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(54) **Title:** COMPACT SOLID DOSAGE FORM OF ASPIRIN AND CLOPIDOGREL

(57) **Abstract:** The present invention provides a solid dosage form comprising two active pharmaceutical agents; acetylsalicylic acid and clopidogrel or pharmaceutically acceptable salts thereof, wherein the total amount of these active pharmaceutical agents present in the solid dosage form is more than 55% of the total weight of the solid dosage form, and wherein clopidogrel is released immediately upon contact with aqueous environment.



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COMPACT SOLID DOSAGE FORM OF ASPIRIN AND CLOPIDOGREL

FIELD OF THE INVENTION

The present invention provides a solid dosage form comprising two active pharmaceutical agents; acetylsalicylic acid and clopidogrel or pharmaceutically acceptable salts thereof, wherein the solid dosage form is compact.

BACKGROUND OF THE INVENTION

There are many reports showing advantages of concurrent administration of clopidogrel and aspirin owing to mutual complementary antiplatelet action. Acetylsalicylic acid, also known as Aspirin, is often used as an analgesic, antipyretic and anti-inflammatory. Acetylsalicylic acid is stable in dry air, but gradually hydrolyses in contact with moisture to acetic acid and salicylic acid. In solution with alkalis, the hydrolysis proceeds rapidly and the clear solutions formed may consist entirely of acetate and salicylate. Acetylsalicylic acid decomposes rapidly in solutions of ammonium acetate or of the acetates, carbonates, citrates or hydroxides of the alkali metals. Aspirin is a substituted phenyl ester and has good leaving group due to the presence of an aromatic ester. This makes it unstable in moist conditions and it gets easily hydrolyzed in weakly alkaline medium. Thus the pH is always maintained to control the stability and composition of aspirin drug. Increase in temperature, humidity, etc. leads to degradation of acetyl salicylic acid into salicylic acid. At a relative humidity level of 35, 50 and 75 %, the enteric coated tablets degrades less as compared to core aspirin tablet. Salicylic acid can have serious effects on gastric mucosa and on direct exposure it may cause severe reaction in stomach such as vomiting, allergic reactions, swelling and stomach bleeding. This is why enteric coated aspirin was designed to reduce these reactions as it does not get dissolved in stomach immediately. Enteric coating prevents tablets from hydrolysis while the core being in uncoated form immediately degrades into salicylic acid in stomach. Clopidogrel bisulfate is practically insoluble in water at neutral pH but is freely soluble at pH 1.0. It also dissolves freely in methanol; it dissolves sparingly in methylene chloride, and is insoluble in ethyl ether. It is known that clopidogrel or its salt has poor handling properties, which makes it difficult to formulate into pharmaceutical compositions.

Clopidogrel or its salt, including clopidogrel bisulfate, exhibits an interaction with conventionally used pharmaceutical excipients, which also brings about stability problems. In

addition, the high surface static electricity of clopidogrel or its salt also causes sticking to the punches during the manufacture of tablets, which makes it difficult to perform industrial mass production. The difficulty to formulate clopidogrel along with another drug like aspirin adds to the complications while preparing a combination of clopidogrel and aspirin in a single unit dosage form.

The therapeutic advantage of the combination of acetylsalicylic acid (or aspirin) and clopidogrel is known in the art. Many such combinations are disclosed in patent applications such as WO97/29753, US2011/0038931A1, WO2013/133620A1 and WO2015/014766A1. None of the references in the literature, have provided a means of making a very small, easy to swallow solid dosage form having both these active ingredients, in a single dosage form. There lies an urgent need of a significantly smaller sized solid dosage form having acetylsalicylic acid (or aspirin) and clopidogrel that would make better patient compliance, particularly geriatric and patients suffering from dysphagia, who face difficulty in swallowing large tablets.

The present inventors have found an improved solid dosage form containing acetyl salicylic acid and clopidogrel or their pharmaceutically acceptable salts that possesses advantages in that the solid dosage form is compact, and thus, makes administration easy, particularly, for a geriatric patient population or patients suffering from dysphagia. Further, it is found that the solid dosage form according to the present invention is stable.

SUMMARY OF THE INVENTION

The present invention relates to a solid dosage form comprising two active pharmaceutical agents; acetylsalicylic acid and clopidogrel or pharmaceutically acceptable salts thereof, wherein the total amount of these active pharmaceutical agents present in the solid dosage form is more than 55% of the total weight of the solid dosage form, and wherein clopidogrel is released immediately upon contact with aqueous environment.

Particularly, it relates to a solid dosage form which is in the form of a tablet comprising

- a) a compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients;

- b) an enteric coating surrounding the compressed core of (a); and
- c) a layer comprising clopidogrel or pharmaceutically acceptable salts thereof, surrounding the compressed core (b).

5 DETAILED DESCRIPTION OF THE INVENTION

The term 'compact' as used herein mean that the solid dosage form of the present invention is such that the both the active ingredients. i.e aspirin and clopidogrel it its pharmaceutically acceptable salt are present in a single unit and their amounts in the single unit is more than 55% by weight, for eg., 55,56,57,58,59,60, 61, 62, 63, 64,65, 66, 67, 68 ,69, 71, 72, 73, 74, 10 75% by total weight of the solid dosage form. This means that the single unit compact solid dosage form such as a compressed tablet, may contain about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35%, 36, 37, 38,39,40,41,42,43,44, or 45% of inert excipients other than the active ingredients. When the solid dosage form is a compressed tablet, the ratio of the diameter of the tablet to the thickness/height of the tablet is less than 1.9, preferably, less than about 1.8, 15 most preferably 1.5. The diameter is between 7 mm to 12 mm, for eg. 8, 9, 10, 11 mm and width of less than 5.5 mm, for eg., 3,4,5,5.1,5.2, 5.3, 5.4, 5.5 or 5.6 mm.

The term 'stable' as used herein means the active ingredient maintain the therapeutically effective amounts throughout the shelf life of the product. This can be determined by real time studies or accelerated storage conditions. The assay of the each drug along with the 20 known and unknown impurities may be determined by methods known in the art.

The term 'wherein the clopidogrel is released immediately upon contact with aqueous environment' means that upon oral ingestion, the clopidogrel part is released without any delay and there is no lag time.

The solid dosage form contains 50 mg to 200 mg of aspirin, such as, 50, 51,52,53,54,55,56, 25 57, 58, 59, 60, 610, 62,63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75 mg. or it may be to 150 mg per unit solid dosage form. The amount of aspirin present in the unit solid dosage form ranges from 25 % to 50 % by weight.

In an embodiment of the current invention, the acetylsalicylic acid in the solid dosage form is present in an amount ranging from 50 mg to 200 mg, preferably 60 mg to 175 mg and most 30 preferably 70 mg to 160 mg. Similarly, in another embodiment in accordance of the current invention the amount of clopidogrel present ranges from 80 mg to 120 mg, preferably 90 mg

- to 110 mg and most preferably 95 mg to 105 mg. The solid dosage form of the present invention may be available in different embodiments, such as, one, contains 97.875 mg of clopidogrel hydrogen sulphate (equivalent to 75 mg clopidogrel) and 75 mg of acetylsalicylic acid and another contains 97.875 mg of clopidogrel hydrogen sulphate (equivalent to 75 mg clopidogrel) and 100 mg of acetylsalicylic acid. In embodiment where aspirin is present as 150 mg and clopidogrel (as sulfate) is present as 75 mg, and solid dosage form is a compressed tablet, the dimensions of the circular tablet are: diameter of about 5 to 10.5 mm, more preferably 8 to 10 mm and thickness of about 3 to 7 mm, more preferably 4 mm to 5.6 mm.
- 10 The weight percentage of the acetylsalicylic acid is between 20 % to 50% total weight of dosage form, more preferably 25% to 45% total weight of dosage form. The weight percentage of clopidogrel or its pharmaceutically acceptable salt present in the solid dosage form ranges from 15% to 45%, more preferably 20% to 40% by total weight of the solid dosage form. In another embodiment of the current invention, the total weight of the dosage form ranges from 225 mg to about 475 mg, preferably 250 mg to 450 mg and most preferably 250 mg to 400 mg.

In specific embodiments, the solid dosage form is a compressed tablet. The tablet contains a

- a) a compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients;
- 20 b) an enteric coating surrounding the compressed core of a); and
- c) a layer comprising clopidogrel or pharmaceutically acceptable salts thereof, surrounding the compressed core (b).

The compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients is prepared by techniques known in the art such as wet granulation, dry granulation, direct compression. Excipients compatible with acetyl salicylic acid are mixed together and converted into either granules or extrudates. These are then compressed into the core. The compressed core is then coated with enteric polymer. Enteric coating is required to delay the release of aspirin, in the stomach as it causes irritation to the gastric mucosa. The enteric polymers used in the present invention is not limited to Methacrylic Acid Copolymer (Eudragit L 100-55), Eudragit L 30D 55, Hypromellose Acetate succinate (AS-LF), methacrylate copolymers, hypromellose phthalate, cellulose acetate phthalate, hypromellose acetate succinate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl

methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, poly(methacrylic acid, methyl methacrylate) 1:1; poly (methacrylic acid, ethyl acrylate) 1:1; and compatible mixtures thereof. The amount of enteric polymers used may range from 5% to 25%, preferably from 10% to 20% of the total weight of the compressed core.

The solid dosage form further contains clopidogrel or its pharmaceutically acceptable salt, in the form of layer surrounding the compressed core of aspirin. The deposition of layer of clopidogrel on the enterically coated aspirin core, was critical. In that, the clopidogrel or its pharmaceutically acceptable salt when deposited on the enteric coated acetyl salicylic acid, using non aqueous medium, for eg. isopropyl alcohol, dichloromethane, having very low amount of water, such solid dosage form was also stable, when stored under accelerated conditions. Furthermore, it was found by inventors that advantageously the solid dosage form of the present invention was stable inspite of having no coating between the core of the acetyl salicylic acid or the enteric coating and/or in between the enteric layer and the layer comprising clopidogrel or pharmaceutically acceptable salts thereof.

It may be noted that the compact nature of the solid dosage form is achieved because of the very less amount of the inert excipients used in the layer of the clopidogrel containing composition. The need of not using many excipients may be attributed to the use of very fine particle size distribution of clopidogrel or its pharmaceutically acceptable salt. In one specific embodiment, the particle size distribution of the clopidogrel or its pharmaceutically acceptable salt is such that D_{50} is less than 50 microns and D_{90} is less than 25 microns. Particularly, the particle size distribution of clopidogrel or its salt is such that it enables spray coating of its suspension very efficiently without any process related issues. In one specific embodiment, the present inventors prepared the compact tablet by spray coating clopidogrel or its pharmaceutically acceptable salt, onto the core containing aspirin. The core of aspirin may be enterically coated with an enteric polymer. In the embodiment, where clopidogrel is spray coated on the core of aspirin that is enterically coated, this is generally achieved by dissolving and/or suspending clopidogrel or its pharmaceutically acceptable salt in a non-aqueous solvent, along with low viscosity polymers as suspending agents. The layer on the compressed core containing clopidogrel and polymers includes, but is not limited to, various grades of hydroxypropyl methyl cellulose, known in the art in a suspension of non-aqueous solvents. The polymers used in the coating layer are between 3 to 12%, preferably 4 to 10% of the total weight of the tablet. In such embodiments, the clopidogrel drug to binder ratio is

95:5 to 60:40; more preferably, 85:15 to 75:25. At these ratios, it is possible to achieve a compact size of the tablet. In addition, such a range permits less processing time and accomplish significant stability. A further increase in quantity of binder or excipient at drug layering stage may lead to increase in the size of the tablet as layering components are increased; processing time may get increased to many folds; and also it may lead to challenges in stability as Clopidogrel is sensitive to moisture, number and quantum of excipients.

The non-aqueous solvent used in the present invention includes are those known in the art but is not limited to Isopropyl Alcohol, ethanol, Acetone, Methylene Chloride, dichloromethane, Triethyl citrate or liquid mixtures thereof.

The seal coating of the dosage form of the present invention, includes, but is not limited to, polymers like low viscosity grades of hydroxypropyl methyl cellulose, polyethylene Glycol etc and combination thereof. The seal coating layer of the present invention is between 3 to 12%, preferably 4 to 10% of the total weight of the tablet.

It is also possible to however, apply the coating of clopidogrel or its pharmaceutically salts, by a powder coating technique, with limited use of any solvent. It is important to note that the particle size distribution of the clopidogrel sulphate is such that it contains majority of fines. In one specific embodiment, the D_{50} is less than 50 microns and D_{90} less than 25 microns. In one specific embodiment, the D_{90} of clopidogrel or its pharmaceutically acceptable salt is less than 20 microns, preferably, 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 or 20 microns. Suitably, the clopidogrel used is a sulfate salt. Clopidogrel or pharmaceutical acceptable salt thereof may be in either of the polymorphic forms form I or form II.

In an embodiment of the present invention, the dosage form is a capsule, pellet, granule, tablet, minitabets, caplets etc. The tablet of the present invention may be in a form such as tablets, pellet, minitabets or minipellet. The powder or granules may also be filled into hard gelatin capsules.

A unit of solid dosage form as a tablet may contain about 25 to 45 %, preferably 20 to 30 % of inert excipients. The inert excipients used are the ones used conventionally known in the art. The excipients include, but are not limited to, diluent, a binder, a lubricant, coloring agents etc. Examples of the diluent include microcrystalline cellulose (for example, CeolusTM), starch, pregelatinized starch, lactose, corn starch etc. Examples of the binder

include, but are not limited to, hydroxypropyl cellulose, Copovidone etc. Examples of the lubricant include talc, zinc stearate, magnesium stearate, colloidal silicon dioxide, etc. Examples of the coloring agents includes metal oxides like titanium dioxide, iron oxide red, iron oxide yellow, iron oxide black; aluminium lakes; FD&C Blue # 2 (indigo carmine);
 5 FD&C Blue # 1 (brilliant blue); FD&C yellow # 6 (sunset yellow) etc.

While the present invention is disclosed generally above, additional aspects are further discussed and illustrated with reference to the examples below. However, the examples are presented merely to illustrate the invention and should not be considered as limitations
 10 thereto.

EXAMPLES 1

Table 1: Composition details of tablet comprising Acetylsalicylic acid and Clopidogrel

Ingredients		mg per compact tablet	% by weight of individual layer	% by wt. of tablet
Compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients	Acetylsalicylic Acid	150.0	66.66	39.5
	Corn Starch	21.0	9.3	5.5
	Tartaric acid	15.0	6.7	3.9
	Microcrystalline cellulose	30.0	13.3	7.9
	Stearic acid	2.0	0.9	0.53
	Polyvinyl pyrrolidone and polyvinyl acetate copolymer	5.0	2.2	1.32
	Colloidal Silicon Dioxide	2.0	0.9	0.53
Enteric coating surrounding the core	Poly(methacrylic acid-co-ethyl acrylate) 1:1	20.8	83.4	5.5
	Triethyl citrate	2.10	8.3	0.6
	Colloidal Silicon Dioxide	2.10	8.3	0.6
Coating comprising clopidogrel or pharmaceutically acceptable salts	Clopidogrel Bisulfate	97.8	85.1	25.8
	Isopropyl Alcohol	-	-	-
	Methylene chloride	-	-	-
	Hypromellose	?	?	?
Seal coating	Hydroxypropyl	28.0	72.3	7.4

	methylcellulose			
	PEG 6000	2.3	15.3	0.6
	Talc	0.6	4.06	0.16
	Titanium Dioxide	1.1	7.3	0.003
	Ferric oxide	0.15	1	0.04

Corn Starch, Tartaric Acid, Microcrystalline cellulose PH 112, Stearic Acid, Copovidone (Kollidone VA 64) and Colloidal Silicon Dioxide are shifted through # 40 sieve using a mechanical sifter. Aspirin and the sifted material are transferred to a blender and mixed for 15 minutes. Tablets are compressed using suitable tooling having prefixed average weight.

Methacrylic Acid (Eudragit L 100-55) is dispersed in isopropyl alcohol with continuous stirring. Triethyl citrate and colloidal silicone dioxide are added to the above dispersion with continuous stirring and further acetone is added with continuous stirring. The acetylsalicylic acid core tablets of step 1 are coated with above enteric coating suspension.

A colloidal suspension is prepared by mixing clopidogrel bisulfate with required amount of isopropyl alcohol and methylene chloride by stirring for 30 minutes. After obtaining a homogenous colloidal suspension hypromellose and remaining solvent is added and mixture stirred slowly and continuously. Enteric coated aspirin tablets are coated with above clopidogrel drug layering suspension. The drug layers tablets were kept for drying for 1 hour.

Hydroxypropyl methylcellulose is dispersed in purified water at 65-80°C with continuous stirring. Remaining quantity of purified water is added in to the above dispersion with continuous stirring and is allowed to cool to get a clear solution. Polyethylene glycol 6000 is added into it with continuous stirring and allowed to dissolve.

Talcum, Titanium dioxide and Ferric oxide (Red) are colloid milled in 4.0 kg of Purified water and are added in to polymer solution of step 1 under stirring. The remaining quantity of Purified water is used for rinsing purpose and added to the above solution.

Dimensions of the above tablet are as follows:

Diameter	9.9 mm
Thickness	5.6 mm
Total Avg. Wt	380.00 mg

The compact tablets prepared as per the present invention were packed in Aluminum Aluminum blister pack and were stored at ambient conditions or accelerated storage

conditions and analysed for the chemical assay of each drug. Further, the in vitro dissolution was determined at initial time points and the results are provided as below:

Condition	Initial	40/75% relative humidity _6 Months
Assay of Aspirin	104.2	94.84
Assay of Clopidogrel	101.1	96.77
Clopidogrel Related comp. C (Chiral Impurity)	Not Detected	0.133
Clopidogrel Related comp. A (Hydrolytic Impurity)	0.023	1.12
Salicylic acid	0.365	5.147
Total Impurities	0.042	1.284

Content Uniformity is verified at R&D Scale. Results are presented below:

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Uniformity of dosage unit by content uniformity		
	Aspirin	Clopidogrel
Mean	97.64	99.02
Minimum	92.23	92.22
Maximum	103.15	107.34
% RSD	3.05	4.82
Acceptance Value	8.01	11.45

- 10 **In vitro Dissolution Testing and results:** *Media for Aspirin includes* 0.1 M Hydrochloric acid followed by mixed phosphate buffer pH 6.8, Basket, 100RPM, 900ml. 2 Hrs. in acid stage and 15, 30, 45, 60 minutes in buffer stage. Not more than 10% in acid stage and not less than 70%(D) in 45 mins in buffer stage.

Media for Clopidogrel includes 0.1 M Hydrochloric acid, Basket, 100RPM, 900 ml.

- 15 Time points: 15,30,45 minutes, no less than 80% (Q) in 30 mins.

Dissolution of Aspirin (min)	Initial	40/75% Relative Humidity 6 Months
2 hours	0	0
45 min	93	90
Dissolution of Clopidogrel (min)		
30 min	99	92

20

EXAMPLES 2

Example 2 is made using 100mg of Acetylsalicylic Acid and 97.9mg of Clopidogrel Bisulfate along with proportionate amount of excipients as used in Example 1. The compact tablets are prepared using the same method of Example 1.

- 5 Dimensions of the above tablet are as follows:

Diameter	8.9 mm
Thickness	5.1 mm
Total Avg. Wt	300.00 mg

EXAMPLES 3

- 10 Example 3 is made using 75mg of Acetylsalicylic Acid and 97.9mg of Clopidogrel Bisulfate along with proportionate amount of excipients as used in Example 1. The compact tablets are prepared using the same method of Example 1.

Dimensions of the above tablet are as follows:

Diameter	8.3 mm
Thickness	5.6 mm
Total Avg. Wt	262.50 mg

EXAMPLES 4

- 15 Example 4 is prepared using 75mg of Acetylsalicylic Acid and 97.8 mg of Clopidogrel Bisulfate along with proportionate amount of excipients as used in Example 1.

Ingredients		mg per compact tablet	% by weight of individual layer	% by wt. of tablet
Compressed core comprising Aspirin and pharmaceutically acceptable excipients	Acetylsalicylic acid (Crystalline grade)	75.00	68.18	27.77
	Corn Starch	10.00	9.09	3.70
	Tartaric Acid	5.00	4.55	1.85
	Microcrystalline Cellulose (Avicel PH 112)	13.00	11.81	4.81
	Stearic Acid	1.00	0.91	0.37
	Crospovidone Xl type A	5.50	5.00	2.03
	Colloidal silicon Dioxide	0.50	0.45	0.19
Seal coating surrounding the core	Hypromellose (Methocel E15)	6.67	83.37	2.47

	Premium)			
	Polyethylene Glycol 6000	1.33	16.62	0.49
	Isopropyl Alcohol	42.50	-	-
	Methylene Chloride	63.70	-	-
Enteric coating surrounding the seal coated core	Eudragit L 30 D 55	8.69	72.35	3.22
	Triethyl citrate	1.73	14.40	0.64
	Talc	1.59	13.23	0.59
	Water	27.74	-	-
Coating comprising clopidogrel or pharmaceutically acceptable salts	Clopidogrel Bisulfate	97.85	83.63	36.24
	Hypromellose (Methocel E3LV Premium)	19.150	16.36	7.09
	Acetone	276.00	-	-
	Methylene Chloride	184.00	-	-
Seal coating	Hypromellose (Methocel E15 Premium)	14.26	62.00	5.28
	Polyethylene Glycol 6000	3.45	15.00	1.28
	Talc	2.76	12.00	1.02
	Titanium Dioxide	2.30	10.00	0.85
	Ferric oxide (Yellow)	0.23	1.00	0.09
	Isopropyl Alcohol	144.10	-	-
	Methylene Chloride	216.11	-	-
	Total Avg. wt.	270.00	-	100.00

Dimensions of the above tablet are as follows:

Diameter	8.05
Thickness	5.55
Total Avg. Wt	270.00

The compact tablets prepared as per the present invention were packed in Aluminum
 5 Aluminum blister pack and were stored at ambient conditions or accelerated storage conditions and analysed for the chemical assay of each drug. Further, the in vitro dissolution was determined at initial time points and the results are provided as below:

Condition	Initial
Assay of Aspirin	99.66
Assay of Clopidogrel	96.17
Clopidogrel Related comp. C (Chiral Impurity)	0.569

Clopidogrel Related comp. A (Hydrolytic Impurity)	0.238
Salicylic acid	1.495
Total Impurities	0.815

In vitro Dissolution Testing and results: Media for Aspirin includes 0.1 M Hydrochloric acid followed by mixed phosphate buffer pH 6.8, Basket, 100RPM, 900ml. 2 Hrs. in acid stage and 15, 30, 45, 60 minutes in buffer stage
 5 Not more than 10% in acid stage and not less than 70%(D) in 45 mins in buffer stage.

Media for Clopidogrel includes 0.1 M Hydrochloric acid, Basket, 100RPM, 900 ml. Time points: 15,30,45 minutes, no less than 80% (Q) in 30 mins.

Dissolution of Aspirin (min)	Initial
2 hours	0
45 min	80
Dissolution of Clopidogrel (min)	
30 min	93

Content Uniformity is verified at R&D Scale. Results are presented below:

Uniformity of dosage unit by content uniformity		
	Aspirin	Clopidogrel
Mean	97.52	93.62
Minimum	92.90	90.80
Maximum	101.37	97.33
% RSD	2.61	2.15
Acceptance Value	7.10	9.70

Content Uniformity is also verified at scale up studies. Results are presented below:

Uniformity of dosage unit by content uniformity		
	Aspirin	Clopidogrel
Mean	99.10	99.08
Minimum	95.97	90.80
Maximum	101.37	95.25
% RSD	2.15	3.02
Acceptance Value	5.11	7.18

EXAMPLE 5

Tablets as per the Example 5 were prepared as per the procedure given in Example 1.

Ingredients		mg per compact tablet	% by weight of individual layer	% by wt. of tablet
Compressed core comprising Aspirin and pharmaceutically acceptable excipients	Acetylsalicylic acid (Finer grade)	75.00	68.18	27.27
	Corn Starch	10.00	9.09	3.64
	Tartaric Acid	5.00	4.55	1.82
	Microcrystalline Cellulose (Avicel PH 112)	13.00	11.82	4.73
	Stearic Acid	1.00	0.91	0.36
	Crosspovidone XL Type A	5.50	5.00	2.00
	Colloidal silicon Dioxide	0.50	0.45	0.18
Seal coating surrounding the core	Hydroxypropyl cellulose (Type SSL)	12.00	100.00	4.36
	Isopropyl Alcohol	159.42	-	-
Enteric coating surrounding the seal coated core	Hypromellose Acetate succinate (AS-LF)	12.26	94.34	4.46
	Triethyl citrate	0.74	5.66	0.27
	Isopropyl Alcohol	121.80	-	-
	Acetone	81.20	-	-
Coating comprising clopidogrel or pharmaceutically acceptable salts	Clopidogrel Bisulfate	97.85	83.63	35.58
	Hypromellose (Methocel E3LV Premium)	19.15	16.37	6.96
	Acetone	276.00	-	-
	Methylene Chloride	184.00	-	-
Seal coating	Hypromellose (Methocel E15 Premium)	14.26	62.00	5.19
	Polyethylene Glycol 6000	3.45	15.00	1.25
	Talc	2.76	12.00	1.00
	Titanium Dioxide	2.30	10.00	0.84
	Ferric oxide (yellow)	0.23	1.00	0.08
	Isopropyl Alcohol	144.10	626.52	
	Methylene Chloride	216.11	939.61	
	Total Avg. wt	275.00	-	100.00

Dimensions of the above tablet are as follows:

Diameter	8.10
Thickness	5.85
Total Avg. Wt	275.00

The compact tablets prepared as per the present invention were packed in Aluminum Aluminum blister pack and were stored at ambient conditions or accelerated storage conditions and analysed for the chemical assay of each drug. Further, the in vitro dissolution

5 was determined at initial time points and the results are provided as below:

Condition	Initial
Assay of Aspirin	100.35
Assay of Clopidogrel	98.6
Clopidogrel Related comp. C (Chiral Impurity)	0.879
Clopidogrel Related comp. A (Hydrolytic Impurity)	0.257
Salicylic acid	0.54
Total Impurities	1.187

In vitro Dissolution Testing and results: Media for Aspirin includes 0.1 M Hydrochloric acid followed by mixed phosphate buffer pH 6.8, Basket, 100RPM, 900ml. 2 Hrs. in acid stage and 15, 30, 45, 60 minutes in buffer stage
 10 Not more than 10% in acid stage and not less than 70%(D) in 45 mins in buffer stage.

Dissolution of Aspirin (min)	Initial
2 hours	0
45 min	93.39
Dissolution of Clopidogrel (min)	
30 min	98.87

15 Media for Clopidogrel includes 0.1 M Hydrochloric acid, Basket, 100RPM, 900 ml. Time points: 15,30,45 minutes, no less than 80% (Q) in 30 mins.

Content Uniformity is verified at R&D Scale. Results are presented below:

Uniformity of dosage unit by content uniformity		
	Aspirin	Clopidogrel
Mean	100.79	97.59
Minimum	94.05	93.64
Maximum	104.41	103.90
% RSD	2.90	4.00

Acceptance Value	7.01	10.27
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EXAMPLE 6

Tablets as per the Example 6 were prepared as per the procedure given in Example 1.

Ingredients		mg per compact tablet	% by weight of individual layer	% by wt. of tablet
Compressed core comprising Aspirin and pharmaceutically acceptable excipients	Acetylsalicylic acid (90% starch coated, Rhodine)	75.00	68.18	27.27
	Corn Starch	10.00	9.09	3.64
	Tartaric Acid	5.00	4.55	1.82
	Cellactose 80	13.00	11.82	4.73
	Stearic Acid	1.00	0.91	0.36
	Crosspovidone XL Type A	5.50	5.00	2.00
	Colloidal silicon Dioxide	0.50	0.45	0.18
Seal coating surrounding the core	Hydroxypropyl cellulose (Type SSL)	12.00	100.00	4.36
	Isopropyl Alcohol	159.42	-	-
Enteric coating surrounding the seal coated core	Hypromellose Acetate succinate (AS-LF)	12.26	94.34	4.46
	Triethyl citrate	0.74	5.66	0.27
	Isopropyl Alcohol	121.80	-	-
	Acetone	81.20	-	-
Coating comprising clopidogrel or pharmaceutically acceptable salts	Clopidogrel Bisulfate	97.85	83.63	35.58
	Hypromellose (Methocel E3LV Premium)/HPC SL/Povidone K 30	19.15	16.37	6.96
	Acetone	276.00	-	-
	Methylene Chloride	184.00	-	-
Seal coating	Hypromellose (Methocel E15 Premium)	14.26	62.00	5.19
	Polyethylene Glycol 6000	3.45	15.00	1.25
	Talc	2.76	12.00	1.00
	Titanium Dioxide	2.30	10.00	0.84
	Ferric oxide (yellow)	0.23	1.00	0.08
	Isopropyl Alcohol	144.10	-	-
	Methylene Chloride	216.11	-	-
	Total Avg. wt.	275.00	-	100.00

Dimensions of the above tablet are as follows:

Diameter	8.10
Thickness	5.85
Total Avg. Wt	275.00

The compact tablets prepared as per the present invention were packed in Aluminum Aluminum blister pack and were stored at ambient conditions or accelerated storage conditions and analysed for the chemical assay of each drug. Further, the in vitro dissolution was determined at initial time points and the results are provided as below:

Condition	Initial
Assay of Aspirin	103.060
Assay of Clopidogrel	99.090
Clopidogrel Related comp. C (Chiral Impurity)	1.060
Clopidogrel Related comp. A (Hydrolytic Impurity)	0.250
Salicylic acid	0.551
Total Impurities	1.146

In vitro Dissolution Testing and results: *Media for Aspirin includes* 0.1 M Hydrochloric acid followed by mixed phosphate buffer pH 6.8, Basket, 100RPM, 900ml. 2 Hrs. in acid stage and 15, 30, 45, 60 minutes in buffer stage. Not more than 10% in acid stage and not less than 70%(D) in 45 mins in buffer stage.

Dissolution of Aspirin (min)	
2 hours	0
45 min	92.09
Dissolution of Clopidogrel (min)	
30 min	96.67

Media for Clopidogrel includes 0.1 M Hydrochloric acid, Basket, 100RPM, 900 ml. Time points: 15,30,45 minutes, no less than 80% (Q) in 30 mins.

Content Uniformity is verified at R&D Scale. Results are presented below:

Uniformity of dosage unit by content uniformity		
	Aspirin	Clopidogrel
Mean	101.88	95.92
Minimum	100.36	86.45
Maximum	103.13	100.25

% RSD	0.87	5.45
Acceptance Value	2.52	15.13

COMPARATIVE EXAMPLE 1

The comparative example was prepared as per example 1 procedure, except the clopidogrel
5 was dissolved in water, instead of suspending in organic solvent.

Ingredients		mg per compact tablet	% by weight of individual layer	% by wt. of tablet
Compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients	Acetylsalicylic Acid	150.0	66.66	39.5
	Corn Starch	21.0	9.3	5.5
	Tartaric acid	15.0	6.7	3.9
	Microcrystalline cellulose	30.0	13.3	7.9
	Stearic acid	2.0	0.9	0.53
	Polyvinyl pyrrolidone and polyvinyl acetate copolymer	5.0	2.2	1.32
	Colloidal Silicon Dioxide	2.0	0.9	0.53
Enteric coating surrounding the core	Poly(methacrylic acid-co-ethyl acrylate) 1:1	20.8	83.4	5.5
	Triethyl citrate	2.10	8.3	0.6
	Colloidal Silicon Dioxide	2.10	8.3	0.6
Coating comprising clopidogrel or pharmaceutically acceptable salts	Clopidogrel Bisulfate	97.8	85.1	25.8
	Aqueous Solvent	q.s	q.s	q/s?
Seal coating	Hydroxypropyl methylcellulose	28.0	72.3	7.4
	PEG 6000	2.3	15.3	0.6
	Talc	0.6	4.06	0.16
	Titanium Dioxide	1.1	7.3	0.003
	Ferric oxide	0.15	1	0.04

The solid dosage form of the comparative example, was subjected the chemical stability under accelerated storage conditions i.e 40 °C and 75 % relative humidity. Also, the in vitro dissolution was checked.

	Initial	40°C and 75% Relative Humidity	
		1 month	
Assay of Aspirin	102.14	98.15	Discontinued from stability
Assay of Clopidogrel	102.58	89.92	
Clopidogrel Related comp. C (Chiral Impurity) (NMT 1.5%)	Not Detected	0.112	Discontinued from stability
Clopidogrel Related comp. A (Hydrolytic Impurity) (NMT 1.2%)	0.683	9.086	
Salicylic acid (NMT 3.0%)	0.368	0.932	
Total Impurities	0.691	9.198	

The above data indicates that when the clopidogrel or pharmaceutically acceptable salts thereof, was deposited on an enterically coated core of acetyl salicylic acid, clopidogrel degraded significantly (to more than 10 %) in a period of one month, although acetyl salicylic acid remained stable. It may be noted that it is critical to use non aqueous solution and not aqueous solution, to obtain chemically stable solid dosage form, containing, both and acetyl salicylic acid in a single unit dosage form. Hence, further investigations on stability are discontinued.

Claims:

1. A solid dosage form comprising two active pharmaceutical agents; acetylsalicylic acid and clopidogrel or pharmaceutically acceptable salts thereof, wherein the total amount of these active pharmaceutical agents present in the solid dosage form is more than 55% of the total weight of the solid dosage form, and wherein clopidogrel is released immediately upon contact with aqueous environment.
2. The solid dosage form of claim 1 in the form of a tablet comprising
 - a. a compressed core comprising acetylsalicylic acid and pharmaceutically acceptable excipients;
 - b. an enteric coating surrounding the compressed core of (a); and
 - c. a layer comprising clopidogrel or pharmaceutically acceptable salts thereof, surrounding the compressed core (b).
3. The solid dosage form of claim 1, wherein the total amount of active pharmaceutical agents present in the tablet ranges from 55% to 75% of the total weight of the tablet.
4. The solid dosage form of claim 2, wherein the tablet does not require any coating between the enteric coating and the layer comprising clopidogrel or pharmaceutically acceptable salts thereof.
5. The solid dosage form of claim 2, wherein the layer comprising clopidogrel is sprayed onto the enteric coated compressed core using non-aqueous medium.
6. The solid dosage form of claim 1, wherein the particle size distribution of the clopidogrel or its pharmaceutically acceptable salt is such that D_{50} is less than 50 microns and D_{90} is less than 25 microns.

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2016/050288

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 31/616 (2006.01); A61K 31/4365 (2006.01) 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 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) TXTE, TXTG, TXTCN, TXTKR, EPODOC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2792836 A1 (SANOFI) 03 November 2000 (03.11.2000) examples 11,14; claims 1,5,6	1,3
X	CN 102805749 A (WANG DINGHAO) 05 December 2012 (05.12.2012) abstract; whole document/online translated TFLY	1,3
X	CA 2611741 A1 (ELAN PHARMA INTERNATIONAL, LIMITED) 28 December 2006 (28.12.2006) whole document, in part. claim 1 and example F	1,3,6
X	CN 102389436 A (BEIJING FUKANGREN BIOPHARMACEUTICAL TECHNOLOGY CO., LTD) 28 March 2012 (28.03.2012) abstract; whole document/online translated by TFLY	1,3
☒ 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 15 December 2016 (15.12.2016)		Date of mailing of the international search report 28 December 2016 (28.12.2016)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24-535		Authorized officer KRENN M. Telephone No. +43 / 1 / 534 24-435

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2016/050288

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 20140130579 A (KOREA UNITED PHARM. INC) 11 November 2014 (11.11.2014) abstract; whole document/online translated by KIPO	1,3
X	WO 2015014766 A1 (SANOFI) 05 February 2015 (05.02.2015) whole document	1-3

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2016/050288

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.: because they relate to subject matter not required to be searched by this Authority, namely: 2. ☒ Claims Nos.: 4,5 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: .Claim 4 lacks a clear technical teaching. The term "...does not require..." (claim 4) does not exclude the presence of a coating. The features of claim 5 are not provable at the final product. 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 / IN 2016/050288

Patent document cited in search report			Patent family member(s)			Publication date
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			EP	A1	3027176	2016-06-08
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			JP	A	2015526498	2015-09-10
			KR	A	20160037967	2016-04-06
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			AR	A1	097193	2016-02-24
			TW	A	201601721	2016-01-16
			WO	A1	2015015062	2015-02-05
			PH	A1	12016500121	2016-04-25
			DO	A	P2016000024	2016-03-31