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EFFECT OF LUBRICANTS ON THE STABILITY OF CLOPIDOGREL BISULPHATE TABLETS

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Abstract:

The objective of the current study was to develop oral formulation of Clopidogrel Bisulphate 75mg tablet and perform the accelerated stability study to obtain the stable product by using the various lubricants like magnesium stearate, stearic acid and pregelatinized starch.

Three different formulations of tablets were prepared and coded as F1, F2 and F3 containing the various lubricants i.e. magnesium stearate, stearic acid and combination of magnesium stearate and pregelatinized starch respectively. Tablets were prepared by direct compression method and the compressed tablets were film coated.

The tablets were placed in a stability chamber and accelerated stability studies at 40^0C and 75% RH were carried out at time 0, 3 and 6 months duration. In accelerated stability study, various tests were performed including hardness, disintegration, chemical assay and in-vitro dissolution test.

After preparation of tablets, the physical and chemical parameters of tablets at zero period of time were tested, and were found within their specification. After test the tablets were kept in the stability chamber for six months. After three and six months the physical and chemical parameters of tablets were also tested.

According to the results, the formulations containing the magnesium stearate and stearic acid degraded with the passage of time but the formulation containing the combination of pre-gelatinized starch and magnesium stearate were more stable as compared to the formulations containing the lubricants as magnesium stearate and stearic acid.

Key words: *Clopidogrel Bisulphate, Pregelatinized starch, Accelerated stability studies, In-vitro dissolution.*

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INTRODUCTION:

Stability of pharmaceutical products is important for patient's safety [1] and stability calculations of expiration date of the product [2]. Stability of a pharmaceutical product means the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications [3, 4]. In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instructions. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation [5]**.** Pharmaceutical products adopt various pathways of chemical degradation including hydrolysis, oxidation, deamination and cyclization [6]. Accelerated stability studies are performed in order to predict the long term stability of pharmaceutical products [7]. They also help to identify the major degradation products; degradation pathways and stability indicating potential of analytical procedure used [8]. These studies are performed by exposing the representative sample of pharmaceutical product to stress conditions of temperature, humidity, light and radiations. Most companies conduct some types of accelerated degradation studies but companies' practices vary widely in term of when and how these studies are to performed [9].

Clopidogrel is a routine component of the clinical management of patients after acute coronary syndrome. It has been reported that this drug would reduce rates of major cardiovascular adverse events [10]. It is approved for the reduction of atherosclerotic events in patients with stroke, myocardial infection, cardiovascular disease and acute coronary syndrome. Its action may be related to an adenosine diphosphate (ADP) receptor on platelet cell membranes. It specifically and irreversibly inhibits the platelet P2Y12 subtype of the ADP receptor, which is important in the aggregation of platelets and cross-linking by the protein fibrin [11]. As a result, activation of the glycoprotein IIb/IIIa complex, which is involved in platelet activation and stabilization of the platelet aggregate, is also inhibited [12].

The preparation of useful formulations of Clopidogrel bisulphate is complicated due to stability issues. The objective of the current study was to develop oral formulation of Clopidogrel Bisulphate 75mg tablet and perform the accelerated stability study to obtain the stable product by using the various lubricants like magnesium stearate, stearic acid and pregelatinized starch.

MATERIALS AND METHODS:

Materials

Clopidogrel bisulphate powder (as a gift from Panacea pharmaceuticals Islamabad), Avicel -102 (JRS Pharma Germany), Lactose spray dried (SD) (New Zealand,), Pregelatinized starch (Maya Corporation Pakistan), Magnesium stearate (Taiwan), Stearic acid (Taiwan), Talcum (China), Hydrochloric Acid (Lab Scan, Thailand) and Potassium Chloride (Merck , Germany).

Instrumentation

Rotary Z-P 19 (China), Monsanto hardness tester, Friabilator (Curio FB-2020), Disintegrator (Curio DT-2020), Sonicator USA (NY-(12203) , UV Spectrophotometer , Tech Comp (UV 2300), pH meter Hanna Instruments (PH-210), Dissolution Apparatus (Curio Pakistan 2020) and Stability Chamber (Galvano Scientific GSC-150S).

Methods

Formulation of Clopidogrel bisulphate tablets:

Clopidogrel bisulphate tablets were prepared by direct compression method according to the formulations as shown in Table 1. The self-designed formulation containing magnesium stearate was coded as F1, formulation containing stearic acid as F2 and formulation containing both magnesium stearate and pregelatinized starch as F3.

Table 1: Formulations of Clopidogrel bisulphate tablet

S.No	Ingredients	F1(mg/tablet)	F2 (mg/tablet)	F3 (mg/tablet)
1	Clopidogrel Bisulphate (76.63%)	97.9	97.9	97.9
2	Avicel PH102	104	104	104
3	Lactose (SD)	22.1	22.1	19.52
4	Magnesium Stearate	3	-	0.58
5	Stearic acid	-	3	-
6	Pregelatinized Starch	-	-	5
7	Talcum	5	5	5
	Total weight of tablet	**232**	**232**	**232**

Preparation of tablets: [13,14]
Clopidogrel bisulphate, Lactose SD, Avicel-102 were sieved through mesh 30 and lubricants through mesh 60. Clopidogrel bisulphate, lactose SD, Avicel-102 were mixed in a polythene bag by geometrical mixing. Lubricants were added to this powder and mixed for 15 minutes. The powder blend was compressed through rotary machine under the given weight of tablet. Friability test results of all the three formulations were within the limits. After compression the compressed tablets were film coated.

Accelerated Stability Studies
Clopidogrel bisulphate 75 mg film coated tablets in the form of packs in triplets were placed in stability chamber with controlled temperature and humidity of class IV climatic conditions as recommended by ICH guidelines 2007. Temperature was maintained at 40 $\pm 2^0$ C and relative humidity was controlled by KCI solution at RH 75±5 %.

Evaluation of Clopidogrel bisulphate film coated tablets
The film coated tablets were evaluated for hardness, disintegration, chemical assay and dissolution. These tests were performed during accelerated stability study.

Hardness test
Ten tablets from each formulation were selected randomly and subjected to hardness test by using the Monsanto hardness tester.

Disintegration test
The disintegration test was carried out in accordance to USP 30 specifications by using Disintegration Tester. Six tablets from each formulation were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the last tablet to disintegrate completely was recorded in minutes.

Chemical assay
Limits: 90 – 110 %
Preparation of 0.1M HCl Solution
8.5ml Concentrated HCl was taken in 1000ml volumetric flask and distilled water was added to make up the final volume.

Preparation of Standard solution
Standard solution was prepared by taking powder equivalent to 100 mg of Clopidogrel working standard in 50ml of volumetric flask. Then added 0.1M HCl up to the mark. Solution was stirred on sonicator for 5 minutes to dissolve the drug completely. Filter, if necessary, and dilute 5 ml of the filtrate to 25 ml with 0.1 M HCl.

Preparation of Sample Solution
20 tablets were accurately weighed and crushed. The sample solution was prepared by taking powder equivalent to 100mg of Clopidogrel, in 50ml volumetric flask. Then added 0.1M HCl up to the mark. Solution was stirred on sonicator bath for 5 minutes to dissolve the drug completely. Filter the solution and dilute 5 ml of the filtrate to 25 ml with 0.1 M HCl.
The solution was analyzed on U.V Spectrophotometer and then compared its absorbance with standard curve and calculated its percentage at wave length 270 nm.
% of Clopidogrel bisulphate = (Absorbance of sample/Absorbance of standard) x 100

In-vitro dissolution study
Parameters of dissolution test
Apparatus II: 50 rpm
Time: 30 minutes
Medium: 900ml; pH 2.0 hydrochloric acid buffer
Limits: Not less than 80% of the labeled amount of Clopidogrel should be dissolved in 30 minutes.
Preparation of Hydrochloric acid buffer pH 2.0
Hydrochloric acid Buffer solution pH 2.0 was prepared according to USP 2013.
Potassium chloride 0.2M
14.91gm of potassium chloride was dissolved in water and dilute with water to 1000ml.
HCl buffer solution
50ml of potassium chloride was taken in a 200ml volumetric flask and added the specified volume of HCl solution (13.1ml) then added water to make up the volume.

Preparation of standard solution
Powder equivalent to 100mg of Clopidogrel working standard was accurately weighed and transferred to 100 ml volumetric flask. Dissolution medium was added and volume was made up to the mark. Solution was stirred on sonicator for 5 minutes to dissolve the drug completely. Filter, if necessary, and dilute 8 ml of the filtrate to 100 ml with dissolution medium to obtain a solution having a known concentration corresponding to that of the solution under test**.**
Procedure
The dissolved amount of Clopidogrel bisulphate was determined by employing UV absorption at a wavelength of 270nm on filtered portion of the solution under test in comparison with the standard solution.
% of Clopidogrel bisulphate = (Absorbance of sample/Absorbance of standard) x 100

RESULTS AND DISCUSSION:
Three different formulations of tablets were prepared and coded as F1, F2 and F3 containing the various lubricants i.e. magnesium stearate, stearic acid and pre-

gelatinized-starch. Tablets were prepared by direct compression method and the compressed tablets were film coated. The tablets were placed in a stability chamber and accelerated stability studies were carried out at time 0, 3 and 6 months duration.

The hardness of all formulations tablets during duration of accelerated stability studies were with in range of 3-6 Kg/cm^2 as shown in Table 2 and disintegration test results of all the formulations was less than 15 mints and within the limits of USP as shown in Table 3.

Table 2: Results of Hardness

S.No	Hardness (Kg/cm2) at zero time	Hardness (Kg/cm2) after 3 months	Hardness (Kg/cm2) after 6 months
F1	5	4	4
F2	4	3	3
F3	5	3	4

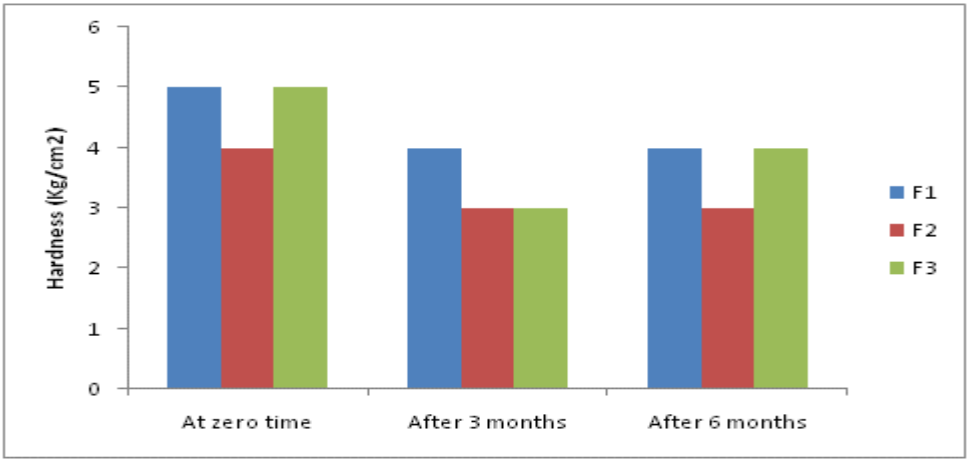

Fig. 1: Graphical presentation of comparison of Hardness

Table 3: Results of Disintegration time

S.No	Disintegration time (minutes) at Zero time	Disintegration time (minutes) after 3 months	Disintegration time (minutes) after 6months
F1	3	4	4
F2	5	5	4
F3	3	4	3

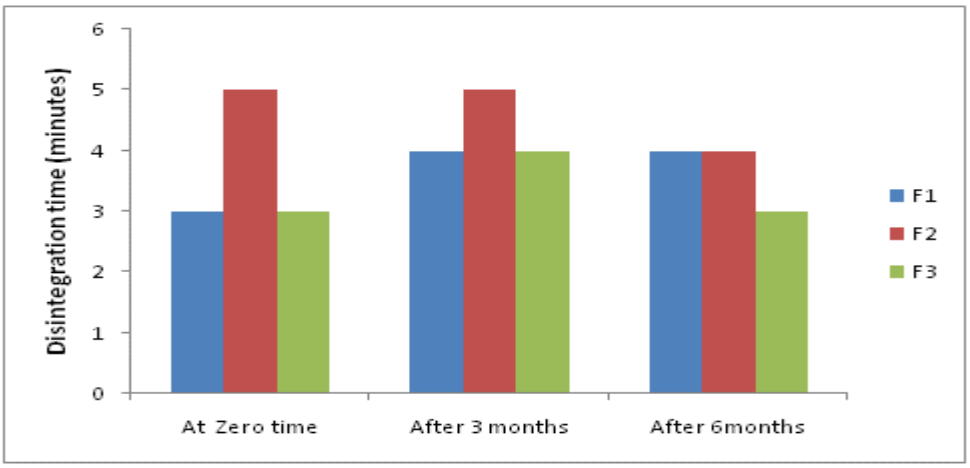

Fig. 2: Graphical presentation of comparison of Disintegration time

Table 4: Results of chemical Assay

S.NO	Chemical assay at zero time (%)	Chemical assay after 3 months (%)	Chemical assay after 6 months (%)
F1	108.66	76.89	72.33
F2	102.54	88.38	72.33
F3	104.71	108.8	103.10

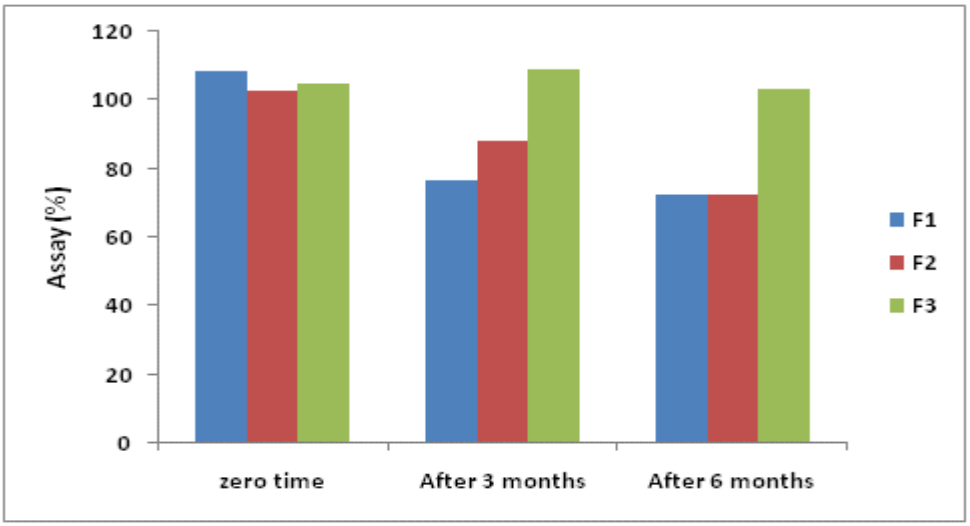

Fig. 3: Graphical presentation of comparison of Chemical assay

Assay of tablets showed that percentage release of drug is stable in formulation F3 containing the pregelatinized starch and magnesium stearate as compared to other formulations containing the magnesium stearate (F1) and stearic acid (F2) within different time durations. Formulation F1 and F2 degraded with the passage of time. Table 4 shows the percentage of assay of different formulations.

Table 5 shows the results of in-vitro dissolution studies carried out on three formulations. In-vitro dissolution result of formulation F1 at time zero 95.51% which is within the limits, after 3 months 68.75% which did not comply the specifications and after 6 months 77.70% which was also below the limits for dissolution test. In-vitro dissolution result of formulation F2 at time zero 96.15% was within limits, after 3 months 76.87% which did not comply the specification and after 6 months 68.15% which was below the specifications. In-vitro dissolution result of formulation F3 at time zero 91.66%, after 3 months 93.12% and after 6 months 85.35% which were all within the specified limits for dissolution test.

Table 5: Results of Dissolution

S.NO	Dissolution (%) at zero time	Dissolution (%) after 3 months (%)	Dissolution (%) after 6 months (%)
F1	95.51	68.75	77.70
F2	96.15	76.87	68.15
F3	91.66	93.12	85.35

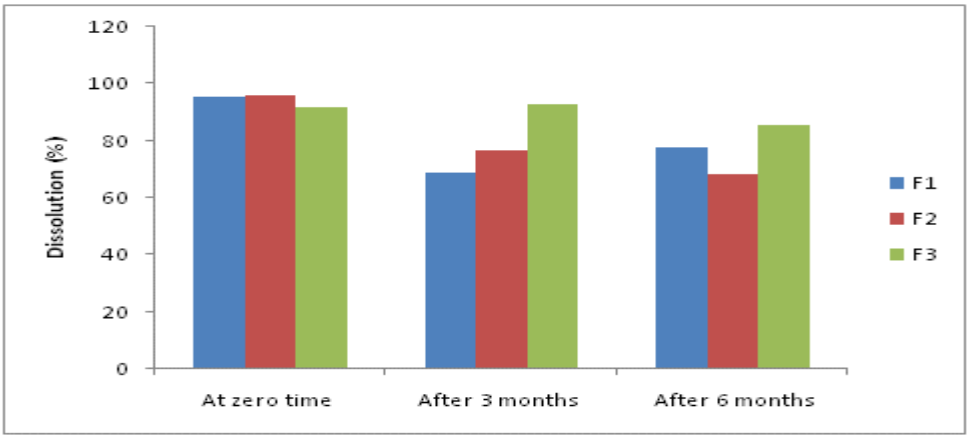

Fig. 4: Graphical presentation of comparison of Dissolution data

CONCLUSION:

It was concluded from the present study that lubricants such as magnesium stearate and stearic acid degraded the product with the passage of time and their concentration in the formulation was lower. If these lubricants are included in the formulations in higher concentrations then the process of degradation will also be higher. On the other hand, the results of chemical assay and dissolution of formulation (F3) containing magnesium stearate and pregelatinized starch were within their specified limits during stability studies. It showed that pregelatinized starch has self lubricating property in combination with other lubricant i.e. magnesium stearate at that concentration which in turn provides stability to the formulation. So it means that formulation (F3) is more stable and also offers patient compliance.

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