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(54) **Title:** INSTANT RELEASE PHARMACEUTICAL PREPARATION OF ANTICOAGULANT AND PREPARATION METHOD THEREFOR

(54) 发明名称: 一种抗凝剂的速释药物制剂及其制备方法

(57) **Abstract:** The present invention relates to the technical field of medicine and relates to an instant release pharmaceutical preparation of an anticoagulant and a preparation method therefor. The instant release pharmaceutical preparation of an anticoagulant comprises a vicagrel compound or a pharmaceutically acceptable form thereof, the preparation is a tablet or a capsule, the vicagrel or the pharmaceutically acceptable form thereof is provided at a suitable particle size, and the D90 thereof < 50 μm. With regard to the drug-containing particles obtained by the present invention, a pharmaceutical preparation formed therefrom exhibits rapid release characteristics in an in vitro dissolution test and exhibits considerable advantages in pharmacokinetics in vivo, showing a greater degree (AUC) and rate (C_{max}) of drug absorption. Further provided by the present invention is a method for preparing an instant release pharmaceutical preparation of an anticoagulant; according to the prescription of the drug-containing particles as disclosed by the present invention, a capsule or tablet instant release preparation having excellent stability may be obtained by means of a combination of optional preparation steps.

(57) 摘要: 本发明涉及一种抗凝剂的速释药物制剂及其制备方法，属于医药技术领域。所述抗凝剂的速释药物制剂包含维卡格雷化合物或其药学上可以接受的形式，其中所述制剂为片剂、胶囊的形式，所述维卡格雷或其药学上可接受形式以适当粒径提供，其D90＜50μm。本发明获得的含药颗粒，其形成的药物制剂在体外溶出测试中表现出快速释放的特征，并且在体内药代动力学上表现出相当的优势，表现为更大的药物吸收程度(AUC)和速率(C_{max})。本发明还提供了所述抗凝剂的速释药物制剂制备方法，根据本发明公开的含药颗粒处方，通过可选制备步骤的组合，可以得到稳定性优异的胶囊或片剂速释制剂。

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INSTANT RELEASE PHARMACEUTICAL PREPARATION OF ANTICOAGULANT AND PREPARATION METHOD THEREFOR

FIELD OF THE INVENTION

The present invention relates to the technical field of medicine, and provides an instant release pharmaceutical preparation, specifically including an instant release tablet or capsule comprising an anticoagulant vicagrel and an acceptable salt carrier thereof. The present invention also provides a method for preparing the instant release pharmaceutical preparation.

BACKGROUND OF THE INVENTION

Vicagrel, as a novel antiplatelet aggregation drug, can be used to overcome the clinical application defects of existing antiplatelet drugs, such as "clopidogrel resistance" and high risk of bleeding with prasugrel. Vicagrel has entered the stage of clinical research and is expected to be developed into a safer and more effective novel antiplatelet drug.

Patent CN103254211B has disclosed a method for preparing vicagrel and derivatives thereof. Patent CN103720700A has disclosed a composition of vicagrel and aspirin for use in prevention or treatment of diseases caused by thrombosis. However, at present, there is no report on the formulation process of a preparation with vicagrel as a single active ingredient. As an anticoagulant drug, it is required to quickly reach an effective blood drug concentration in vivo to exert its therapeutic effect, and the development of an oral instant release preparation is particularly necessary.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide an instant release preparation of vicagrel. In view of this, the present invention designs an oral pharmaceutical preparation for instant release that may be a capsule or tablet or granule, which comprises vicagrel or a pharmaceutically acceptable form thereof.

The technical solution adopted by the present invention is as follows.

An instant release pharmaceutical preparation of an anticoagulant comprises a vicagrel compound or a pharmaceutically acceptable form thereof, wherein the

preparation is a tablet or a capsule, the vicagrel or the pharmaceutically acceptable salt thereof is provided at a suitable particle size, and the D90 thereof < 50 μm.

The pharmaceutically acceptable form of vicagrel described in the present invention includes, but is not limited to, a salt, a solvate and other pharmaceutically acceptable carriers of vicagrel, which have the pharmaceutical activity of vicagrel.

With regard to the instant release preparation provided by the present invention, the bulk drug is pulverized, and the particle size thereof is preferably D90 < 50 μm, further preferably D90 < 30 μm, and most preferably D90 < 15 μm.

In one embodiment of the present invention, the instant release pharmaceutical preparation is in the form of drug-containing particles for filling into a capsule or forming a tablet, which comprise:

a) an active ingredient of vicagrel: vicagrel or a pharmaceutically acceptable form thereof;

b) one or more fillers;

c) one or more disintegrants;

d) one or more binders; and

e) one or more glidants/lubricants.

Preferably, the proportions of the components are as follows:

a) the active ingredient of vicagrel comprising 0.5%-30%wt of a tablet or capsule filling;

b) the fillers in the range of 1%-95%wt of the tablet or capsule filling;

c) the binders in the range of 0%-20%wt of the tablet or capsule filling;

d) the disintegrants in the range of 0%-20%wt of the tablet or capsule filling;

e) the glidants/lubricants in the range of 0%-5%wt of the tablet or capsule filling; and

f) the stablizers in the range of 0%-5%wt;

the sum of the percentages of all components being 100%.

In one embodiment, the drug-containing particles comprise vicagrel and one or m ore fillers. Suitable fillers include, for example, microcrystalline cellulose, lactose, pre

gelatinized starch/starch, mannitol, or other commonly used fillers known in the art, or a combination thereof. In other embodiments, the drug-containing particles optionally comprise one or more of the following adjuvants: (1) one or more binders; (2) one or more disintegrants; and (3) one or more glidants/lubricants. Suitable binders include, f or example, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrol idone, and others known in the art. Suitable disintegrants include, for example, low-su bstituted hydroxypropyl cellulose, croscarmellose sodium, sodium carboxymethyl star ch, crospovidone, and others known in the art. Suitable glidants/lubricants include, for example, silica, magnesium stearate, sodium stearyl fumarate, and others known in the art.

When the drug-containing particles are filled in capsules or compressed into tablets, vicagrel is present in the form of 1-30 mg per unit preparation, and the daily dose is 1-30 mg, which can be administrated in a single dose or multiple doses, 1-4 times a day.

The present invention provides an instant release pharmaceutical preparation, including tablet and capsule preparations, which comprises an anticoagulant drug: vicagrel or a salt, a solvate, or other pharmaceutically acceptable carriers of vicagrel.

The instant release preparation of the present invention may be a capsule or a tablet, and is embodied as drug-containing particles filled into a capsule or compressed into a tablet.

The "drug-containing particles" described herein include, but are not limited to, particles prepared by mixing particles obtained through internally adding adjuvant with externally added adjuvant by means of high shear granulation, roller compaction, spray drying granulation, layering granulation, etc., and also include mixed powders formed by directly mixing API with appropriately selected excipients.

The instant release preparation of the present invention may comprise the pharmaceutical excipients indicated herein, to aid in forming particles, particulates, or powders for filling capsules or tableting.

The proportions in the drug-containing particles of the present invention are

equivalent in metrics to the weight percentages of the materials before tableting or capsule filling without adding any stabilizer (optional).

In the drug-containing particles of the present invention, the proportion of the vicagrel or the pharmaceutically acceptable form thereof is 0.5%-30%wt, preferably 1%-20% based on the drug-containing particles.

The fillers in the drug-containing articles are present in the range of 1%-95%wt, more preferably 10%-85%wt based on the drug-containing articles. The fillers include, but are not limited to, microcrystalline cellulose, lactose, starch, pregelatinized starch, mannitol, sorbitol, and fillers known to be commonly used in the art. Microcrystalline cellulose, lactose, pregelatinized starch and mannitol are preferred, wherein lactose is present in the range of 10%-75% of the drug-containing particles, mannitol is present in the range of 10%-75% of the drug-containing particles, pregelatinized starch is present in the range of 5%-65% of the drug-containing particles, and microcrystalline cellulose is present in the range of 10% to 60% of the drug-containing particles.

The binders are present in an amount ranging from 0%-20%wt, preferably 1%-10% wt based on the drug-containing particles. Suitable binders include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, et hyl cellulose, or other conventional binders, or a mixture thereof. Hydroxypropyl meth ylcellulose and hydroxypropyl cellulose are preferred.

The disintegrants are present in an amount ranging from 0%-20%wt, preferably 1%-10%wt based on the drug-containing particles. Suitable disintegrants include, but are not limited to, low-substituted hydroxypropyl cellulose, sodium carboxymethyl starch, croscarmellose sodium, and crospovidone. Sodium carboxymethyl starch and low-substituted hydroxypropyl cellulose are preferred.

The glidants/lubricants are present in an amount ranging from 0%-5%wt, preferably 0.2%-2% based on the drug-containing particles. Suitable glidants/lubricants include hydrogenated vegetable oils, silicon dioxide, magnesium stearate, sodium stearyl fumarate, preferably stearic acid and sodium stearyl fumarate.

According to the present invention, a preferred formulation of the drug-containing

particles is as follows:

Raw material	Possible application range (wt% based on drug-containing particles)	Preferred range
vicagrel	0.5-30%	1-20%
filler	1-95%	10-85%
lactose	0-95%	10-75%
microcrystalline cellulose	0-95%	10-60%
pregaletinized starch	0-95%	5-65%
mannitol	0-95%	10-75%
binder	0-20%	1-10%
hydroxypropyl methylcellulose	0-20%	1-10%
hydroxypropyl cellulose	0-20%	1-10%
disintegrant	0-20%	1-10%
sodium carboxymethyl starch	0-20%	1-10%
low-substituted hydroxypropyl cellulose	0-20%	1-10%
lubricant/glidant	0-5%	0.2-2%
magnesium stearate	0-5%	0.2-2%
sodium stearyl fumarate	0-5%	0.2-2%

The present invention further provides a method for preparing the instant release preparation, which comprises the following steps:

a) providing micronized active ingredient powders of vicagrel, D90 < 50 μm, wherein the active ingredient powder of vicagrel refers to a micronized form of vicagrel or a pharmaceutically acceptable form thereof;

b) mixing the vicagrel active ingredient powders with additives to make drug-containing particles; and

c) subjecting the drug-containing particles to filling, tableting or filling, to obtain vicagrel capsules or tablets.

In step a) of the present method, the pulverization method of micronization is performed by conventional pulverization techniques in the art, including, but not limited to, grinding, extrusion, collision, and shearing, and the pulverization device used includes, but is not limited to, a ball mill, a jet mill and a hammer mill. More preferably, a jet mill device is used.

In step b) of the present method, the preparation of the drug-containing granules

can be carried out by means of dry granulation, wet granulation or direct mixing, specifically:

b1) An active ingredient of vcagrel is mixed together with one or more fillers in any desired order; in other embodiments, vicagrel or a pharmaceutically acceptable carrier thereof may be mixed together with one or more fillers and optionally one or more of the following compounds in any desired order: one or more binders; one or more disintegrants; and one or more glidants/lubricants; the mixing method uses a conventional mixing apparatus in the art including, but not limited to, a three-dimensional mixer, a V-type mixer, or a device with the mixing principle of stirring or fluidization.

b2) Optionally, the wet or dry method is used for granulation. With the wet granulation method, the mixed materials in b1) are aggregated to form particles by a wet granulation apparatus after spraying a binder, and then the particles are dried and sized; and with the dry granulation method, the mixed materials in b1) are rolled by a dry granulator after adding a lubricant to form a material strip, and the strip is pulverized and sieved to obtain particles. The wet granulation method includes conventional methods such as high-shear mixing granulation, fluidized bed granulation, non-perforated pan layering granulation and the like. The dry granulation means that the material is pre-compacted, and then rolled through a horizontal or vertical roller to form a material strip, and then the strip is pulverized to form particles.

b3) Optionally, if the wet granulation method is used, the particles need to be dried, and the temperature of the material during the drying process is controlled below 60°C; the apparatus used in the drying process includes, but is not limited to, a blast drying oven, a fluidized bed.

b4) The particles from the step b1), b2) or b3) are mixed with glidants/lubricants, and/or disintegrants and fillers that need to be added, to obtain drug-containing particles.

In step c) of the present method, one or more stabilizers may be also added in the drug-containing particles for filling, tableting or filling; the weight ratio of the

stabilizers to the drug-containing particles is 0-5:100, preferably 0.2-1:100.

The stabilizer is selected from fumaric acid, citric acid, citric acid, hydrogenated castor oil, hydrogenated soybean oil, glyceryl behenate, methyl silicone oil, and dimethyl silicone oil.

Still further, for the tablet obtained in c), a coating step may be taken to obtain a coated vicagrel tablet, and a coating component does not contain polyethylene glycol and talc. A film-forming component of a coating solution may be hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl alcohol. A lake may be added to adjust the color, and includes iron oxide, titanium dioxide and other common lakes/pigments for coating in the art. Commercially available coating formulations often contain a plasticizer polyethylene glycol and an anti-sticking agent talc, while the present invention does not contain polyethylene glycol and talc.

With regard to the drug-containing particles obtained according to the present invention, a pharmaceutical preparation formed therefrom exhibits rapid release characteristics in an in vitro dissolution test and exhibits considerable advantages in pharmacokinetics in vivo, showing a greater degree (AUC) and rate (C_{max}) of drug absorption.

According to the formulation and preparation method of the drug-containing particles provided by the present invention, an instant release preparation with high in vivo bioavailability and blood drug concentration can be provided, and according to the formulation of the drug-containing particles provided by the present invention, a capsule or tablet instant release preparation having excellent stability can be obtained by means of a combination of optional preparation steps.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a dissolution curve of a vicagrel preparation at different particle sizes.

FIG. 2 is a blood drug concentration curve of M9-2 in dogs after administration of a vicagrel preparation prepared with different particle sizes. A: D90 = 23 μm; B: D90 = 86 μm; C: D90 = 9 μm; and D: D90 = 49 μm.

FIG. 3 is a blood drug concentration curve of M15-1 in dogs after administration

of a vicagrel preparation prepared with different particle sizes. A: D90 = 23 μm; B: D90 = 86 μm; C: D90 = 9 μm; and D: D90 = 49 μm.

FIG. 4 is a blood drug concentration curve of M15-2 in dogs after administration of a vicagrel preparation prepared with different particle sizes. A: D90 = 23 μm; B: D90 = 86 μm; C: D90 = 9 μm; and D: D90 = 49 μm.

DETAILED DESCRIPTION OF THE INVENTION

The Detailed Description is given below. It should be understood that the present invention is not limited to these specific embodiments. Those skilled in the art can make various modifications and changes to the present invention without departing from the spirit and scope of the present invention. Such improvements are considered to be included within the scope of the claims appended to this application. Examples are a further description of the contents of the present invention to illustrate the innovation of the present invention.

Example 1 Vicagrel capsule

Raw material	Amount mg/capsule
vicagrel	20
pregaletinized starch	100
microcrystalline cellulose	79.5
glyceryl behenate	0.5
total	200

Vicagrel was pulverized by a hammer mill (Frewitt) with a 0.20 mm sieve, at 6000 rpm, and a 1 kg/min feed rate, and it was determined that D90 = 43 μm. The pulverized vicagrel was mixed with microcrystalline cellulose and lactose in a three-dimensional mixer for 15 min, hydrogenated castor oil was added and mixed, and the resulting particles were filled in size 3 capsules.

Example 2 Vicagrel capsule

Raw material	Amount mg/capsule
vicagrel	5.5
microcrystalline cellulose	100

lactose	80
sodium carboxymethyl starch	20
hydroxypropyl methylcellulose	6.5
water	q.s
magnesium stearate	0.5
total	212.5

The raw materials were pulverized using a QL-100 jet mill at a pressure 0.8 MPa, a working temperature of 15°C, and a pulverization time of 10 min, and it was determined that D90 = 9 μm. The pulverized vicagrel hydrochloride was mixed with microcrystalline cellulose, lactose, sodium carboxymethyl starch, and hydroxyl propyl methylcellulose in a three-dimensional mixer at 35 rpm for 10 min, the mixture was removed and placed in a high-shear wet granulator, stirred at 500 rpm, and granulated at a shearing rate of 1,000 rpm with added water. Particles were then sized by passing through a 16-mesh sieve, and dried in an air dry oven at 60°C, removed, and sized by passing through a 24-mesh sieve, and magnesium stearate was added and mixed. The drug-containing granules were filled in size 3 capsules to obtain vikagrel instant release capsules.

Example 3 Vicagrel capsule

Raw material	Amount mg/ capsule
vicagrel	15
pregaletinized starch	49.5
lactose	140
sodium carboxymethyl starch	20
hydroxypropyl methylcellulose	5
water	q.s
sodium stearyl fumarate	0.5
total	230

The pulverized vicagrel salt was placed with pregelatinized starch, lactose, and sodium carboxymethyl starch in a fluidized bed, fluidized mixing is started for 10 min, and 5% hydroxypropyl methylcellulose is prepared as a binder. At an air inlet temperature of 80°C, the binder was sprayed while maintaining a bed temperature at 40-50°C. The formed particles were dried for 30 min while the bed temperature was

maintained at 50-60°C, and were discharged. Sodium stearyl fumarate was added and mixed for 5 min, and the particles were filled into capsules.

Example 4

Vicagrel was pulverized into powders with different particle sizes, and drug-containing particles were prepared and filled in capsules. The dissolution rate was measured at 50 rpm using a pH 4.0 acetate buffer containing 0.2% SDS as a medium, according to the USPII method. The results are shown in the following table and Figure 1.

In treatments 1, 2, and 3, when the particle size of API was below 50 μm, the release rate at 30 min of > 85% could be satisfied. In particular, when the particle size was < 30 μm, the release rate at 15 min was > 85%. In treatment 4 and treatment 5, the particle size of API was >50 μm, and the in vitro release rate was slow, and the dissolution rate at 45 min was less than 85%.

Time (min)	Treatment 1 D90 = 9 um	Treatment 2 D90 = 23 um	Treatment 3 D90 = 49 um	Treatment 4 D90 = 86 μm	Treatment 5 D90 = 103 um
15	87.36	86.98	76.36	50.9	61.51
30	94.85	94.35	88.07	62.6	75.64
45	95.88	96.28	92.57	71.6	83.67
60	96.67	98.91	95.95	77.8	88.83
90	/	100.59	97.62	94.9	93.06
120	/	/	99.69	/	96.09
180	/	/	100.11	/	98.92

Following the method in Example 2, vicagrel capsules were prepared with the raw materials of different particle sizes, and the blood drug concentration and pharmacokinetic parameters of active metabolites were measured after administration to Beagle dogs, specifically as follows:

8 healthy beagle dogs, male, age 7-8 months, weight 8-10 kg, cross-over. The dogs were fasted for 12 h before the test and provided with food 4 h after the administration, and water was not forbidden throughout the test. The wash-out period between cycles was 7 days. The administration was done with 40 ml water. 1 ml of venous blood was taken from limb veins at the following set time points: before administration (0 h) and 10 min, 20 min, 40 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 12 h and 24 h after

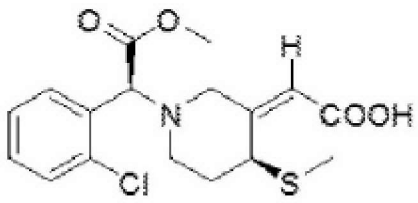
administration, and the samples were processed according to relevant standard operating procedures, and then cryopreserved in a refrigerator at -70°C for test. The concentrations of a metabolite M9-2 and active metabolites M15-1 and M15-2 of vicagrel in plasma were determined using LC-MS/MS method. The main pharmacokinetic parameters of a metabolite M9-2 and active metabolites M15-1 and M15-2 of vicagrel after administration to beagle dogs were calculated using a non-compartmental approach with PhoenixWinNonlin6.4 software. The results are shown in the table below (n=8).

Main metabolite	PK parameter	Particle size (μm)			
		9	23	49	86
active metabolite M9-2	C_{max}(ng/mL)	95.4*	60.5＊	62.3＊	46.7
	AUC_{0-1}(ng•h/mL)	244	242＊	249＊	190
active metabolite M15-1	C_{max}(ng/mL)	195.8*	87.9	90.1	80.0
	AUC_{0-1}(ng•h/mL)	121.6*	83.9	88.6	86.7
active metabolite M15-2	C_{max}(ng/mL)	76.4*	40.1	40.3	32.3
	AUC_{0-1}(ng•h/mL)	53.6*	37.3	38.3	33.8

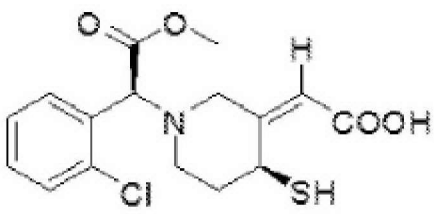
* indicates P < 0.05 compared with a particle size group of 23, 49, or 86 μm.

＊ indicates P < 0.05 compared with a particle size group of 86 μm.

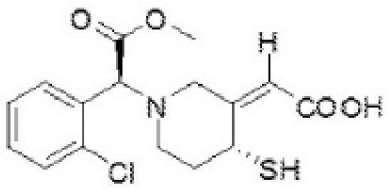
The structural formula of M9-2 is:



The structural formula of M15-1 is:



The structural formula of M15-2 is:



Blood drug concentration curves of M9-2, M15-1 and M15-2 in dogs after administration of a vicagrel preparation prepared with different particle sizes are shown in FIG.2, FIG.3 and FIG.4, respectively.

When the particle size of the raw material is less than 50 μm, it can be seen that the AUC of the drug is significantly higher than that of the particle size group of 86 μm. In particular, when the particle size of the drug is less than 15 μm, it is observed that the area under blood drug concentration-time curve of active metabolites A, B, and C, and the C_{max} of active metabolites B and C are significantly higher than those of other groups with a particle size >15 μm. This is very beneficial for the anticoagulant drugs to exert their effects.

Example 5 Vicagrel tablet

Raw material	Amount mg/tablet
vicagrel	5
pregaletinized starch	57.5
mannitol	22.5
low-substituted hydroxypropyl cellulose	10
hydroxypropyl methylcellulose	4
water	q.s
sodium stearyl fumarate	1
total	200

The pulverized vicagrel was subjected to stirred mixing with pregelatinized starch, mannitol, low-substituted hydroxypropyl cellulose, and hydroxypropyl methyl cellulose in a high-shear granulator for 5 min, stirred at a linear speed of 4 m/s, and sheared with a shearer at 800 rpm, and granulated with added water, the particles were deagglomerated through a 10-mesh sieve, and dried in a fluidized bed while maintaining the bed temperature below 60°C during drying. The particles were

removed, and sized through a 24-mesh sieve, and sodium stearyl fumarate was added and mixed, and tableting was performed on a 10-punch rotary tablet press (ZP-10A, Sinopharm Longli), with a 8 mm shallow concave punch.

Example 6 Vicagrel tablet

Raw material	Amount mg/tablet
vicagrel	10
pregaletinized starch	40
microcrystalline cellulose	102
croscarmellose sodium	20
polyvinylpyrrolidone	7
water	q.s
magnesium stearate	1
total	180

The pulverized vicagrel was mixed with pregelatinized starch, microcrystalline cellulose, polyvinylpyrrolidone, and half of the amount of croscarmellose sodium and half of the amount of magnesium stearate in a V-type mixer for 10 min. The material was put into a dry granulator (LGJ-300) where granulation was operated at parameters of a feed rate of 20 Hz, roller speed of 15 rpm, extrusion force of 6 bar, screen of 20 mesh, and shearing speed of 300 rpm. The particles were mixed with the rest of the disintegration and the lubricant for 5 min to obtain drug-containing particles, which were subjected to further tableting operation.

Example 7 Vicagrel tablet

Raw material	Amount mg/tablet
vicagrel	10
pregaletinized starch	35
lactose	108
low-substituted hydroxypropyl cellu lose	11
hydroxypropyl methylcellulose	4
water	q.s
sodium stearyl fumarate	1
glyceryl behenate	1
total	170

The pulverized vicagrel was subjected to stirred mixing with pregelatinized starch, lactose, low-substituted hydroxypropyl cellulose, and hydroxypropyl methyl cellulose in a wet granulator, and granulated with added water. The particles were sized through a 16-mesh sieve and dried in an air dry oven at 55°C, removed, and ground and sized through a conical mill. Sodium stearyl fumarate was added and mixed for 3 min, and the stabilizer glyceryl behenate was added and mixed for 3 min. The particles were removed, and tableted with a 7.5 mm shallow concave punch, having a hardness ≥ 6 kgf.

Example 8 Vicagrel tablet

Raw material	Amount mg/tablet
vicagrel	10
pregaletinized starch	42
mannitol	106
low-substituted hydroxypropyl cellu lose	12
hydroxypropyl methylcellulose	8
water	q.s
sodium stearyl fumarate	1
fumaric acid	1
total	170

The pulverized vicagrel was subjected to stirred mixing with pregelatinized starch, mannitol, low-substituted hydroxypropyl cellulose, and hydroxypropyl methyl cellulose in a wet granulator, and granulated with added water. The particles were sized through a 16-mesh sieve and dried in an air dry oven at 55°C, removed, and ground and sized through a conical mill. Sodium stearyl fumarate was added and mixed for 3 min, and the stabilizer glyceryl behenate was added and mixed for 3 min. The particles were removed, and tableted with a 7.5 mm shallow concave punch, having a hardness ≥ 6 kgf.

Example 9 Coated vicagrel tablet

The tablet core prepared in Example 8 was coated with a BG-10 type coating machine using Opadry II coating powder, with the coating powder being free of

polyethylene glycol and talc. The tablet core was 600 g, the air inlet temperature was 50°C, the coating flow rate was 4 g/min, the air inlet volume was 60 m^3/h, and the bed temperature was 35-45°C. Vicagrel coating tablets were obtained.

Example 10 Effect comparison of stabilizers

Vicagrel tablets were prepared following Example 7 and Example 8, except that no stablizers were added after drug-containing particles were obtained. The resulting tablets were sealed in HDPE bottles and placed at 60°C for 10 days, and the related substances and the dissolution were determined.

Impurity		Maximum single impurity and total impurity after placing in 60°C HDPE bottles for 10 days			
		Example 7	Example 7 (without stabilizer)	Example 8	Example 8 (without stabilizer)
maximum single impurity		0.88	2.04	0.79	1.76
total impurity		1.09	2.78	0.97	2.21
dissolution (45 min)	0 day	95.1%	94.6%	92.8%	93.1%
	10 days	94.3%	83%	93%	85%

It can be seen that, when the drug-containing particles are mixed with the stabilizer and tableted, the increase in related substances is reduced, and the dissolution is not significantly reduced.

Example 11 Stability comparison of coated tablets

Vicagrel tablet was prepared following Example 8, and coated in accordance with the parameters in Example 9, except that the coating solution contains a common plasticizer polyethylene glycol and anti-sticking agent talc.

Impurity		Maximum single impurity and total impurity after placing in 60°C HDPE bottles for 10 days			
		Example 9 (without polyethylene glycol and talc in coating powder)	Example 9 (with polyethylene glycol and talc in coating powder)	Example 9 (with polyethylene glycol in coating powder)	Example 9 (with talc in coating powder)
maximum single impurity		0.88	3.04	1.89	2.69
total impurity		1.11	4.06	2.62	3.67
dissolution (45 min)	0 day	94.6%	95.1%	96.9%	93.0%
	10 days	93.8%	81.4%	85.8%	87.3%

It is surprisingly found that when the coating component does not contain polyethylene glycol and talc, the vicagrel tablet can still provide a good coating membrane and is easy to prepare, and its stability is significantly increased compared to coated tablets with the above ingredients added.

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CLAIMS

1. An instant release pharmaceutical preparation wherein the preparation is a tablet or a capsule, and comprises the following components:

a) a vicagrel compound, or a pharmaceutically acceptable salt thereof in the range 0.5%-30% wt of the tablet or capsule filling;

b) one or more fillers in the range of 1%-95% wt of the tablet or capsule filling, wherein the filler is selected from microcrystalline cellulose, lactose, starch, pregelatinized starch, mannitol or sorbitol;

c) one or more binders in the range of 0%-20% wt of the tablet or capsule filling, wherein the binder is selected from hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone or ethyl cellulose;

d) one or more disintegrants in the range of 0%-20% wt of the tablet or capsule filling, wherein the disintegrant is selected from low-substituted hydroxypropyl cellulose, sodium carboxymethyl starch, croscarmellose sodium, or crospovidone; and

e) one or more glidants/lubricants in the range of 0%-5% wt of the tablet or capsule filling, wherein the glidant/lubricant is selected from hydrogenated vegetable oil, silicon dioxide, magnesium stearate or sodium stearyl fumarate;

wherein the vicagrel compound or the pharmaceutically acceptable salt thereof is provided in the form of particles, wherein 90% of said particles have a diameter (D90) of less than 50 μm.

2. The instant release pharmaceutical preparation according to claim 1, and comprising the following components:

a) a vicagrel compound, or a pharmaceutically acceptable salt thereof in the range 0.5%-30% wt of the tablet or capsule filling;

b) one or more fillers in the range of 1%-95% wt of the tablet or capsule filling, wherein the filler is selected from microcrystalline cellulose, lactose, starch, pregelatinized starch, mannitol or sorbitol;

c) one or more binders in the range of 0%-20% wt of the tablet or capsule filling, wherein the binder is selected from hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone or ethyl cellulose;

d) one or more disintegrants in the range of 0%-20% wt of the tablet or capsule filling, wherein the disintegrant is selected from low-substituted hydroxypropyl cellulose, sodium carboxymethyl starch, croscarmellose sodium, or crospovidone;

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e) one or more glidants/lubricants in the range of 0%-5% wt of the tablet or capsule filling, wherein the glidant/lubricant is selected from hydrogenated vegetable oil, silicon dioxide, magnesium stearate or sodium stearyl fumarate; and

f) one or more stabilizers selected from fumaric acid, citric acid, hydrogenated castor oil, hydrogenated soybean oil, or glyceryl behenate, wherein the weight ratio of the one or more stabilizers to the tablet or capsule filling is 0.2-5 : 100;

wherein the vicagrel compound or the pharmaceutically acceptable salt thereof is provided in the form of particles, wherein 90% of said particles have a diameter (D90) of less than 50 μm.

3. The preparation according to claim 1, wherein the preparation consists of the following components:

a) the vicagrel compound, or a pharmaceutically acceptable salt thereof, in the range of 0.5%-30%wt of the tablet or capsule filling;

b) the fillers in the range of 1%-95%wt of the tablet or capsule filling;

c) the binders in the range of 0%-20%wt of the tablet or capsule filling;

d) the disintegrants in the range of 0%-20%wt of the tablet or capsule filling; and

e) the glidants/lubricants in the range of 0%-5%wt of the tablet or capsule filling;

wherein the sum of the percentages of all components being 100%.

4. The preparation according to claim 2, wherein the preparation consists of the following components:

a) the vicagrel compound, or a pharmaceutically acceptable salt thereof, in the range of 0.5%-30%wt of the tablet or capsule filling;

b) the fillers in the range of 1%-95%wt of the tablet or capsule filling;

c) the binders in the range of 0%-20%wt of the tablet or capsule filling;

d) the disintegrants in the range of 0%-20%wt of the tablet or capsule filling; and

e) the glidants/lubricants in the range of 0%-5%wt of the tablet or capsule filling; and

f) the stabilizers in the range of 0.2%-5% wt of the tablet or capsule filling;

wherein the sum of the percentages of all components being 100%.

5. The preparation according to any one of claims 1- 4, wherein the D90 is less than 30 μm.

6. The preparation according to claim 5, wherein the D90 is less than 15 μm.

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7. A method for preparing an instant release pharmaceutical preparation according to claim 1, comprising the following steps:

a) providing micronized active ingredient powders of vicagrel with a D90 less than 50 μm, wherein the active ingredient powder of vicagrel refers to a micronized form of vicagrel or a pharmaceutically acceptable salt thereof;

b) mixing the vicagrel active ingredient powders with (i) one or more fillers; (ii) one or more binders; (iii) one or more disintegrants; (iv) one or more glidants/lubricants to make drug containing particles; and

c) filling and tableting the drug-containing particles to obtain vicagrel capsules or tablets.

8. A method for preparing the instant release pharmaceutical preparation according to claim 2, comprising the following steps:

a) providing micronized active ingredient powders of vicagrel with a D90 less than 50 μm, wherein the active ingredient powder of vicagrel refers to a micronized form of vicagrel compound or a pharmaceutically acceptable salt thereof;

b) mixing the vicagrel active ingredient powders with (i) one or more fillers; (ii) one or more binders; (iii) one or more disintegrants; (iv) one or more glidants/lubricants to make drug-containing particles; and

c) adding one or more stabilizers to the drug-containing particles and then filling and tableting to obtain vicagrel capsules or tablets, wherein the weight ratio of the stabilizers to the drug-containing particles is 0.2-5 : 100.

9. The preparation method according to claim 7 or 8, wherein for the tablet obtained in c), a coating step is further taken to obtain a coated vicagrel tablet, and a coating component does not contain polyethylene glycol and talc.

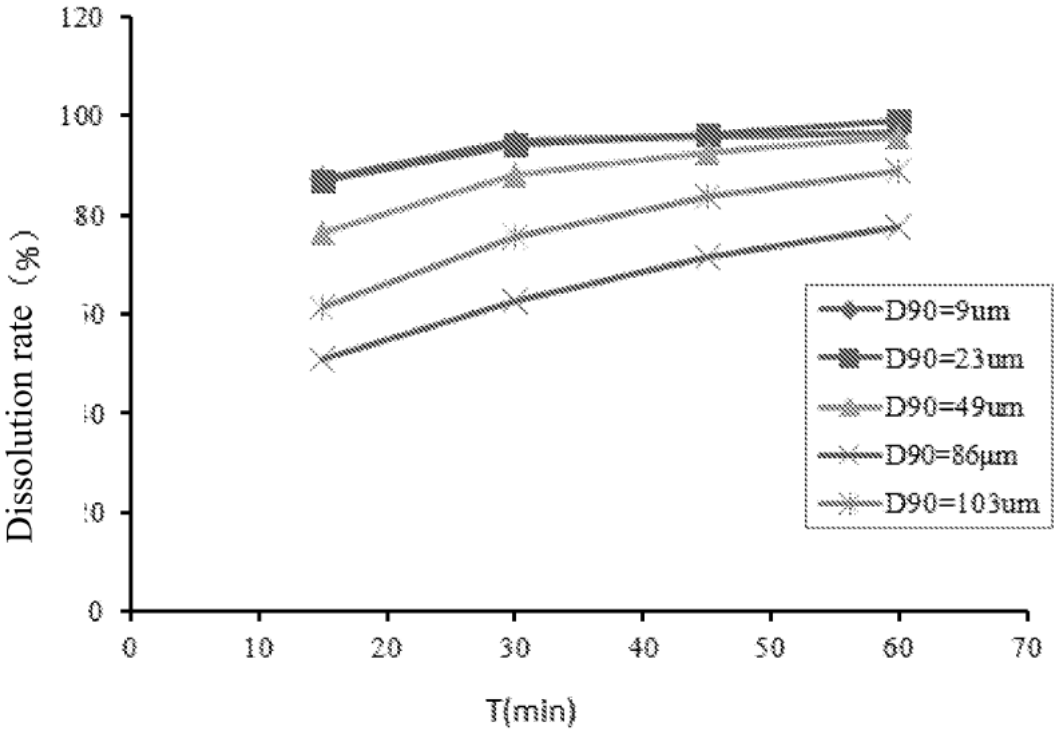
120
100
80
60
40
20
0
Dissolution rate（%）
0
10
20
30
40
50
60
70
T(min)
D90=9um
D90=23um
D90=49um
D90=86μm
D90=103um

FIG. 1

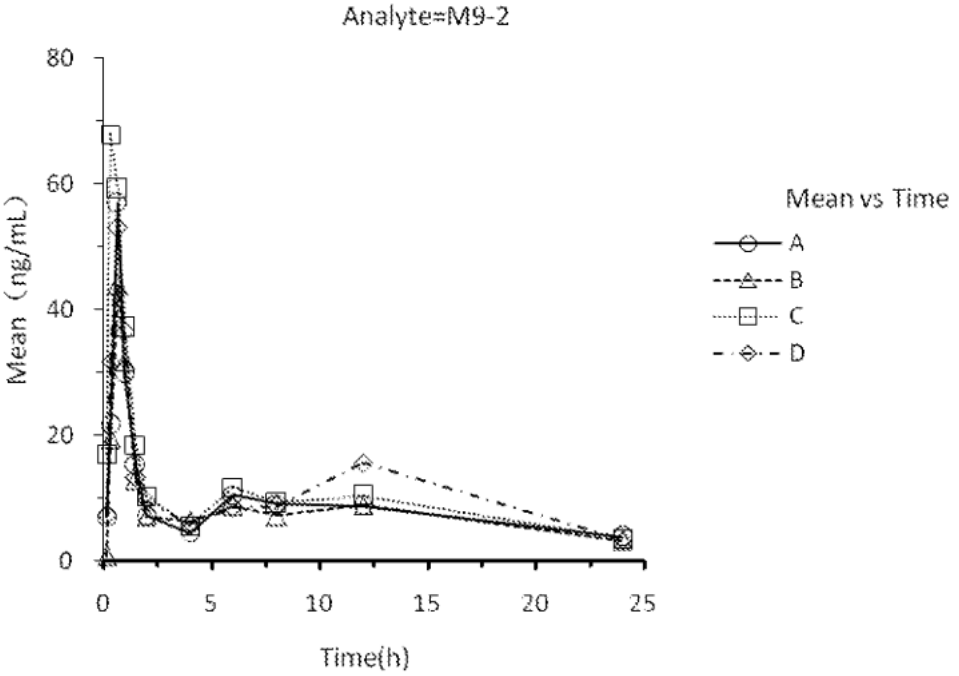
Analyte=M9-2
80
60
40
20
0
Mean（ng/mL）
0
5
10
15
20
25
Time(h)
Mean vs Time
A
B
C
D

FIG. 2

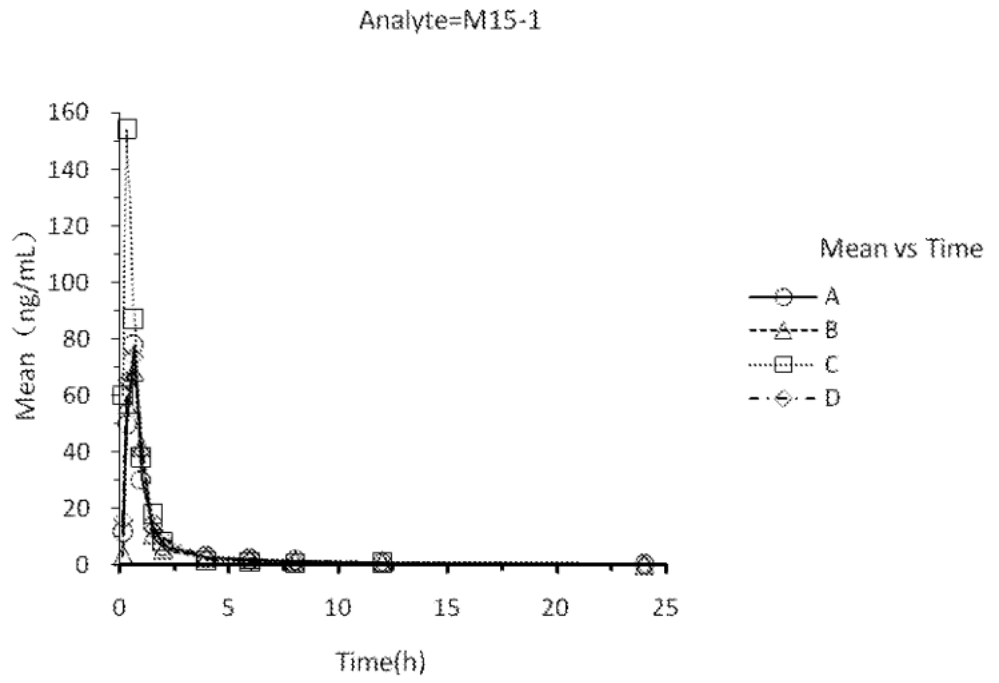
Analyte=M15-1
160
140
120
100
80
60
40
20
0
Mean（ng/mL）
0
5
10
15
20
25
Time(h)
Mean vs Time
A
B
C
D

FIG. 3

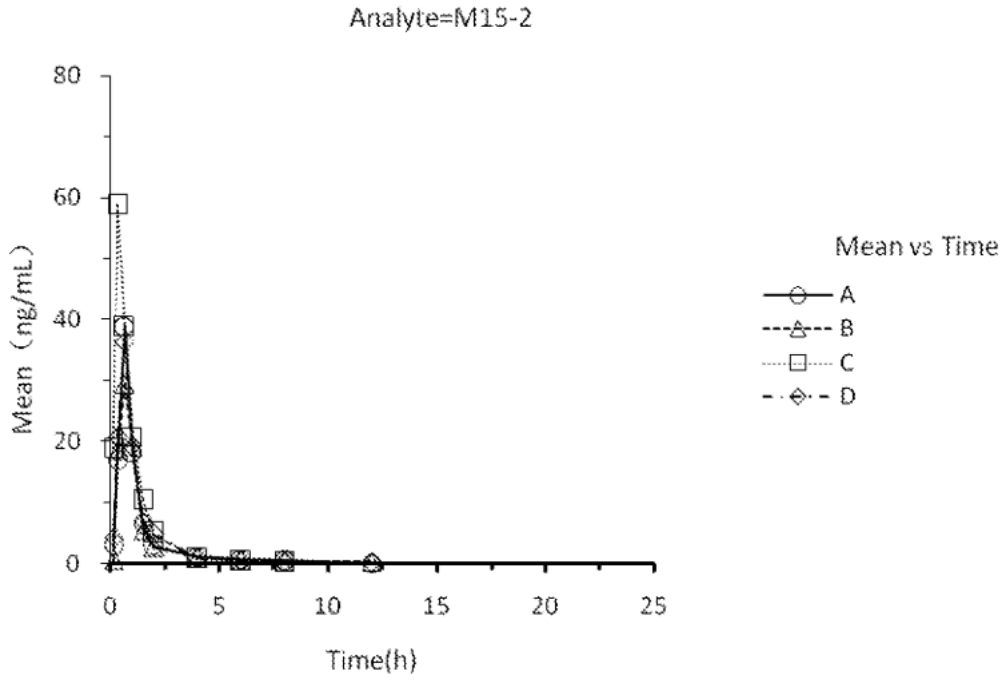
Analyte=M15-2
80
60
40
20
0
Mean（ng/mL）
0
5
10
15
20
25
Time(h)
Mean vs Time
A
B
C
D

FIG. 4