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FORMULA OPTIMIZATION OF IMMEDIATE RELEASE TABLET OF CLOPIDOGREL BISULPHATE FREE FROM SURFACE IRREGULARITIES

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ABSTRACT

Clopidogrel Bisulphate is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Immediate release tablet of clopidogrel bisulphate (form II) was prepared by using direct compression technique. Clopidogrel Bisulphate is very hygroscopic and show rapid degradation when processed with alkali salt as Mg^{++}, Ca^{++} etc picking, sticking, or other kind of surface irregularities are other processing problems associated with it so, selection of excipients were done for preparation of stable dosage form which was free from any surface irregularities. Lubricants used were hydrogenated castor oil and poly-12-hydroxy stearate.

INTRODUCTION: Clopidogrel bisulfate is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. Chemically it is methyl (+)-(S)-α-(2-chlorophenyl) - 6, 7-dihydrothieno [3, 2-c] pyridine-5(4H)-acetate sulfate. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme [1, 2].

The active metabolite has an elimination half-life of about eight hours and acts by forming a disulfide bridge with the platelet ADP receptor. Adverse effects of clopidogrel include hemorrhage, severe neutropenia, and Thrombotic Thrombocytopenic Purpura (TTP) [3].

Commercially clopidogrel is available in the tablet sold by Bristol-Meyer squibb as PlavixTM containing 97.875 mg of clopidogrel hydrogen sulphate (equivalent of 75 mg of clopidogrel). A clopidogrel base occurs as an amorphous semi-solid paste-like mass & its physical state create problems related to processing and preparation of pharmaceutical dosage form.

Particularly clopidogrel bisulphate is extremely hygroscopic and cause picking, sticking, adhesion and other kinds of surface irregularities leading to finished product with poor quality and appearance [4].

Selection of excipients is also important factor because clopidogrel exhibit rapid degradation when co-processed with certain excipients, alkaline metal salts such as magnesium stearate and sodium stearyl fumerate. Study also involves new lubricants such as hydrogenated castor oil and poly-12-hydroxy stearate which has low moisture content and good lubrication property [1, 4, 5, 6].

MATERIAL AND METHOD:

Material: Clopidogrel bisulphate (form II) procured from Aarti chemical, Mumbai (Maharashtra, India), Lactose DCL 21 was procured from DMV international, Avicel 112 procured from FMC biopolymer, Pearlitol SD200 procured from Roquette (France), Klucel LF procured form Aqualon, HPC LH11 procured from Shin-Etsu.

Poly-12-hydroxy stearate (Acryflow-L) obtained as gift sample from Corel pharmaceutical Ltd. (Gujarat, India).

Method:

Formulation 1: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieves). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 2: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 3: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 4: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with hydroxypropylcellulose LH11. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 5: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with hydroxypropylcellulose LH11. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 6: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with hydroxypropylcellulose LH11. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 7: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with mannitol and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 8: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with mannitol and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 9: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with mannitol and remaining half mixed with hydroxypropylcellulose LH11. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 10: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with mannitol and remaining half mixed with hydroxypropylcellulose

LH11. Both powder mixture mixed together and passed through #40 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 11: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Klucel LF passed through #30 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 12: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Half quantity of microcrystalline cellulose mixed with lactose and remaining half mixed with crospovidone. Both powder mixture mixed together and passed through #40 sieve. Klucel LF passed through #30 sieve. Sieved mixture mixed with Aerosil (passed through #40 sieve). Whole mixture was mixed in double cone blender for 30 min. It was observed that sticking to machine punch and die surface did not occurred.

Formulation 13: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Microcrystalline cellulose mixed with lactose, hydrogenated castor oil (Cutina HR) crospovidone geometrically and powder mixture passed through #40 sieve. Sieved mixture mixed with Aerosil and passed through #40 sieve. Klucel LF passed through #30 sieve. Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 14: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Microcrystalline cellulose mixed with lactose, hydrogenated castor oil (Cutina HR), crospovidone geometrically and powder mixture passed through #40 sieve. Sieved mixture mixed with Aerosil and passed through #40 sieve. Klucel LF passed through #30 sieve. Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

Formulation 15: Clopidogrel Bisulphate mixed with Acryflow-L and passed through #40 sieve. Microcrystalline cellulose mixed with lactose, hydrogenated castor oil (Cutina HR) crospovidone geometrically and powder mixture passed through #40 sieve. Sieved mixture mixed with Aerosil and passed through #40 sieve. Klucel LF passed through #30 sieve. Whole mixture was mixed in double cone blender for 30 min. severe sticking found to lower punch and die surface.

TABLE 1: TRIAL BATCH FORMULATIONS FOR UNCOATED TABLET

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15
Clopidogrel Bisulfate	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875	97.875
DCL 21	62.205	58.845	56.445	-	-	62.445	57.645	52.845	-	-	51.645	50.445	50.925	49.725	49.725
Pearlitol PH 200	-	-	-	58.845	57.885	-	-	-	52.845	51.885	-	-	-	-	-
MCC PH 112	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800	70.800
Klucel LF	-	-	-	-	-	-	-	-	-	-	7.200	7.200	7.200	7.200	7.200
HPC LH 11	-	-	-	-	-	4.800	9.600	14.400	14.400	14.400	-	-	-	-	-
Acryflow-L	1.920	2.880	2.880	2.880	3.840	2.880	2.880	2.880	2.880	3.840	2.880	2.880	1.200	2.400	1.200
Crospovidone	6.000	8.400	10.800	8.400	8.400	-	-	-	-	-	8.400	9.600	9.600	9.600	9.600
Cutina HR	-	-	-	-	-	-	-	-	-	-	-	-	1.200	1.200	2.400
Aerosil	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200	1.200
Total wt. (mg)	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**
Presence of sticking	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes

Note: All the above formulations were observed for sticking and disintegration time resemble to Innovator's tablets.

RESULT AND DISCUSSION: The study was undertaken with an aim to formulate clopidogrel bisulphate immediate release tablet free from any type of surface irregularities. Formulation of tablet was done by direct compression technique.

Excipients selection was done by considering all the attributes in mind i.e. anhydrous or low moisture content and only directly compressible grades of fillers having acceptable flow properties were taken into study.

All the results for formula optimization are given in **table 1**.

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