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FORMULATION, DEVELOPMENT AND OPTIMIZATION OF SUSTAINED RELEASE DELIVERY SYSTEM OF ANTI-PLATELET DRUGS

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ABSTRACT

Antiplatelet medications currently on the market interfere with one or more phases in the platelet release and aggregation process, leading to a meaningful decrease in thrombosis risk that cannot be separated from an elevated risk of bleeding. In this article we have made bilayered tablet of cilostazol and ticagrelor. Compression was initiated using a 10 mm, round, ambidextrous punch of cilostazol as the first layer, and plain on both sides and a mixture of ticagrelor as the second layer.

Keywords: Antiplatelet, Cardiovascular diseases, Bilayered Tablets, Cilostazolas, Ticagrelor.

INTRODUCTION

Cardiovascular diseases (CVD) are a leading cause of death in the world. The mortality and recurrence rates for ischemic heart disease (IHD) and ischaemic stroke remain high despite excellent treatment protocols. Anti platelet therapy lowers the risk of recurrent heart attacks and strokes and is an effective treatment. Due to their ability to adhere to the damaged blood vessel wall, attract additional platelets to the site of injury, release vasoactive and prothrombotic mediators that cause vasoconstriction and promote coagulation, respectively, and form aggregates that affect primary hemostasis, platelets are essential parts of normal hemostasis and key players in atherothrombosis.

Preparation of Bilayered Tablets

a) Preparation of Immediate Release layer: Ticagrelor

The Immediate release layer contains uniform mixture of Ticagrelor, Mannitol, HPMC were weighed, followed by shifting through 40# sieve and mixed well with binder solution as a HPMC to make a damp mass. Later the damp mass was passed through sieve 20# and dried. Finally prepared granules were lubricated with magnesium stearate and the well mixed powder were used as immediate release layer.

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Formula of Ticagrelor layer:

Formulation of Ticagrelor Layer

Sr. No.	Ingredients	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tab	F6 mg/tab
1.	Ticagrelor Ph. Eur.	60.00	60.00	60.00	60.00	60.00	60.00
2.	Mannitol USP-NF	50.80	68.80	55.80	14.80	14.80	74.80
3.	Ferric Oxide	0.20	0.20	0.20	0.20	0.20	0.20
4.	Calcium Hydrogen Phosphate Dihydrate USP-NF	70.00	50.00	60.00	100.00	100.00	40.00
5.	Sodium Starch Glycolate USP-NF	4.00	5.00	6.00	5.00	5.00	5.00
6.	Povidone K-30 USP-NF	5.00	6.00	8.00	7.00	7.00	10.00
7.	Purified water	QS	QS	QS	QS	QS	QS
8.	Sodium Starch Glycolate USP-NF	8.00	7.00	9.00	10.00	10.00	5.00
9.	Magnesium stearate USP-NF	5.00	8.00	4.00	3.00	3.00	5.00
	Total weight	200.00	200.00	200.00	200.00	200.00	200.00

(b) Preparation of Sustained Release layer: Cilostazol Part

Dispensing & Sifting

All the ingredients were dispensed in individual polybags, labelled properly and sifted through mesh 40 sieves.

Formula of Cilostazol part:

Formulation of Cilostazol Layer

Sr. No.	Ingredients	Fl mg/tab	F2 mg/tab	F3mg/tab	F4 mg/tab	F5mg/tab	F6mg/tab
1.	Cilostazol USP	100.00	100.00	100.00	100.00	100.00	100.00
2.	Lactose anhydrous USP-NF	90.00	79.00	85.00	110.00	110.00	110.00
3.	HPMC K-15M USP-NF	5.00	6.00	10.00	30.00	45.00	40.00
4.	HPMC K100M USP-NF	85.00	95.00	75.00	45.00	30.00	35.00
5.	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
6.	Povidone K-30 USP-NF	8.00	10.00	7.00	8.00	10.00	10.00
7.	Magnesium stearate USP-NF	7.00	5.00	8.00	7.00	5.00	5.00
	Total weight	300.00	300.00	300.00	300.00	300.00	300.00

Compression of Bilayered tablet:

Compression was initiated using the blend by setting Cilostazol as first layer using 10mm, round,

biconcave punch, and plain on both sides. All the physical parameters of the core tablets presented in the following table were found to be satisfactory.

Final formula of Bilayered tablet:

Ticagrelor Tablet- Immediate Release layer			
Sr. No.	Ingredients	Functions	Formula (mg/tablet)
1.	Ticagrelor Ph. Eur.	Active Drug	60.00
2.	Mannitol USP-NF	Additive	74.80
3.	Ferric Oxide Yellow IH	Colorant	0.20
4.	Calcium Hydrogen Phosphate Dihydrate USP-NF	Additive	40.00
5.	Sodium Starch Glycolate USP-NF	Disintegrant	5.00
6.	Povidone K-30 USP-NF	Binder	10.00
7.	Purified water	Aqueous solvent	QS
8.	Sodium Starch Glycolate USP-NF	Disintegrant	5.00
9.	Magnesium stearate USP-NF	Lubricant	5.00
	Total weight of Ticagrelor Layer		200.00
Sustained Release layer: Cilostazol			
1.	Cilostazol USP	Active Drug	100.00
2.	Lactose anhydrous USP-NF	Additive	110.00
3.	HPMC K K-15MUSP-NF	SR Polymer	35.00
4.	HPMC K100M USP-NF	SR Polymer	10.00
5.	Purified water	Aqueous solvent	Q.S
6.	Povidone K-30 USP-NF	Binder	10.00
7.	Magnesium stearate USP-NF	Lubricant	5.00
8.	Total weight of CilostazolLayer		300.00 mg
Total weight of bilayered tablet			500.00 mg

Evaluation of Ticagrelor and Cilostazol tablets-

The prepared tablets were evaluated for drug content, hardness, friability, swelling index, and dissolution profile.

Drug content of Ticagrelor and Cilostazol

Five tablets were accurately weighed and crushed using a mortar and pestle. Powder equivalent to 50 mg of Ticagrelor and Cilostazol was transferred to a 50 ml volumetric flask and volume was made up with methanol. The sample was sonicated for 15 minutes, then filtered through 0.2µfilter and injected into HPLC system. The experiment was performed in triplicates. Drug content was expressed as % of the theoretical amount of Ticagrelor and Cilostazol

Appearance and Description

The bilayer tablets were identified visually by checking the difference in colour. Circular, biconvex, uncoated, bilayered tablets of which one layer is light yellow to yellow coloured and the other layer is off-white to white coloured. Plain on both sides.

- Thickness

Tablet thickness was measured using a verniercaliper (Mitiutoyo,Japan).

- Hardness

Tablet hardness was evaluated by measuring the hardness of 5 tablets using Dr. Schleunizer 8M hardness tester.

- Friability

Tablet friability was evaluated using an Electro lab USP friabilator. Accurately weighed 10 tablets were tumbled at 25 rpm for 4 minutes. The tablets were then de-dusted, weighed, and the percent weight loss was calculated.

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after revolution

- Weight variation:

Ten tablets were chosen at random from each batch and weighed separately. 20 pills' average weight and standard deviation were computed. If no more than two of the individual tablet weights depart from the average weight, the batch passes the weight variation test.

Weight variation of tablet

Average weight of tablet	Percentage deviation allowed
80mg or less	±10
60mg but < 250 mg	±7.5
250 mg or more	±5

Physical characteristics of the tablet

Sr. No.	Parameters	Observed values
1.	Avg. weight of Ticagrelorlayer (mg)	200
2.	Avg. weight of Cilostazollayer (mg)	300
3.	Avg. weight of bilayered tablets (mg)	500
4.	Hardness (kp)	8 to 12
5.	Diameter (mm)	10
6.	Thickness(mm)	4 to 5
7.	Friability (%)	0.2

- Swelling Studies

The swelling property of HPMC was studied by introducing the matrix tablets in to the dissolution medium used for release studies. The tablets were removed periodically and weight of each tablet was determined. Swelling was calculated as per the following formula:

%Swelling = (Wt-Wo) / Wo*100

Where, Wt is the weight of the matrix after swelling and Wo is the initial weight of the matrix. The test was performed for five tablets.

- In vitro dissolution studies of bilayered tablets -

In-vitro dissolution studies for Ticagrelor:

In vitro dissolution profiles of the tablets was carried out on USP dissolution type II apparatus using paddle.

Dissolution limits of Cilostazol ER tablets

TimePoints(hrs.)	Limits: The percentages of the labelled amount of Cilostazol dissolved at the specified times.	%Cilostazolreleased
2	Not more than 10 %	3.5
8	30% to 50%	43.5
12	60% to 80%	70.5
20	Not less than 80%	89.5

In-vitro dissolution studies for Ticagrelor:

Dissolution of the tablets was carried out on USP dissolution type II apparatus using paddle.

Dissolution limit profile of Ticagrelor

Time (Min.)	Limits	% Release Ticagrelor
10 min	70%*(Q)of the labelled amount of Ticagrelor dissolved at 45 minutes	70.30
15 min		82.54
20 min		84.55
30 min		88.21
45 min		95.22
60 min		96.40

Selection of optimised Formulation:

The optimised formulation was selected based on the results obtained from the drug in-vitro release of bilayered tablets of Ticagrelor and Cliostazol.

The target for dissolution of immediate release part of Ticagreloris 70 %*(Q) of the labelled amount of Ticagrelor dissolved at 45 minutes. The target for Cilostazol extended release tablets at2 hrs - Not more than 10 %, 8 hrs- 30% to 50%, 12 hrs- 60% to 80% and at 20 hrs- Not less than 80%.

.The batches charged for stability test shown in below Table.

Ticagrelor Tablet- Immediate Release layer				
Sr. No.	Ingredients/Batchno	SB1 (mg/tablet)	SB2 (mg/tablet)	SB3 (mg/tablet)
1.	Ticagrelor Ph. Eur.	60.00	60.00	60.00
2.	Mannitol USP-NF	74.80	74.80	74.80
3.	Ferric Oxide Yellow IH	0.20	0.20	0.20
4.	Calcium Hydrogen Phosphate Dihydrate USP-NF	40.00	40.00	40.00
5.	Sodium Starch Glycolate USP-NF	5.00	5.00	5.00
6.	Povidone K-30 USP-NF	10.00	10.00	10.00
7.	Purified water	QS	QS	QS
8.	Sodium Starch Glycolate USP-NF	5.00	5.00	5.00
9.	Magnesium stearate USP-NF	5.00	5.00	5.00
	Total weight of Ticagrelor Layer	200.00	200.00	200.00
Sustained Release layer: Cilostazol				
1.	Cilostazol USP	100.00	100.00	100.00
2.	Lactose anhydrous USP-NF	110.00	110.00	110.00
3.	HPMC K-15M USP-NF	35.00	35.00	35.00
4.	HPMC K100M USP-NF	10.00	10.00	10.00
5.	Purified water	Q.S	Q.S	Q.S
6.	Povidone K-30 USP-NF	10.00	10.00	10.00
7.	Magnesium stearate USP-NF	5.00	5.00	5.00
	Total weight of Cilostazol Layer	300.00 mg	300.00 mg	300.00 mg
Total weight of bilayered tablet		500.00 mg	500.00 mg	500.00 mg

DISCUSSION

Dual antiplatelet therapy, usually accompanied with a P2Y12 receptor antagonist and aspirin, is generally acknowledged as a vital approach in treating ACS patients, partly because of the increased occurrence of thrombogenesis. Dual antiplatelet therapy has been also regarded as a standard therapy especially after PCI according to several clinical guidelines.

Ticagrelor and Cilostazol completely absorbed in gastric pH but rapidly hydrolyzed in intestinal mucosa. Thus, Bilayer formulation reducing its oral bioavailability. Therefore, an attempt was made to increase oral bioavailability of Ticagrelor and Cilostazol by retaining the dosage form in stomach for longer period of time.

These tablets mainly prepared for reduction of lag time and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding frequency of dosing and subsequently degradation of drug in intestine. For the formulation of bilayered tablets different concentrations of povidone, was used as disintegrating agents, HPMC K100, and Sodium Starch Glycolatewere used as sustained release polymer.

Other excipients used are, HPMC, Mg stearate, (lubricating agent) aerosol, mannitol. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The prepared bilayered tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, and in-vitro dissolution studies. It was observed that Formulations F6 gave maximum drug release upto 99.84% within 12 hrs for SR and L4 gave maximum drug release upto 99.85% within 30 minutes for IR. F6 was subjected for drug release kinetics studies viz. Zero order, First order, Higuchi matrix, model equations and it followed zero order release kinetics. Based on various evaluation parameters formulation F6 was selected as optimized formulation for (SR) and L4 for (IR) was further subjected for stability study. The formulation showed good stability and values were within limit. Thus conclusion can be made that stable dosage form can be developed for Cilostazol for the sustained release and Ticagrelor for immediate release by bilayered tablets.

CONCLUSION

Ticagrelor is an oral P2Y12 receptor antagonist that demonstrates some desirable pharmacological advantages over thienopyridines, including reversibility of action. Its greater potency of platelet inhibition compared with clopidogrel translates to a reduction in MACE following ACS at the cost of increased spontaneous bleeding events.

Antiplatelet therapy was associated with reduced mortality. Among individual antiplatelet agents, Cilostazol was more strongly than other agents associated with reduced mortality overall, and in younger patients, older patients, and patients with prior ischemic stroke at the time of antiplatelet diagnosis. Accordingly, antiplatelet therapy generally, and Cilostazol particularly, shows observational evidence of potential benefit as medical treatment for patients with antiplatelet therapy; these findings merit validation by testing in formal randomized clinical trials.

Incomplete protection and bleeding complications associated with the use of the currently available antiplatelet agents represent areas of development and deserve further investigation in order to appropriately manage CVD patients and provide better guidance in the search for new antiplatelet targets. Ticagrelor remains a key drug in the management of patients with CAD, and in particular ACS, that may be extended to other atherosclerotic conditions. As research continues in this field, pioneering clinical trials will establish further uses and constraints of Ticagrelor within specific patient populations and management strategies, and will determine whether the aforementioned novel regimens are incorporated into standard clinical practice.

The ease of manufacturing of bilayer tablet accompanied with minimal production cost and scalability provides an interesting prospect for polymeric drug delivery of poorly soluble drugs. The free flowing ability, granulating and compression characteristics render them useful in formulating solid oral dosage forms such as tablets.

The Present study was conducted to formulate and evaluate the immediate release tablet of Ticagrelor and sustained release of Cilostazol. The optimized formulation was subjected to accelerated stability studies and was found to be stable without any remarkable physicochemical changes. The above results indicate that the formulation of bilayered tablet of Ticagrelor and Cilostazol would be very beneficial for the patients for antiplatelet medication prevent from blood clot. Immediate release of Ticagrelor will significantly reduce the dose related side effects and thereby improve compliance, safety, and efficacy of drug.

The industrial acceptance of a product or process depends upon the cost utility and its analytical performance. In this case, the preparation involve simple wet granulation process in Rapid Mixer Granulator (RMG) and is a solvent free process in contrast use of organic solvents. Moreover, the raw materials and equipment required for preparation of bilayered tablets are very cheap and cost effective.

The bilayer tablets of Ticagrelor and Cilostazol was more palatable, and it is mostly helpful to the patients for the treatment of acute coronary syndrome, cardiac angina for antiplatelet therapy.

Thus, it can be concluded that bilayered tablet of Ticagrelor (immediate release) and Cilostazol (extended release) oral formulations prepared using wet granulation process are stable, efficacious and cost effective as compared to the other dosage form designs

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