°C)	Energy consumption per Kg (kW·h)	Percentage torque
1-3	30	160	125	12	51%
2-1	60	200	137	6	59%
2-2	30	200	136	7	34%
2-3	25	160	136	4	12%
2-4	25	150	136	4	12%

[0094] For specific processes, see the preparation of the pharmaceutical compositions in Examples 1-4. As shown in Table 5-1, compositions prepared with a mixed carrier material have lower energy consumption per Kg and produce lower percent torque by comparison with Composition 1-3 and 2-1 prepared with a single carrier material, demonstrating that a pharmaceutical composition prepared with a mixed carrier material can significantly decrease the energy consumption and instrument torque in a hot melt extrusion process, and greatly increase the operability thereof.

2. Pulverization process

[0095]

Table 5-2. Parameters of extrudate pulverization process

Composition	Weight of extrudate (g)	Pulverization period (s)	Weight of granules passing through 60 mesh sieve (g)	Sieving efficiency* w/w(%)
1-3	20.0	30	16.5	82.5
2-1	20.3	30	1.6	7.9
2-2	20.5	30	6.8	33.2
2-3	22.8	30	11.6	50.9
2-4	20.0	30	10.7	53.5
Note: * means the weight ratio of granules after sieving to overall granules before sieving.				

[0096] The extrudate obtained in the preparation of each pharmaceutical composition was cut into a stick of about 2 cm, and was pulverized for 30s using a small-sized coffee grinder (KG40, Delonghi, Italy). The pulverized granules were sieved using a 60 mesh sieve, the sieved powders were weighted, and the sieve efficiency was calculated. As shown in Table 5-2, a pharmaceutical composition prepared with a mixed carrier material comprising VA64 or a single carrier material VA64 has a higher sieving efficiency by comparison with the sieving efficiency (7.9%) of Composition 2-1 prepared with a single carrier material HPMCAS, demonstrating better operability of the pulverization process thereof.

3. Tableting process

[0097]

Table 5-3. Composition of tablet formulations (wt.%) and parameters of tableting processes

	Composition 1-3	Composition 2-1	Composition 2-2	Composition 2-3	Composition 2-4
Solid powders*	55.0	55.0	55.0	55.0	55.0
Crystalline cellulose	29.6	29.6	29.6	29.6	29.6
Crosslinked sodium carboxymethyl cellulose	13.8	13.8	13.8	13.8	13.8
Silicon dioxide	1.0	1.0	1.0	1.0	1.0
Magnesium stearate	0.6	0.6	0.6	0.6	0.6
Tableting pressure (cm)	13.8	13.8	13.8	13.8	13.8
Filling amounts of materials (mg)	800	800	800	800	800
Tablet hardness (kg)	38.5	1.9	8.7	15.5	21.0

(continued)

	Composition 1-3	Composition 2-1	Composition 2-2	Composition 2-3	Composition 2-4
Disintegrating time (min)	21.9	0.3	0.6	2.0	3.3
Note: * means the solid powders before mixed with the pharmaceutical excipients in the preparation of the compositions in Examples 1-4.					

[0098] The solid powders sieved using a 60 mesh sieve and other pharmaceutical excipients in the amounts shown in Table 5-3 were homogeneously mixed, and were tableted using a single-punch tablet machine (DP-5, Shanghai Tianfan Pharmaceutical Machinery Factory) at the same pressure and the same filling amounts of materials, in order to evaluate the compressibility (hardness tester, YD-35, Tianjin Tianda Tianfa Technology Co., Ltd.) and disintegration performance (disintegration tester, ZB-1, Tianjin Tianda Tianfa Technology Co., Ltd.) of various formulations. The results are shown in Table 5-3. It can be seen from Table 5-3 that with the decrease of VA64 content in the carrier material, the hardness of the tablets decreases, and the disintegration time decreases.

Example 6. *In vivo* pharmacokinetic study of posaconazole - Kollidon® VA64/HPMCAS pharmaceutical compositions (pharmaceutical compositions having mixed carriers)

[0099] An open, randomized, two-period, double crossover, self-control, comparative pharmacokinetic study was conducted in human subjects under fasted condition.

1. Method

[0100] The subjects were 9 healthy male subjects in the age of 20 to 45, having a body mass index (BMI) of 19 to 25. All subjects fully understood the content of the test and had signed the informed consent form voluntarily.

[0101] The subjects checked in care units for clinical trial at 18:00 and started fasting at 20:00 on day 1. On day 2, blood samples (blank samples before administration) were collected at 7:00, and Composition 2-1 or Composition 2-2 (see Example 2 for their specific composition) comprising 100 mg posaconazole were administered to the fasted subjects with 240 ml of water under the guidance of a physician at 8:00. Blood samples were collected at 1,2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after administration (12 times, 3 ml/time). The blood samples were transferred to heparin anticoagulation tubes, shaken homogeneously, centrifuged for 5 min at 4000 rpm to obtain plasma samples, which were divided into two parts and stored at -20°C for the determination of plasma drug concentration. On day 9, cross-over administration was carried out using the same method as on day 2, and then blood samples were collected in the same way. Vital signs and adverse events of the subjects were observed throughout the experiment in order to ensure their safety.

[0102] The concentration of posaconazole in each plasma sample (plasma drug concentration) was determined by a LC-MS/MS method, and was calculated by DAS 3.2.5, a statistical software for pharmacokinetics, in order to perform biological statistical analysis to get the pharmacokinetic parameters of Composition 2-1 and Composition 2-2. The ratio of arithmetic mean value of each parameter was calculated (Composition 2-2/Composition 2-1) and the distribution of 90% confidence interval of AUC and C_{max} of Composition 2-2 was evaluated. The C_{max}, $AUC_{0\text{-}72h}$, and $AUC_{0\text{-}\infty}$ of Composition 2-2 and Composition 2-1 were subjected to logarithm transformation, and then subjected to variance analysis. A two one-side T test was also performed.

2. Results

[0103] The experimental results are shown in Table 6-1 and Figure 5. The results show that for C_{max}, $AUC_{0\text{-}72h}$, and $AUC_{0\text{-}\infty}$ of posaconazole, significant difference exists between Composition 2-1 and Composition 2-2. The 90% confidence interval of C_{max} of Composition 2-2 is calculated to be (106%~ 147%), the 90% confidence interval of $AUC_{0\text{-}72h}$ is calculated to be (115.8%~147.1%), and the 90% confidence interval of $AUC_{0\text{-}\infty}$ is calculated to be (117.9%~ 146.7%), with a sample size of n = 9.

Tablet 6-1. Pharmacokinetic parameters of posaconazole

Pharmacokinetic parameters (arithmetic mean values, n = 9)	Composition 2-1	Composition 2-2
C_{max} ($ng \cdot ml^{-1}$)	432.8	533.2
AUC_{0-72h} ($ng \cdot h \cdot ml^{-1}$)	11793	15214
$AUC_{0-\infty}$ ($ng \cdot h \cdot ml^{-1}$)	13251	17276

[0104] It can be seen from Figure 5 and Table 6-1 that posaconazole in the composition having a Kollidon® VA64/HPMCAS mixed carrier material (Composition 2-2) achieves faster absorption speed, higher plasma drug concentration, and correspondingly higher bioavailability *in vivo* by comparison with the composition having a single carrier material HPMCAS (Composition 2-1). The ratio of arithmetic mean value of C_{max} (Composition 2-2/Composition 2-1) is 1.23; the ratio of arithmetic mean value of AUC_{0-72h} (Composition 2-2/Composition 2-1) is 1.29; and the ratio of arithmetic mean value of $AUC_{0-\infty}$ (Composition 2-2/Composition 2-1) is 1.30. The data show that on the premise of ensuring the dissolution at pH 6.8 is comparable to comparative composition 2-1, by increasing the dissolution or solubility of posaconazole under an acidic condition, the absorption of the drug in stomach *in vivo* is increased, and thus the absorption speed and availability of the drug *in vivo* are increased, such that the bioavailability of Composition 2-2 *in vivo* is increased.

Claims

1. A pharmaceutical composition comprising posaconazole and a carrier material, wherein the carrier material comprises a vinylpyrrolidone-vinyl acetate copolymer or a polymer containing ethylene glycol units.

2. The pharmaceutical composition according to claim 1, wherein the weight ratio of vinylpyrrolidone units to vinyl acetate units in the vinylpyrrolidone-vinyl acetate copolymer is in the range of 1:9 to 9:1, preferably 4:6 to 6:4.

3. The pharmaceutical composition according to claim 1 or 2, wherein the polymer containing ethylene glycol units is a polyethylene glycol/N-vinylcaprolactam/vinyl acetate copolymer.

4. The pharmaceutical composition according to any one of claims 1-3, wherein the carrier material further comprises one or more enteric polymers selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, methyl cellulose phthalate, ethylhydroxymethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose acetate maleate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl cellulose, polyvinyl butyrate phthalate, polyvinyl acetate phthalate, a methacrylic acid/ethyl acrylate copolymer and a methacrylic acid/methyl methacrylate copolymer.

5. The pharmaceutical composition according to claim 4, wherein the enteric polymer is hydroxypropylmethyl cellulose acetate succinate.

6. The pharmaceutical composition according to any one of claims 1-5, wherein the weight ratio of posaconazole to the carrier material is in the range of 1:1-1:5, preferably 1:3.

7. The pharmaceutical composition according to claim 4 or 5, wherein the vinylpyrrolidone-vinyl acetate copolymer or the polymer containing ethylene glycol units is present in an amount of 10 wt.% to 100 wt.%, preferably 25 wt.% to 100 wt.%, more preferably 25 wt.% to 50 wt.%, even more preferably 20 wt.% to 40 wt.%, and most preferably 25 wt.% to 37.5 wt.%, based on the total weight of the vinylpyrrolidone-vinyl acetate copolymer or the polymer containing ethylene glycol units and the enteric polymer(s).

8. The pharmaceutical composition according to any one of claims 1-7, further comprising D-α-tocopherol polyethylene glycol 1000 succinate as a solubilizing agent.

9. The pharmaceutical composition according to claim 8, wherein D-α-tocopherol polyethylene glycol 1000 succinate is present in an amount of 1-12 wt.%, based on the total weight of posaconazole, the carrier material and D-α-tocopherol polyethylene glycol 1000 succinate.

10. The pharmaceutical composition according to claim 8 or 9, further comprising one or more pharmaceutically acceptable excipients selected from the group consisting of a surfactant, a pH modifier, a diluent, a disintegrant, a binder, and a lubricant.

11. The pharmaceutical composition according to any one of claims 1-10, wherein posaconazole is dissolved in or dispersed at a molecular level in the carrier material.

12. A method for the prevention and/or treatment of fungal infections and related diseases in a mammal, comprising administering an effective amount of a pharmaceutical composition according to any one of claims 1-11 to the mammal.

13. A method for the preparation of a pharmaceutical composition according to any one of claims 1-11, comprising:

preheating a hot melt extruder to 120°C-180°C;
feeding a homogeneously-mixed stoichiometric mixture of posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients into the hot melt extruder, or stoichiometrically feeding posaconazole, a carrier material, and optionally one or more pharmaceutically acceptable excipients into the hot melt extruder directly;
extruding; and
cooling, pulverizing and sieving the extrudate, optionally mixing it with one or more pharmaceutically acceptable excipients, thereby obtaining the pharmaceutical composition.

14. A pharmaceutical formulation in the form of a powder, a granule, a pill, a capsule or a tablet, comprising the pharmaceutical composition according to any one of claims 1-11.

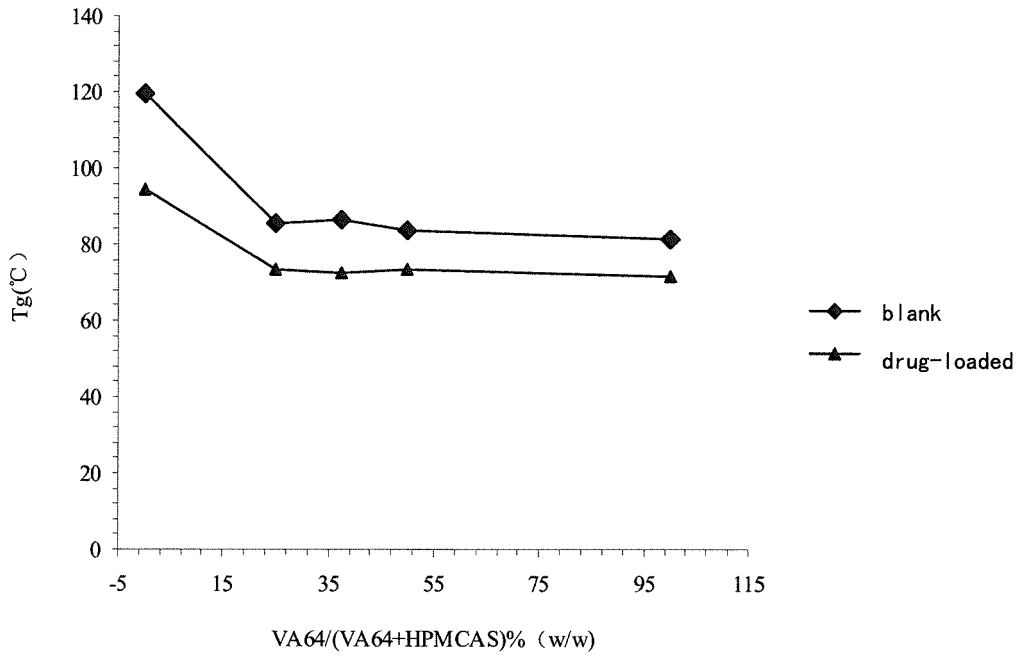


Figure 1

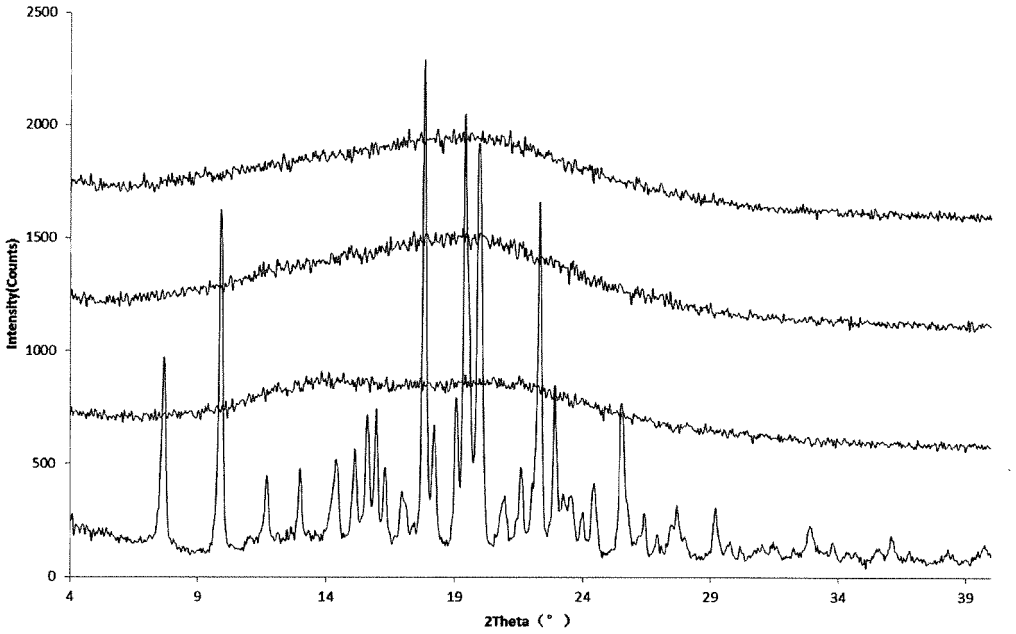


Figure 2

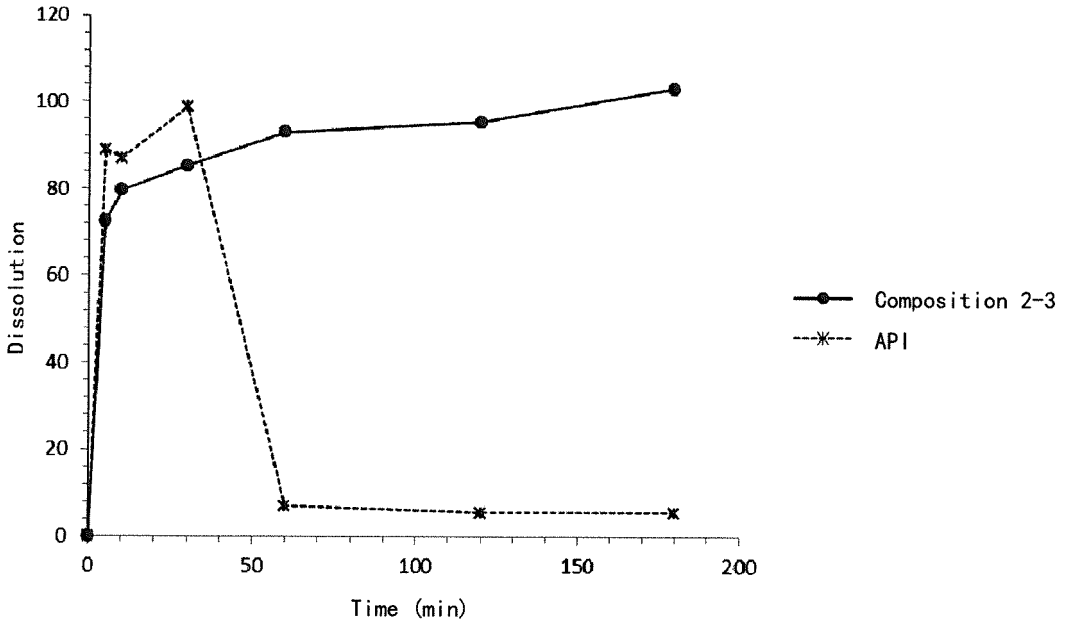


Figure 3

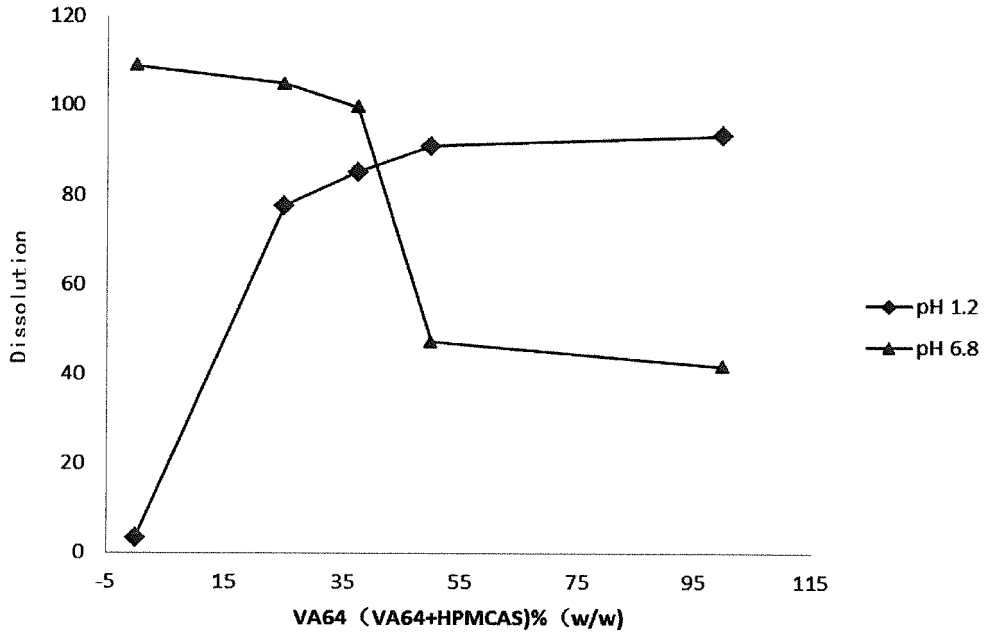


Figure 4

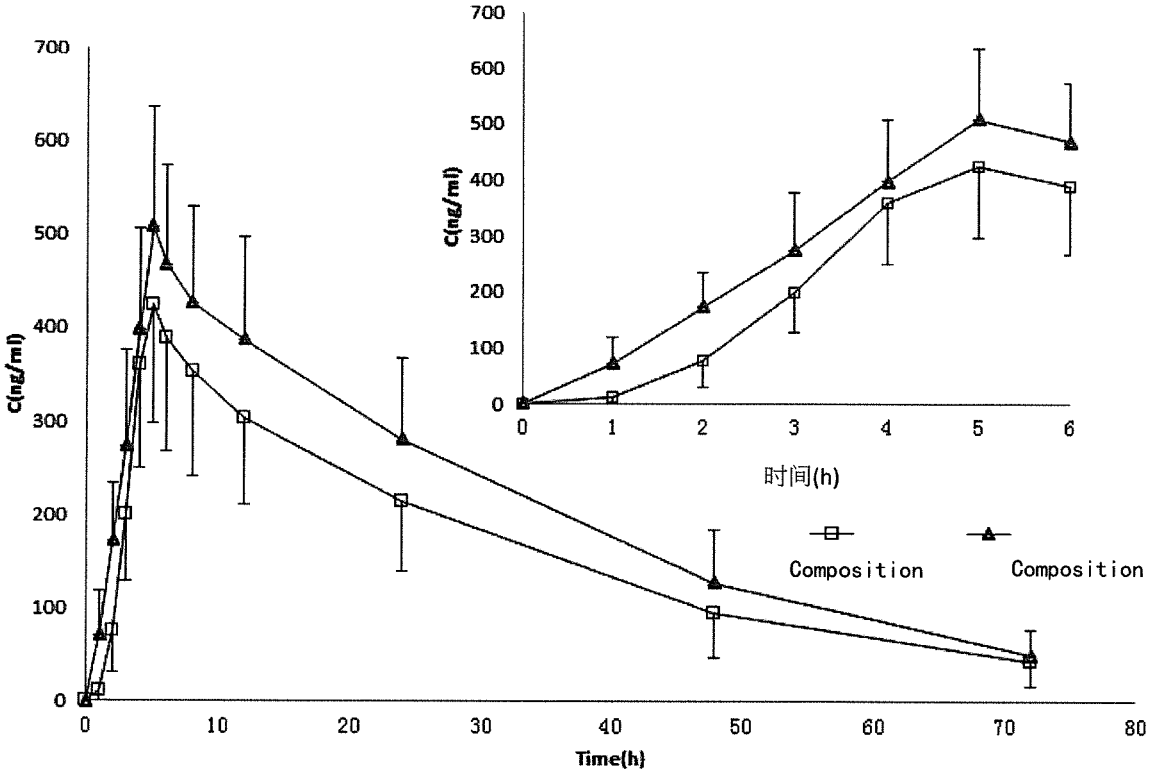


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/076299

A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/32 (2006.01) i; A61K 47/34 (2006.01) i; A61K 31/496 (2006.01) i; A61P 31/10 (2006.01) i
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)

A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNKI, DWPI, SIPOABS, CA, MEDLINE, EMBASE: posaconazole, PVP/VA, PVP-VA, Kollidon VA64, N-VinylPyrrolidone/Vinyl Acetate Copolymers, Poly(N-VinylPyrrolidone)/Vinyl Acetate, PCA-PVA-PEG, soluplus, Ethylene oxide-vinyl acetate-N-vinylcaprolactam graft copolymer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101495096 A (ELAN PHARMA INT LTD) 29 July 2009 (29.07.2009) , see claims 1, 6 and 11	1, 4-11, 13, 14
A	CN 101495096 A (ELAN PHARMA INT LTD) 29 July 2009 (29.07.2009) , see claims 1, and 11	2, 3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 July 2015	15 July 2015
Name and mailing address of the ISA State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No. (86-10) 62019451	Authorized officer LIU, Qiming Telephone No. (86-10) 62412173

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/076299

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:12
because they relate to subject matter not required to be searched by this Authority, namely:
the subject-matter of claim 12 is directed to a therapeutical method of disease.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/076299

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 101495096 A	29 July 2009	MX 2008015275 A	06 February 2009
		US 2007281011 A1	06 December 2007
		CA 2653504 A1	13 December 2007
		EP 2040675 A1	01 April 2009
		BR PI0712130 A2	17 January 2012
		AR 063940 A1	04 March 2009
		EP 2343053 A1	13 July 2011
		WO 2007143390 A1	13 December 2007
		TW 200811145 A	01 March 2008
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		NZ 573555 A	28 September 2012
		AU 2007256983 A1	13 December 2007
		IL 195524 D0	01 September 2009
		SG 170047 A1	29 April 2011
		JP 2009538927 A	12 November 2009

Form PCT/ISA /210 (patent family annex) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5703079 A **[0003]**
- US 5661151 A **[0003]**
- US 2011123627 A **[0007] [0071]**
- US 5426163 A **[0035]**

Non-patent literature cited in the description

- **H. FIKENTSCHER.** *Cellulose-Chemie,* 1932, vol. 13, 58-64, 71-74 **[0036]**