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ABSTRACT

A solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

To
The Controller of Patents
The Patent Office
At Mumbai - 400037

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We claim

1. A solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

2. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{50} is not less than 150 microns.

3. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{90} is not more than 750 microns.

4. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 75 % by weight of the solid dosage form.

5. A solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate wherein not more than 30 % particles pass through a sieve mesh of 100 # and 100 % of the particles pass through a sieve mesh 18 # having an opening size of 1000 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

6. A solid dosage form as claimed in claim 5 wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 75 % by weight of the solid dosage form.

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7. A solid dosage form as claimed in claim 1 wherein the dosage form is a tablet and

wherein the agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the tablet,

a lubricant is present in an amount of 1 % to about 7 % by weight of the tablet and disintegrant is present in an amount of about 15 % by weight of the tablet.

Dated this 10th day of July 2014

SUNIL AJMERA

COMPANY SECRETARY

SUN PHARMACEUTICAL INDUSTRIES LTD.

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FIELD OF INVENTION

The present invention relates to a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

BACKGROUND OF THE INVENTION

Clopidogrel is S-(+)-methyl-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-C]pyrid-5-yl) acetate sulphate (1:1), or Methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulphate (1:1) and is well known to have antithrombotic activity. It is commercially available in the products sold by Bristol-Meyers Squibb as PLAVIX™ tablets that contain 97.875 mg of clopidogrel hydrogen sulfate (the molar equivalent of 75 mg clopidogrel), 195.75 mg of clopidogrel hydrogen sulfate (the molar equivalent of 150 mg clopidogrel), and 391.5 mg of clopidogrel hydrogen sulphate (the molar equivalent of 300 mg clopidogrel).U.S. Pat. Nos. 6,429,210 and 6,504,030 disclose crystalline Form II of clopidogrel hydrogen sulfate, and processes for its preparation.

Clopidogrel hydrogen sulphate has been reported to show incompatibility with certain excpients. For instance, United State Patent Number US 6,914,141 (hereinafter referred to as US'141 patent) reported that the pharmaceutical tablet comprising Clopidogrel having lubricant such as zinc stearate, stearic acid and sodium stearyl fumarate, prevented the sticking of the tablets during compression. The US '141 identified an interaction between clopidogrel hydrogen sulphate and magnesium stearate. It was shown that presence of magnesium stearate caused degradation of clopidogrel hydrogen sulphate, however, the other lubricants like stearic acid, zinc stearate and sodium stearyl fumarate were found to be compatible and could be used as alternatives.

It is known from the art that clopidogrel hydrogen sulphate shows sticking problem and there are several attempts to solve this problem. For instance, PCT publication number WO2013008981 provides spherical clopidogrel hydrogen sulphate. Yet another PCT publication WO 2008122994

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reported use of hydrophilic polymers to tackle this problem. Thus, the art seems to solve the problem by addition of certain excipients which makes the dosage form bulky.

The below table provides the weight and the dimensions of the tablets of clopidogrel hydrogen sulphate by various manufacturers.

Company	tablet weight in mg	Dimensions
Torrent	269	8.65 mm, circular
Sanofi	256.4	8.71 mm, circular
Mylan	268.0	9.24 mm, circular
DRL	390.0	11.36 mm circular
Aurobindo	244.5	9.24 mm, circular
Sun Pharma * Generic product approved by USFDA	250.0	9.00 mm, circular
Sanofi	1024.0	18.00 mm, elliptical or oval

The dimensions tabulated above indicate that these tablets are not compact and are considerably, bulky in size.

The present invention is an improvement over these known products. The improvement is in achieving reduction in the size of the tablet, while not compromising on the chemical as well as physical stability of clopidogrel hydrogen sulphate.

The present invention addresses the problem of the need of small and non bulky tablets is more, because the bulky tablets may be associated with problems of difficulty in swallowing, resulting in patient non compliance, particularly since the majority of the patient population is geriatric. The geriatric patient in order to avoid swallowing may attempt to chew the tablet. However, clopidogrel tablets may not provide efficacy if chewed and therefore, can cause errors in the medication. Thus, it is very much desirable to provide small tablets that can be easily swallowed without any difficulty. A small, compact solid dosage form would be additionally beneficial since the amount of active ingredient would be same while the quantity of pharmaceutical excipients would be reduced leading to less chances of instability due to incompatibility. The

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inventors have made compact solid dosage form of agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns. Surprisingly, it was found that the agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns could be compressed into compact tablets without the known problems of sticking, poor flow otherwise associated with clopidogrel hydrogen sulphate with less amount of excipients.

DETAILED DECRPTION OF THE INVENTION

The present invention provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

The term 'agglomerates' may be interpreted as coarse particles or micropellets or aggregates of particles of the crystalline clopidogrel hydrogen sulphate. It also means that the agglomerated free flowing powder is substantially free of fines. It may be considered that fines are particle having particle size which is less than 75 microns.

The term 'compact' as used herein, means that the solid dosage form contains more than 55 % by weight of agglomerates of clopidogrel hydrogen sulphate. Preferably, the solid dosage form contains more than 65 % by weight of agglomerates of clopidogrel hydrogen sulphate, most preferably, more than 80 % by weight. The dosage form size reduction is achieved because of the agglomerated nature of the clopidogrel hydrogen sulphate, that is, because of the its particle size distribution having a particle size distribution such that D_{10} is not less than 75 microns.

The reduction in size of the solid dosage form particularly, provides a tremendous ease in swallowing, resulting into patient compliance, for instance, in case of geriatric patients who have more difficulty in swallowing or in patient population who have dysphagia. A geriatric patient in order to avoid swallowing or overcome swallowing may attempt to chew the tablet. However,

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clopidogrel tablets may not provide efficacy if chewed and therefore, can cause errors in the medication. Thus, present invention provides small, compact tablets that can be easily swallowed without any difficulty. The inventors have made compact solid dosage form of agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns. Surprisingly, it was found that the agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns could be compressed into compact tablets using very low amount of excipients without problems of sticking, poor flow. These problems of sticking, poor flow are otherwise known to be associated with clopidogrel hydrogen sulphate which is not agglomerated.

The term "particle size" of a certain particle according to the invention refers to the diameter of an equivalent product being assumed to be spherical and showing the same light scattering pattern as the particle. According to the invention the particle size is measured via laser light diffraction technique. The laser light diffraction technique used for the determination of particle size and its distribution is based on the analysis of the diffraction pattern produced when particles are exposed to a beam of monochromatic light. In one embodiment of the present invention, the particle size distribution was determined using following model of Malvern Mastersizer: Analysis model: Polydisperse, Presentation: BNJE, having a range lens: 300 mm, and Beam length of 2.40 mm.

The term D_x as used herein means the size in micrometers below which x % of the particles are found when measured by Malvern Mastersize analyzer using a lazer diffraction technique. For example, D_{10} of not less than 75 microns means at least 10 % of the particles are not less than 75 microns,that is at least 10 % of the particles are more than 75 microns. Similarly, D_{50} of not less than 150 microns means at least 50 % of the particles are not less than 150 microns, that is at least 50 % of the particles are more than 150 microns. For D_{90}, it can be interpreted as D_{90} of not more than 750 microns means at least 90 % of the particles are not more than 750 microns, that is at least 90 % of the particles are less than 750 microns. In general, it may be said that D_{10}, D_{50}, D_{90} refer to the size in micrometers below which 10, 50, 90%, respectively, of the particles are found.

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The particle size distribution of agglomerates of clopidogrel hydrogen sulphate having D_{10} of not less than 75 microns in the invention can be recorded by various techniques known in the art. The particle size distribution can be measured by performing a sieve analysis or by commercial light scattering instrument based on the theory of Fraunhofer diffraction. This principle is also referred to as static light scattering or low-angle forward light scattering and it applies to particles with dimensions larger than the wavelength of the incoming light. Such systems include Malvern Mastersizer (Malvern Instruments, Malvern, U.K.), and the Microtac Full Range Analyzer (Leeds & Northrup, North Wales Pa). In this technique, a laser light passes through the particles, diffracting the intensity in an angular distribution (*Iw*). Sieve analysis on the other hand provides essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length. The particle diameter obtained by sieving represents the minimum square aperture through which the particle can pass. (See '*Physical Characterization of Pharmaceutical solids*, by Harry G. Brittain, volume 70, Marcel Dekker, Inc, pp. 157-183). Typical sieve analysis involves a nested column of sieves with wire mesh cloth (screen). A representative weighed sample is poured into the top sieve which has the largest screen openings. Each lower sieve in the column has smaller openings than the one above. At the base is a round pan, called the receiver. The column is typically placed in a mechanical shaker. The shaker shakes the column, usually for some fixed amount of time. After the shaking is complete the material on each sieve is weighed. The weight of the sample of each sieve is then divided by the total weight to give a percentage retained on each sieve. The size of the average particle on each sieve is then analyzed to get a cut-off point or specific size range, which is then captured on a screen. The results of this test are used to describe the properties of the aggregate and to see if it is appropriate for various civil engineering purposes such as selecting the appropriate aggregate for concrete mixes and asphalt mixes as well as sizing of water production well screens. The complete procedure for this test is outlined in the American Society for Testing and Materials (ASTM) C 136. A suitable sieve size for the aggregate is selected and placed in order of decreasing size, from top to bottom, in a mechanical sieve shaker. A pan is placed underneath the nest of sieves to collect the aggregate that passes through the smallest. The entire nest is then agitated, and the material whose diameter is smaller

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than the mesh opening passes through the sieves. After the aggregate reaches the pan, the amount of material retained in each sieve is then weighed. Preferably, the particle size of clopidogrel hydrogen sulphate is determined by sieve analysis.

The term 'mesh size' as used herein means that the number of openings in one inch of screen. The number of opening is the mesh size. As the number describing the mesh size increases, the size of the particles decreases. Higher numbers equal finer material. The sieve mesh with corresponding microns is as follows: 14# corresponds to 1400 microns, 28 # corresponds to 700 microns, 60 # corresponds to 250 microns, 100 # corresponds to 150 microns, 200 # corresponds to 74 microns, 270 # corresponds to 53 microns, 325 # corresponds to 44 microns and 400 # corresponds to 37microns. In one embodiment of the present invention, sieve analysis was performed using electromagnetic sieve shaker (Electrolab, EMS-8) in which the nest of ASTM standard sieves (make Electrolab) were arranged in descending order of sieve opening. The instrument was operated for 10 minutes as the magnitude of 10 in continuous mode. About 300 g of material was subjected to sieve analysis. After the completion of shaking cycle, fraction passed through a particular mesh and retained on the next sieve were collected and weighed.

According to the present invention, there is provided a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and D_{50} not less than 150 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, D_{50} not less than 150 microns and D_{90} not more than 750 microns, wherein

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agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

According to the one specific embodiment of present invention, there is provided a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and D_{50} not less than 150 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, D_{50} not less than 150 microns and D_{90} not more than 750 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form.

According to the one specific embodiment of present invention, there is provided a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and D_{50} not less than 150 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form.

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Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, D_{50} not less than 150 microns and D_{90} not more than 750 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form.

According to the one specific embodiment of the present invention, there is provided a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} ranging from 75 microns to 150 microns, D_{50} ranging from 150 microns to 500 microns and D_{90} ranging from 300 microns and 750 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} ranging from 75 microns to 150 microns, D_{50} ranging from 150 microns to 500 microns and D_{90} ranging from 300 microns and 750 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} ranging from 75 microns to 150 microns, D_{50} ranging from 150 microns to 500 microns and D_{90} ranging from 300 microns and 750 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form.

According to one embodiment, the present invention is said to provide a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate wherein not more than 30 % particles pass through a sieve mesh of 100 # and 100 % of the particles pass through a sieve mesh 18 # having an opening size of 1000 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

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Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate wherein not more than 30 % particles pass through a sieve mesh of 100 # and 100 % of the particles pass through a sieve mesh 18 # having an opening size of 1000 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form.

Particularly, the present invention, provides a solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate wherein not more than 30 % particles pass through a sieve mesh of 100 # and 100 % of the particles pass through a sieve mesh 18 # having an opening size of 1000 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form.

One embodiment of the present invention provides a solid dosage form that may include certain excipients such as disintegrants, lubricants or glidants. Since the tablets are compact in nature, it was found that there was no need or requirement of presence of a filler or diluents. In other words, it may be said that the compact solid dosage form of agglomerates of clopidogrel hydrogen sulphate having D_{10} of not less than 75 microns of the present invention is substantially free of diluents or fillers.

Suitable lubricants and glidants that may be used include, but are not limited to, magnesium stearate, zinc stearate, stearic acid, sodium stearyl fumarate, colloidal silicon dioxide, hydrogenated castor oil and talc and mixtures thereof. In one embodiment, colloidal silicon dioxide was found to provide good flow properties. In combination with stearic acid, compact tablets of agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns could be prepared easily. The lubricants may be present in an amount ranging from about 1 % to about 7 %, preferably 5 %. The lubricants can be used singly or in combination. In one embodiment stearic acid is used in the range of 0% to about 7% by weight of the tablet, preferably in the range of about 2% to about 5% by weight of the tablet. In

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another embodiment colloidal silicone dioxide is used in the range of 0% to about 7% by weight of the tablet, preferably in the range of about 2% to about 5% by weight of the tablet.

The solid dosage form of the present invention may include one or more disintegrants. The disintegrants described can be any pharmaceutically acceptable disintegrants, but are not limited to, such as low viscosity cellulose derivatives like hydroxypropyl cellulose, sodium starch glycolate, crospovidone, croscarmellose sodium, preferably crospovidone and/or croscarmellose sodium. Based on the tablet total weight, the disintegrant should be 0.1 %-20 % by weight, preferably 1.0%-15.0% by weight of the tablet. The amount of disintegrants may range from 0 % to 20 %, preferably 5 % to 15 % by weight of the tablets. In one embodiment, low viscosity cellulose derivatives like hydroxypropyl cellulose having a D_{50} of about 40 microns, was used. In one embodiment disintegrants used is crospovidone in the range of 0%-15% by weight of the tablet, preferably in the range of about 3% to about 13% by weight of the tablet.

In one embodiment, the solid dosage form of the present invention is a tablet, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the tablet, a lubricant present in an amount of 1 % to about 7 % by weight of the tablet and disintegrant is present in an amount of about 15 % by weight of the tablet.

In particular embodiment, the solid dosage form of the present invention is a tablet, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the tablet, a lubricant present in an amount of 1 % to about 7 % by weight of the tablet and disintegrant is present in an amount of about 15 % by weight of the tablet.

In particular embodiment, the solid dosage form of the present invention is a tablet, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the tablet, a lubricant present in an amount of 1 % to about 7 % by weight of the tablet and disintegrant is present in an amount of about 15 % by weight of the tablet.

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In one embodiment, the present invention provides a solid dosage form in the form of a tablet comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form, wherein the tablet comprises

1-7 weight % a mixture of lubricant;

about 15 % of a disintegrant

wherein the tablet is prepared by direct compression or dry granulation or wet granulation.

In particular embodiment, the present invention provides a solid dosage form in the form of a tablet comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 65 % by weight of the solid dosage form, wherein the tablet comprises

1-7 weight % a lubricant;

about 15 % of a disintegrant

wherein the tablet is prepared by dry granulation or dry granulation or wet granulation.

In particular embodiment, the present invention provides a solid dosage form in the form of a tablet comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 80 % by weight of the solid dosage form, wherein the tablet comprises

1-7 weight % a lubricant;

about 15 % of a disintegrant

wherein the tablet is prepared by wet granulation or dry granulation or wet granulation.

The solid dosage form of the present invention provided satisfactory chemical and physical stability. The chemical stability was determined by subjecting the compact tablets to accelerated conditions such as 40° C and 75% relative humidity for a period of three months, which

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corresponds to the shelf life of the product. The results of the stability studies revealed that the known as well as unknown impurities were under the acceptable limits. The known hydrolytic impurity (related compound A= (+) -(*S*)-(o-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4*H*)-acetic acid) was found to be less than 1%. Further, impurity B which is Methyl (-)-(*R*)-(o-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5(4*H*)-acetate, hydrogen sulfate, was under control, was found to be less than 0.5 % w/w.

Hereinafter, the invention will be more specifically described with reference to examples. The examples are not intended to limit the scope of the invention and are merely used as illustrations.

Example 1

Table 1: Formulation of the example 1 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	clopidogrel hydrogen sulphate	391.5	81.56
2	Crospovidone	60.5	12.6
3	Hydrated silicon dioxide	8.0	1.67
4	Stearic acid	20.0	4.17
Total weight of core tablet		480.0	100

Crospovidone, hydrated silicon dioxide were sifted through 40 # and stearic acid was sifted through 60#. The sifted material was mixed with the specified amounts of agglomerates of clopidogrel hydrogen sulphate having particle size distribution (70 % particles 100# oversize i.e., 70 % particles are more than 150 µm and 30 % particles 100 # undersize i.e., 30 % particles are less than 150 µm). The powder mixture was blended in a blender for 10 minutes. The lubricated blend was compressed into tablets. The compressed tablets were found to provide satisfactory physical attributes. Hardness was found to be 4-5 kP and the disintegration time was 4-5 minutes.

Particle size analysis by Malvern Mastersizer: About 50 mg sample was dispersed in 100 mL beaker containing 3-5 drops of chloroform to form slurry by mixing with a glass rod. To this was added 5 ml of cyclohexane and the dispersion contained in beaker was swirled. The beaker

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containing drug dispersion was sonicated exactly for 20 seconds to get a homogeneous suspension. This homogeneous suspension was used for measurement of particle size distribution.

The results of Malvern particle size analysis is as follows –

D 10 : 110.162 microns

D 50 : 208.531 microns

D 90 : 366.436 microns

The particle size distribution can also be evaluated using the sieve analysis using ASTM sieves.

Table 2: Sieve Analysis for the agglomerates of clopidogrel hydrogen sulphate is as follows:

Particle size range in µm	% Oversize	% Cumulative oversize
>800	zero	Zero
600-800	0.04	0.04
425-600	0.11	0.15
250-425	18.37	18.52
180-250	39.19	57.71
150-180	19.74	77.45
0-150	22.28	99.73

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Example 2

Table 3: Formulation of the example 2 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	Clopidogrel bisulphate	97.875	55.92
2	Microcrystalline cellulose	28.425	16.24
3	Mannitol	25.0	14.28
4	Hydrated silicon dioxide	8.5	4.86
5	Crospovidone	10.2	5.83
Coating solution			
6	Hydroxypropyl methyl cellulose (low viscosity)	3.1	1.77
7	Polyethylene glycol 6000	0.75	0.43
8	Talc	0.4	0.23
9	Titanium dioxide	0.7	0.4
10	Ferric oxide red	0.05	0.03
11	Isopropyl alcohol	q.s.	
12	Dichloromethane	q.s.	
Total weight of coated tablet		175.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (70 % particles are 100 # oversize i.e 70 % particles are more than 150 μm and 30 % particles 100 # undersize i.e 30 % particles are less than 150 μm) was used to make compressed tablets. Clopidogrel bisulphate, microcrystalline cellulose, mannitol, hydrated silicon dioxide and crospovidone were sifted through 40 # and mixed in a blender for 10 minutes. The blend was compressed into core tablets using 8.0 mm, standard concave punches plain on both sides. Core tablets were coated with the coating dispersion. The compressed core tablets were found to provide satisfactory physical attributes. Hardness was found to be 4-5 kP and the disintegration time was 1-2 minutes. The flow of the material was good, no sticking was observed.

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Example 3

Table 4: Formulation of the example 3 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	clopidogrel hydrogen sulphate	97.87	87.4
2	L-Hydroxypropyl cellulose (D_{50}=40 µm)	11.12	9.9
3	Stearic acid	3.0	2.67
Total weight of core tablet		112.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (50 % particles are 100 # oversize i.e 50 % particles are more than 150 µm and 50 % particles 100 # undersize i.e 50 % particles are less than 150 µm) was used to make compressed tablets. L-Hydroxypropyl cellulose was sifted through 40 #. Stearic acid was sifted through 60# and mixed in a blender for 10 minutes. The lubricated blend was compressed using 6.0 mm, standard concave punches plain on both sides. The compressed tablets were found to provide satisfactory physical attributes. Hardness was found to be 4-5 kP and the disintegration time was 5-6 minutes.

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Example 4

Table 5: Formulation of the example 4 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	clopidogrel hydrogen sulphate	97.87	81.56
2	Crospovidone	15.12	12.60
3	Hydrated silicon dioxide	2.0	1.66
4	Stearic acid	5.0	4.16
Total weight of core tablet		120.0	100.0

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (50 % particles are 100 # oversize i.e 50 % particles are more than 150 μm and 50 % particles 100 # undersize i.e 50 % particles are less than 150 μm) was used to make compressed tablets. Crospovidone and hydrated silicon dioxide were sifted through 40# and stearic acid was sifted through 60# and mixed with agglomerates of clopidogrel hydrogen sulphate. The sifted materials were mixed in blender for 10 minutes. This lubricated powder blend was compressed using a 6.0 mm, standard concave punches plain on both sides.

It was observed that by using about 4 % lubricants, good flow was obtained and there was no sticking during compression when about 500 tablets were compressed. The compressed tablets were found to provide satisfactory physical attributes. Hardness was found to be 4-5 kP and the disintegration time was 4-5 minutes.

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Example 5

Table 6: Formulation of the example 5 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	clopidogrel hydrogen sulphate	97.88	81.6
2	Crospovidone	15.13	12.6
3	Hydrated silicon dioxide	2.0	1.7
4	Stearic acid	5.0	4.2
Total weight of core tablet		120.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (100 % of the particles 100 # oversize i.e 100 % of the particles are more than 150 μm), crospovidone and hydrated silicon dioxide were sifted through 40# and stearic acid through 60# and mixed in a blender for 10 minutes. The lubricated powder blend was compressed using a 6.0 mm, standard concave punches plain on both sides. It was observed that by using about 6 % lubricants, good flow was obtained and there were no issues of sticking during compression.

The compressed tablets were found to provide satisfactory physical attributes. Hardness was found to be 4-5 kP and the disintegration time was 4-5 minutes.

Particle size analysis by Malvern Mastersizer: About 50 mg sample was dispersed in 100 mL beaker containing 3-5 drops of chloroform to form slurry by mixing with a glass rod. To this was added 5 ml of cyclohexane and the dispersion contained in beaker was swirled. The beaker Containing drug dispersion was sonicated exactly for 20 seconds to get a homogeneous suspension. This homogeneous suspension was used for measurement of particle size distribution.

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The results of Malvern particle size analysis is as follows –

D 10 : 142.403 microns

D 50 : 221.714 microns

D 90 : 342.637 microns

The particle size distribution can also be evaluated using the sieve analysis using ASTM sieves.

Table 7: Sieve Analysis for the agglomerates of clopidogrel hydrogen sulphate is as follows:

Particle size range in µm	% Oversize	% Cumulative oversize
>800	zero	Zero
600-800	0.7	0.7
425-600	0.43	1.13
250-425	24.67	25.80
180-250	50.50	76.30
150-180	17.70	94.00
0-150	6.0	100.00

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Example 6

Table 8: Formulation of the example 6 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	Clopidogrel bisulphate	97.85	55.91
2	Microcrystalline cellulose	54.25	31.00
3	Colloidal silicon dioxide	5.10	2.91
4	Crospovidone	8.50	4.85
5	Hydrogenated castor oil	4.30	2.45
Coating solution			
6	Hydroxypropyl methyl cellulose (low viscosity)	3.10	1.77
7	Polyethylene glycol 6000	0.75	0.42
8	Talc	0.40	0.22
9	Titanium dioxide	0.70	0.4
10	Ferric oxide red	0.05	0.02
11	Isopropyl alcohol	26.5	15.14
12	Methylene chloride	40.00	22.85
Total weight of coated tablet		175.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (75 % particles are 100 # oversize i.e 75 % particles are more than 150 μm and 25 % particles 100 # undersize i.e 25 % particles are less than 150 μm) was used to make compressed tablets. Clopidogrel bisulphate sifted through 20 #, microcrystalline cellulose, colloidal silicon dioxide and crospovidone were sifted through 40 # and mixed in a blender for 15 minutes. Hydrogen castor oil sifted through 60 # and blend was lubricated for 5 minutes. The lubricated blend was compressed into core tablets using 8.0 mm, standard concave punches plain on both sides. Core tablets were coated with the coating dispersion. The compressed core tablets were found to

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provide satisfactory physical attributes. Disintegration time was 3-6 minutes. The flow of the material was good, no sticking was observed.

Table 9: Results of the Stability data of formulation of example 6

Condition	Initial	40/75% RH		
		1	2	3
Assay	97.80	98.54	97.78	98.63
Dissolution (NLT 80% (Q) in 30 minutes)	101	97	99	99
Related Substances				
Related compound A (Hydrolytic impurity) (NMT 1.2%)	0.063	0.095	0.126	0.162
Related compound C (Chiral impurity) (NMT 1.5%)	0.139	0.161	0.201	0.251
Highest unknown excluding Related compound B (NMT 0.2%)	0.031	ND	0.031	0.054
Total impurity excluding Related compound B (NMT 2.5%)	0.202	0.256	0.360	0.490
Disintegration time	150 sec	187 sec	157 sec	129 sec
Water Content	4.860	5.770	3.340	3.180

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Example 7

Table 10: Formulation of the example 7 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	Clopidogrel bisulphate	97.85	67.48
2	Microcrystalline cellulose	24.65	17.00
3	Colloidal silicon dioxide	2.60	1.79
4	Crospovidone	11.00	7.58
5	Sodium stearyl fumarate	3.90	2.68
Coating solution			
6	Hydroxypropyl methyl cellulose (low viscosity)	3.625	2.5
7	Polyethylene glycol 6000	0.750	0.517
8	Talc	0.203	0.14
9	Titanium dioxide	0.381	0.26
10	Ferric oxide red	0.041	0.02
11	Purified water	37.50	25.86
Total weight of coated tablet		145.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (85 % particles are 100 # oversize i.e 85 % particles are more than 150 μm and 15 % particles 100 # undersize i.e 15 % particles are less than 150 μm) was used to make compressed tablets. Clopidogrel bisulphate sifted through 20 #, microcrystalline cellulose, colloidal silicon dioxide, crospovidone and sodium stearyl fumarate were sifted through 40 # and mixed in a blender for 30 minutes. The blend was compressed into core tablets using 6.5 mm, standard concave punches plain on both sides. Core tablets were coated with the coating dispersion. The compressed core tablets were found to provide satisfactory physical attributes. Disintegration time was 3-6 minutes. The flow of the material was good, no sticking was observed.

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Table 11: Results of the Stability data of formulation of example 7

Condition	Initial	40/75% RH		
		1	2	3
Assay	102.41	101.46	102.06	100.7
Dissolution (NLT 80% (Q) in 30 minutes)	98	101	98	101
Related Substances				
Related compound A (Hydrolytic impurity) (NMT 1.2%)	0.070	0.078	0.093	0.107
Related compound C (Chiral impurity) (NMT 1.5%)	0.204	0.234	0.252	0.307
Highest unknown excluding Related compound B (NMT 0.2%)	0.080	0.072	0.156	0.140
Total impurity excluding Related compound B (NMT 2.5%)	0.354	0.484	0.658	0.704
Disintegration time	12.00	7.00	4.83	3.58
Water Content	2.240	2.170	1.630	3.610

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Example 8

Table 12: Formulation of the example 8 according to the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	Clopidogrel bisulphate	97.85	78.91
2	Microcrystalline cellulose	1.35	9.15
3	Colloidal silicon dioxide	4.80	3.87
4	Crospovidone	3.00	2.41
5	Hydrogenated castor oil	3.00	2.41
Coating solution			
6	Hydroxypropyl methyl cellulose (low viscosity)	2.90	2.33
7	Polyethylene glycol 6000	0.60	0.48
8	Talc	0.18	0.14
9	Titanium dioxide	0.30	0.24
10	Ferric oxide red	0.02	0.016
11	Isopropyl alcohol	21.20	17.09
12	Methylene chloride	31.80	25.64
Total weight of coated tablet		124.0	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (75 % particles are 100 # oversize i.e 75 % particles are more than 150 μm and 25 % particles 100 # undersize i.e 25 % particles are less than 150 μm) was used to make compressed tablets. Clopidogrel bisulphate sifted through 20 #, microcrystalline cellulose, colloidal silicon dioxide and crospovidone were sifted through 40 # and mixed in a blender for 15 minutes. Hydrogen castor oil sifted through 60 # and blend was lubricated for 5 minutes. The lubricated blend was compressed into core tablets using 6.0 mm, standard concave punches plain on both sides. Core tablets were coated with the coating dispersion. The compressed core tablets were found to provide satisfactory physical attributes. Disintegration time was 3-6 minutes. The flow of the material was good, no sticking was observed.

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Table 13: Results of the Stability data of formulation of example 8

Condition	Initial	40/75% RH		
		1	2	3
Assay	95.84	98.24	99.53	98.59
Dissolution (NLT 80% (Q) in 30 minutes)	94	91	90	89
Related Substances				
Related compound A (Hydrolytic impurity) (NMT 1.2%)	0.083	0.139	0.248	0.342
Related compound C (Chiral impurity) (NMT 1.5%)	0.135	0.183	0.212	0.310
Highest unknown excluding Related compound B (NMT 0.2%)	0.024	0.051	0.020	0.035
Total impurity excluding Related compound B (NMT 2.5%)	0.267	0.373	0.497	0.709
Disintegration time	600 sec	510 sec	911 sec	700 sec
Water Content	1.790	2.190	1.190	1.840

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Example 9

Table 14: Formulation of the example 9 of the present invention

Sr. No	Ingredients	mg/tablet	% w/w
1	Clopidogrel bisulphate	32.625	66.58
2	Microcrystalline cellulose	9.475	19.33
3	Colloidal silicon dioxide	0.233	0.47
4	Crospovidone	3.267	6.66
5	Sodium stearyl fumarate	1.400	2.85
Coating solution			
6	Hydroxypropyl methyl cellulose (low viscosity)	1.450	2.95
7	Polyethylene glycol 6000	0.316	0.64
8	Talc	0.082	0.16
9	Titanium dioxide	0.152	0.31
10	Purified water	54.000	q.s
Total weight of coated tablet		49.000	

Agglomerates of clopidogrel hydrogen sulphate having the following particle size distribution (60 % particles are 100 # oversize i.e 60 % particles are more than 150 μm and 40 % particles 100 # undersize i.e 40 % particles are less than 150 μm) was used to make compressed tablets. Clopidogrel bisulphate sifted through 20 #, microcrystalline cellulose, colloidal silicon dioxide, crospovidone and sodium stearyl fumarate were sifted through 40 # and mixed in a blender for 30 minutes. The blend was compressed into core tablets using 5.00 mm, standard concave punches plain on both sides. Core tablets were coated with the coating dispersion. The compressed core tablets were found to provide satisfactory physical attributes. Disintegration time was 1-3 minutes. The flow of the material was good, no sticking was observed.

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We claim

1. A solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{10} is not less than 75 microns, wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

2. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{50} is not less than 150 microns.

3. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate having a particle size distribution such that D_{90} is not more than 750 microns.

4. A solid dosage form as claimed in claim 1 wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 75 % by weight of the solid dosage form.

5. A solid dosage form comprising agglomerates of clopidogrel hydrogen sulphate wherein not more than 30 % particles pass through a sieve mesh of 100 # and 100 % of the particles pass through a sieve mesh 18 # having an opening size of 1000 microns and wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the solid dosage form.

6. A solid dosage form as claimed in claim 5 wherein agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 75 % by weight of the solid dosage form.

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7. A solid dosage form as claimed in claim 1 wherein the dosage form is a tablet and

wherein the agglomerates of clopidogrel hydrogen sulphate are present in an amount of at least 55 % by weight of the tablet,

a lubricant is present in an amount of 1 % to about 7 % by weight of the tablet and disintegrant is present in an amount of about 15 % by weight of the tablet.

Dated this 10th day of July 2014

SUNIL AJMERA

COMPANY SECRETARY

SUN PHARMACEUTICAL INDUSTRIES LTD.

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