

Formulation Development and Evaluation of Ticagrelor Tablet for Regulatory Market

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ARTICLE INFO

Article history:

Received on: 09/07/2013

Revised on: 16/09/2013

Accepted on: 03/10/2013

Available online: 31/10/2013

Key words:

Ticagrelor, platelet aggregation inhibitor, wet granulation, *in-vitro* dissolution.

ABSTRACT

The aim of the study was to develop a formulation of Ticagrelor 90 mg tablets that is equivalent to the reference product using similar excipients to match the *in-vitro* dissolution profile. A compressed coated tablet was formulated consisting of Ticagrelor and excipients conforming to the USP/BP monograph and below maximum amount allowed per unit dose. The physical characteristics of powder blends were evaluated for bulk density, tapped density, compressibility index, hausner ratio, angle of repose and moisture content. The compressed core and coated tablets were evaluated for thickness, hardness, weight variation, friability, disintegration, dissolution, drug content and stability. The powder blends for all formulations showed satisfactory bulk density, tapped density, compressibility index, hausner ratio, angle of repose and moisture content. All the core and coated tablets showed acceptable pharmaco-technical properties in terms of thickness, hardness, weight variation, friability, disintegration. Dissolution performances were varied depending on the composition of matrix tablet. Finally a formulation batch B05 consisting of Ticagrelor (34.61%), mannitol (61.15%), sodium starch glycolate (2.69%), hypromellose (HPMC-2910, 5cps) (0.77%), purified talc (0.38%), magnesium stearate (0.38%) and opadry grey (21k57558) (2%) showed maximum similarity with the reference product. Using this formulation a pharmaceutical will be able to met regulatory compliance.

INTRODUCTION

According to the USP 29 Monogram, "Tablets are solid dosage forms containing medical substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in this country. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granules. Tablets can be prepared in a wide variety of sizes, shapes, and surface marking, depending upon the design of the punches and dies." **Direct Compression** is by far the easiest method of the processing of tablets, because it only involves the main steps of powder blending, lubrication and compaction. The process by means of **wet granulation** binder liquid is added to the slightly agglomerate of the powder mixture.

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The amount of fluid that will be given in wet powder, because it causes too hard, fragile, they are too soft during the wet ability and the well controlled. Compared with solvent-based systems, the aqueous solution has the advantage that the handling is safe, but to break loose upon hydrolysis may not be appropriate.

Ticagrelor is a platelet aggregation inhibitor which was approved for use in the European Union by the European Commission on December 3, 2010. It was accepted by the US Food and Drug Administration on July 20, 2011 (FDA, 2011). Ticagrelor is indicated for the prevention of thrombotic events (for example stroke or heart attack) in patients with acute coronary syndrome or myocardial infarction with ST elevation.

Combined Ticagrelor with acetylsalicylic acid which unless the latter is contraindicated. (Haberfeld, 2010) Treatment with Ticagrelor for acute coronary syndrome which is superior as compared with Clopidogrel because significantly reduces the rate of death (Husted *et al.*, 2009). The proper dosage regimen's design is an important factor in accomplishing this objective. (Lachman *et al.*, 1976). In addition to the active ingredient (the drug), tablets contain a number of inert components known as additives, added to

impart acceptable manufacturing characteristics and properties to the formulation. The tablet formulation problem can be stated as follows: given the drug with its physical and chemical properties with the most wanted drug dose in the tablet, find the 16 Excipients and their quantities for getting satisfactory properties when mixed & they can be compressed into a tablet. To formulate typically 25% active ingredient is required. Filler is used increase bulk in order to produce a tablet of practical weight for compression (typically 65%), binder is used to impart cohesive properties to the powders by the formulation of granules, Lubricants added to reduce interparticulate friction to prevent adhesion of powder to the surfaces of punches and dies and to facilitate tablet ejection from the die, Disintegrant is incorporate to facilitate rapid breakup and disintegration after administration, Surfactant is used to aid wetting and dissolution of the drug (Rowe, 1993).

Since it is imperative that, the prepared tablet must conform the quality parameters, like, weight and content uniformity, hardness, friability, disintegration time and dissolution and it is known that all these are influenced by both the formulation components and method of research, it is clear that a high degree of technical knowledge and expertise is needed for best formulation requires.

MATERIALS AND METHOD

For the present study Ticagrelor was obtained from Shanghai Panso pharma technology co. ltd., China, Ludipress was procured from BASF, Germany; Hypromellose (HPMC-2910, 5cps) was from the Dow chemicals, USA; Purified talc was from Asian minerals, Thailand. Maize starch & Mannitol were procured from Roquette, France and Pregelatinized starch (Starch 1500) & Opadry grey (21k57558) were from Colorcon, India, Microcrystalline cellulose (Avicel PH101), Microcrystalline cellulose (Avicel PH102) & Croscarmellose sodium were procured from Mingtai chemical co. ltd., Taiwan, others were from local commercial source. Preparation of Ticagrelor tablets were prepared by direct compression method as well as wet granulation method according to formula given in the Table 1.

Direct Compression method

Weigh active ingredient & other excipients accurately, then pass Ticagrelor, ludipress, microcrystalline cellulose (Avicel PH 102), mannitol, dibasic calcium phosphate, pregelatinized starch (Starch 1500), lactose, sodium lauryl sulphate and purified talc through sieve (mesh no.16) where applicable and place in blender and mix properly. After checking Loss on drying (%LOD), lubricated with magnesium stearate prior to compression, all prepared granules were evaluated for several tests such as loose bulk density, tapped bulk density, compressibility index, hausner ratio and angle of repose. The tablets were compressed in CIP 8 station compression machine (China) using 9 mm, round punch.

Wet granulation method

Weigh active ingredient & other excipients accurately, then pass ticagrelor, maize starch, hypromellose (HPMC-2910, 5cps), mannitol, microcrystalline cellulose (Avicel PH 101), microcrystalline cellulose (Avicel PH 102) and sodium starch glycolate through sieve (mesh no.16) where applicable and mix properly in rapid mixer granulator. Add maize starch & hypromellose (HPMC-2910), 5cps solution and mix properly. The lumps thus produced are passed through s.s screen (12mm) using milling machine. The small lumps are dried in FBD at 65°C. These dried small lumps are passed through s.s screen (3mm) and checking loss on drying (%LOD). These granules are blended with sodium starch glycolate (type A) & purified talc for 20 minutes into the blender and blend properly. After that it was lubricated with magnesium stearate and evaluated as direct compression method.

Coating

For all formulations (B01-B05), same coating materials with same amount is applied where using auto coating machine (China) and default coating parameter.

Evaluation of Powder Blend and granules

Before compression of tablets, powdered mixture and granules were applied to determine some parameters such as loose bulk density, tapped bulk density, angle of repose, compressibility index and hausner ratio. To get original data, reading were taken in triplicates and expressed as mean±SD.

Bulk Density

Loose Bulk Density (LBD) and Tapped Bulk Density (TBD) were determined by using Digital Automatic Tap Density Tester (Vegoo, VTAP/ MATCO-II, India). 2 g of powder from each formula (previously lightly shaken to break any agglomerates formed) were taken into a 10 ml measuring container. After observed initial volume, the equipment was on and the cylinder was allowed to fall under its own weight onto a hard surface. The reading of tapping was continued until no further change in volume. Using the following equation (Shah *et al.*, 1997) LBD and TBD was calculated:

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapping volume of the packing}}$$

Compressibility Index

The compressibility index of the powder blend was determined by Carr's compressibility index (Aulton, 2002). Carr's index (%) = {(TBD – LBD) X 100}/TBD

Hausner's Ratio

Hausner ratio which is interconnected with the flow ability of a powder blend or granules. Hausner's factor = Tapped bulk density/Loose bulk density

Angle of Repose

To calculate the angle of repose of the granules Funnel method was used (J Cooper and G gun. 1986). The accurately weighed granules were taken in a funnel. The correctly weighed powder mix was taken in the funnel then the height of the funnel was adjusted in such a way the tip of the funnel just touched the top of the powder mix (Train, 1958). The powder mix was permitted to flow through the funnel freely onto the surface. The powder cone's diameter was measured and angle of repose was calculated using the following equation (Carter, 1986):

$$\text{Angle of Repose } \theta = \tan^{-1} h/r$$

Where, h = Height of the powder cone.

r = Radius of the powder con.

Evaluation of Tablet

The formulated tablets were assessed for average weight, diameter, thickness, hardness, friability, disintegration time and dissolution test. (Gohel *et al.*, 2005; Patel & Baria 2000)

Weight variation test

To evaluate weight variation, twenty tablets from each formulation was weighed and the test was performed.

Thickness

For determining thickness digital slide caliper is used. 5 tablets from each batch (B01-B05) were used and average values were calculated.

Hardness test

Manual tablet hardness tester but digital (Shin Kwang Machinery, type- TH- 20B, Japan) was used to determine the hardness. From each formulation, 6 tablets were crushed and recorded.

Disintegration time

Except chewable tablet, disintegration is a very important parameter which is intended by mouth. Six tablets were taken from each batch and performed disintegration time according to the official monogram.

Friability test

20 tablets of each formulation were weighed with an analytical weighing balance (model: CPA 2245, Sartorius, JAPAN) and determined to check by using a friability tester (Shin kwang machinery co., ltd., Taiwan) at 25 rev/min for 4 min. The tablets were finally weighed and compared with their preliminary weight for obtaining percentage friability.

Content uniformity

At random 20 tablets were weighed and powdered. The powder equivalent to 90 mg was weighed correctly and dissolved in 100 ml of phosphate buffer (dihydrogen phosphate) of pH 3.0

and the solution was shaken thoroughly. The undissolved substance was detached by filtration through whatman filter paper. Finally the serial dilutions were done. The absorbance of the diluted solutions was measured at 222 nm. The concentration of the drug was determined from the standard curve of the Ticagrelor in phosphate buffer of pH 3.0.

In-vitro dissolution testing

In-vitro dissolution of Ticagrelor was done by using Shing kwang machinery, type DT-6 dissolution test apparatus (Japan). The dissolution test was performed using 900 ml of phosphate buffer (pH 3.0) as the dissolution media at 50 rpm and 37°C ±5°C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The prepared samples were evaluated spectrophotometrically at 222 nm for drug dissolved at that time.

Stability Studies

Stability studies were done of one selected batch according to ICH guidelines to assess the drug content and formulation stability (Cartensen, 1995). One selected fabricated tablet batch was alu-alu blister packaged and kept at 40±2°C and 75±5% RH. Samples were withdrawn at one month, two month and three month for evaluation of appearance, hardness, drug content and percentage dissolution during the stability studies.

RESULTS AND DISCUSSION

Properties of Powder blend and Granules

The Powder blend and granules of different prepared formulations (B01 to B05) were evaluated for LBD, TBD, compressibility index angle of repose and LOD (Table. 2). The results of LBD ranged from 0.526±0.02 to 0.635±0.02 g/ml and TBD ranged from 0.682±0.01 to 0.792±0.02 g/ml. The bulk densities of granules for B04 and B05 were quite lower than those of other granules because they were manufactured through wet granulation method where granulation fluid, purified water is incorporated.

The compressibility index (%) found ranged from 14.52±0.03 to 23.21±0.02. According to the USP 29 guidelines, compressibility index 11% to 15% result in good flow properties, 16-20% results in good and 21-25% results in passable flow properties. So the granules of B01 & B05 showed fair flow properties while the batch B02 & B03 revealed fair flow properties and the rest one was passable. The angle of repose ranged from 27.64±0.08 to 30.75±0.04. According to the Pharmaceutical guidelines, the angle of repose (<30°) indicate excellent flow properties of granules for all prepared formulation. For hausner ratio, formulation B01 & B05 were possessed good powder flow property and others were passable. (Table 02)

Table 1: Composition of all prepared formulation of Ticagrelor tablet

Sl	Ingredients (mg/Tablet)	B01	B02	B03	B04	B05
For tablet core						
1	Ticagrelor	90 mg	90 mg	90 mg	90 mg	90 mg
2	Ludipress	----	90 mg	---	----	----
3	Maize starch	----	---	---	38 mg	---
4	Microcrystalline cellulose (Avicel PH 101)	----	---	---	51 mg	---
5	Microcrystalline cellulose (Avicel PH 102)	----	52.5mg	---	70 mg	---
6	Mannitol	151mg	-----	98 mg	---	159 mg
7	Pregelatinized starch (Starch 1500)	----	----	70 mg	---	---
8	Dibasic calcium phosphate	10mg	----	---	---	----
9	Lactose monohydrate	---	20 mg	---	---	---
10	Croscarmellose sodium	---	5 mg	---	---	---
11	Sodium starch glycolate	7 mg	---	---	8 mg	7 mg
12	Hypromellose (HPMC-2910, 5cps)	-----	----	---	---	2 mg
13	Purified talc	1 mg	---	---	1.5 mg	1 mg
14	Magnesium stearate	1 mg	2.5 mg	2 mg	1.5 mg	1 mg
15	*Purified water	----	----	----	50 mg	80 mg
	Compression weight	260 mg	260 mg	260 mg	260	260 mg
For coating materials						
16	Opadry grey (21k57558)			5.200 mg		
17	* Methanol			34.500 mg		
18	*Dichloromethane(methylene chloride)			34.500 mg		

(*Marked items will not appear in the final product)

Table 2 Result of bulk density, Compressibility Index, Hausner ratio and Angle of Repose of different formulation.

Formulation	Loose bulk density (LBD) (gm/ml)	Tapped bulk density (TBD) (gm/ml)	Carr's index (%)	Hausner ratio	Angle of repose	LOD (%)
B01	0.603±0.01	0.710±0.05	15.07±0.04	1.18±0.02	30.33±0.05	2.75
B02	0.635±0.02	0.792±0.02	19.82±0.05	1.25±0.01	30.75±0.04	2.84
B03	0.596±0.02	0.714±0.04	16.53±0.02	1.198±0.01	30.02±0.06	2.69
B04	0.526±0.03	0.685±0.03	23.21±0.02	1.30±0.02	28.30±0.03	2.92
B05	0.583±0.02	0.682±0.01	14.52±0.03	1.17±0.01	27.64±0.08	3.08

Table 3: Physicochemical properties of Tablet of different formulations (B01-B05).

Batch	Average weight (mg)±SD (N=20)	Diameter (mm)	Thickness (mm) ± SD (N=20)	Hardness (kg/cm ²)±SD (N=6)	Friability (%) (n= 20)	Disintegration time (Sec.) ±SD (n= 3)	Drug content (%) ± SD (n = 5)
B01	260.45±0.76		4.12±0.02	4.91±0.44	0.11	92.2±3.4	100.0±1.12
B02	261.68±0.62		4.05±0.05	5.02±0.39	0.23	99±2.7	99.75±0.98
B03	260.95±0.80	9	4.28±0.04	5.90±0.57	0.10	95.02±1.9	100.41±0.87
B04	259.23±0.71		4.34±0.04	6.80±0.25	0.24	96.17±3.3	100.02±1.20
B05	259.39±0.66		4.31±0.03	6.98±0.34	0.27	90.9±2.9	99.97±1.01

Table 4: Stability study of best formulation from B05.

Characteristics	Initial	1 st month	2 nd month	3 rd month
Hardness (kg/cm ²)	4.90±0.34	4.51±0.29	4.53±0.35	4.41±0.30
Assay (%)	99.97±1.01	99.52±1.29	98.57±1.54	98.35±1.40
Disintegration time (sec)	95.9±2.9	93.87±1.25	93.51±1.01	92.47±1.15
Dissolution (%)	96.6±1.57	96.17±1.87	95.45±2.09	94.07±1.94
Appearance	off white	no change	no change	No change

For Tablets

The results of physical parameters (average weight, diameter, thickness, hardness, friability and disintegration time) and drug content of the prepared tablets are given in Table. 3. The thickness of the tablets were found between 4.05±0.05 mm to 4.34±0.04 mm. Different density and porosity indicate different hardness of a tablet. The hardness range of tablets was found from 4.91±0.44 kg/cm² to 6.98±0.25kg/cm². Friability ranged from 0.10% to 0.27% which was observed from my experiments. According to the British Pharmacopoeia (BP-2011), the weight variations of all formulated tablets were complied. . In all batches (B01-B05), core and coated tablets were disintegrated within 2 minutes (Table 03). Formulation batch B05 showed the lowest disintegration time (90.9±2.9 sec) where as formulation

batch B02 showed the highest disintegration time (99±2.7 sec). After coating the weight gain achieved was about 1.67% w/w with 45 seconds as the disintegration time increased of coated tablets. The drug content of each formulation was found near about to 100% of labeled content. From observing all physical properties, it is said that physical properties and drug content of the compressed tablets were acceptable. (Table. 3)

The content of active ingredients in the formulation was found in between 99.75±0.98% to 100.41±0.87% w/w.

In vitro release studies of the formulations B01, B02 and B03 prepared through direct compression method by using ludipress, microcrystalline cellulose (Avicel PH 102), lactose monohydrate, croscarmellose sodium & sodium starch glycolate (where applicable) with different amount. The drug released from

the formulation B01 to B03 was found to be 93.8 ± 0.27 , 93.19 ± 0.46 , and $94.09 \pm 0.4\%$ for Ticagrelor respectively. (Figure 1)

In-vitro release studies of B04 and B05 formulated through wet granulation method & the drug released were found 94.8 ± 0.17 & 96.6 ± 0.25 for Ticagrelor respectively. (Figure 1)

The best release rate found from B05 formulation when compared to other formulations this is due to the incorporation of hypromellose (HPMC-2910, 5cps) as a granulation agent.

When the %cumulative drug release of B05 formulation compared with the innovators (Brilinta) sample at different time intervals, similar result was found (Figure 2). The tablets were found to release more than 90% after 25 min. Maximum release was found to be 96.6 % by B05 formulation. On the other hand, the Brilinta tablet was found to release of 97% of drug. So, the formulation B05 was similar with the innovator. (Figure 2)

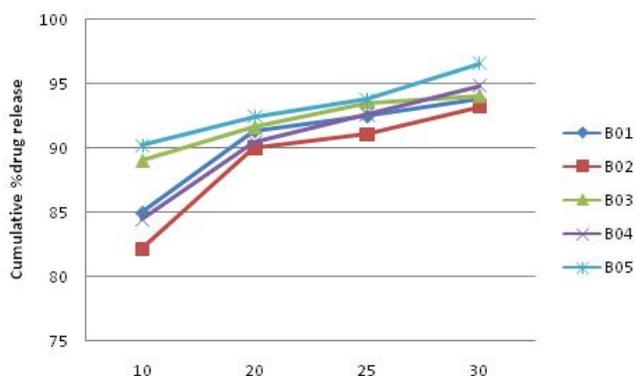


Fig. 1: Comparison of *in-vitro* dissolution studies of different formulations.

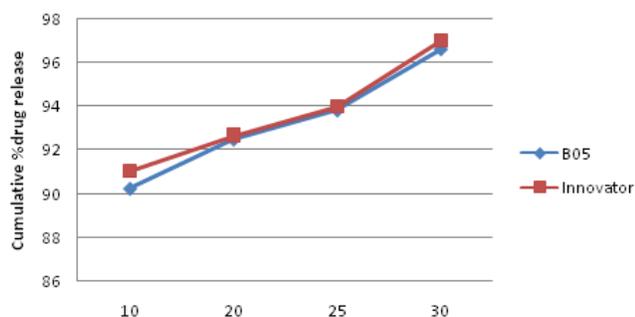


Fig. 2: Comparison of drug release profile of B05 with innovator brand.

Accelerated stability studies

The selected batch B05 was evaluated after three months of the stability study. They were checked at $40 \pm 2^{\circ}\text{C}$ and $75 \pm 5\%$ RH and the result are mentioned in table 04. It was establish that the Ticagrelor tablets are stable in the Alu-alu pack of stability period.

CONCLUSION

The present research was carried out to develop a tablet dosage form of Ticagrelor evaluated from direct compression and wet granulation method. We found most suitable method is wet granulation where less excipient were used like mannitol, hypromellose (HPMC-2910, 5cps) & sodium starch glycolate etc.

The tablet was evaluated for flow property and after compression parameters. The dissolution result of formulation B05 showed equivalent or more % release of drug as compared to the innovator products. The stability result of formulation B05 revealed that the alu-blister was the suitable packing for Ticagrelor tablet. Further pharmacokinetic and pharmacodynamic study is badly needed *in-vivo* for recommendation of B05 in suitable animal models.

ACKNOWLEDGEMENT

The authors are grateful to the Management and Staff of General Pharmaceuticals Ltd., Gazipur, Bangladesh for providing the all facilities like gift sample and standard of Ticagrelor.

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How to cite this article:

Md. Shafayat Hossain, Md. Anisuzzaman, Md. Anwar Hossain and Vikash Kumar Shah. Formulation Development and Evaluation of Ticagrelor Tablet for Regulatory Market. *J App Pharm Sci*, 2013; 3 (10): 114-118.