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Compatibility and Chemical Stability Study of Bilayer Tablets Pharmaceutical Dosage Form of Aspirin/Clopidogrel as Eudragit L100 Polymer Main Excipient

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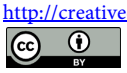

Abstract

Due to the multiple diseases in the same patients, and the multiple medications they were taking, it was necessary to formulate medications containing two or more pharmaceutical substances to reduce the patient's dosage and, as a result, reduce side effects. In this study aspirin and clopidogrel were formulated together in a pharmaceutical dosage form that ensures the chemical and physical stability. By wet granulation method as a first layer for clopidogrel as eduragit L100 as a polymer, which is considered an inner granule that achieves acceptable properties. The study formulates bilayer tablets containing aspirin and clopidogrel, using Eudragit L100-coated clopidogrel granules to minimize direct contact between the two drugs. Tablets were produced by wet granulation and evaluated for physical quality, dissolution, disintegration, and accelerated stability (40˚C/60% RH, three months) for the first study, and another condition (50˚C/75% RH, three months). Results show acceptable tablet hardness, friability, disintegration, and 94% - 99% drug content after accelerated testing, indicating chemical compatibility. The authors conclude that the bilayer design with Eudragit L100 improves stability of the aspirin-clopidogrel combination.

Subject Areas

Analytical Chemistry

Keywords

Aspirin, Clopidogrel, Bilayer Film Coated Tablet, Physical Property, Chemical Stability

1. Introduction

Aspirin is the genericized trademark for acetylsalicylic acid (ASA), a nonsteroidal anti-inflammatory drug (NSAID) used to reduce pain, fever, and inflammation at high doses, and as an antithrombotic at low doses [1]. Specific inflammatory conditions that aspirin is used to treat include Kawasaki disease, pericarditis, and rheumatic fever. Aspirin is also used long-term to help prevent further heart attacks, ischemic strokes, and blood clots in people at high risk. Inhibition of cyclo-oxygenase (COX) synthesis, which leads to inhibition of the biosynthesis of prostaglandins and thromboxane from arachidonic acid, causes prevention of vasoconstriction and a decrease in platelet aggregation [2]. Clopidogrel is an antiplatelet medication used to reduce the risk of heart disease and stroke in those at high risk. It is also used together with aspirin in heart attacks and following the placement of a coronary artery stent (dual antiplatelet therapy) [3]. Clopidogrel is used to prevent heart attack and stroke in people who are at high risk of these events, including those with a history of myocardial infarction and other forms of acute coronary syndrome, stroke, and those with peripheral artery disease. Present for treatment with a myocardial infarction with ST-elevation, including a loading dose given in advance of percutaneous coronary intervention (PCI), followed by a full year of treatment for those receiving a vascular stent, a loading dose given in advance of fibrinolytic therapy, continued for at least 14 days. Present for treatment of a non-ST elevation myocardial infarction or unstable angina including a loading dose and maintenance therapy in those receiving PCI and unable to tolerate aspirin therapy. Maintenance therapy for up to 12 months in those at medium to high risk for whom a noninvasive treatment strategy is chosen. The investigation was concerned with design and chemical stability characterization of oral bi-layer tablets of aspirin/clopidogrel, in order to improve efficacy with compatibility and better patient compliance [4]. By necessity, design bilayer tablets remain the most considered one for administration of drugs with two or more pharmaceutical active ingredients still the ruling dosage for multiple diseases [5]. For many reasons bilayer tablets are formed; to achieve delivery rate control of two or more different active pharmaceutical ingredient(s), to ensure the compatible active pharmaceutical ingredients from each other, to control active pharmaceutical ingredients release from one layer by utilizing the physical property of the other layer (such as, osmotic property), to improve bioavailability, reduce the waste of drugs, and the most important one to ensure solubility of drugs and stability of the chemical property [6]. Utilizing bilayer tablet approach is the goal of this study to administer aspirin/clopidogrel bilayer that formulated to improve bioavailability, solubility, chemical stability and to get maximum therapeutic benefits by patients that need the combination of aspirin and clopidogrel in cases of in acute coronary syndromes, acute myocardial infarction and unstable angina, and in coronary stenting [7] [8].

2. Materials and Methods

2.1. Material

Aspirin powder supplies by saphnix lifesciences, ultrathya paonta, India, Clopidogrel Powder (Zhejiang Menovo Pharmaceutical Co., LTD, China), microcrystalline cellulose (Avesil PH 101) by Ranbaxy fine chemicals New Delhi, India Polyvinylpyrrolidone (PVP) by FMC, JRS pharma Croscarmellose by Anmol chemicals Mumbai, India, Edragit L100 by Evonik India pv TLTD, starch powder by signet chemicals, lactose monohydrate by Anmol chemicals Mumbai, India, Talc(Afco, India), castor oil by Anmol chemicals Mumbai, India, stearic acid by Anmol chemicals Mumbai, India.

2.2. Strategy for Physicochemical Examinations

The required sampling rules were observed physicochemical tests were collected separately. Samples for microbial analysis were collected using sterile tools after taking preventive rolls such as wearing a breath mask, sterile gloves, sterile bags, and sterile plastic tools as well.

3. Method of Manufacturing [9] (Table 1)

3.1. Granulation

Clopidogrel bisulfate was loaded into a mixer and stirred for 5 minutes to prevent powder particles from clumping, then granulated with eduragit L100 after being dissolved in ethanol for wet granulation for 20 min for inner granules [10].

Table 1. Bi-layer tablets' ingredients formulation.

Excipients/API	Asp	Clo
API	100	97.8
MCC	12	15
PVP	5	-
Eudragit L 100	-	3.2
Croscarmellose	7	7
Lactose	7	12
Starch	5	-
Talc	3	4
Stearic Acid	1	-
Castor Oil	-	1
Tablet wight	140 mg	140 mg
Bi-layer tablets wight = 280 mg		

3.2. Sieving

Materials transferred to an air bed to dry the granules (wet granulation), then sifting through mesh # 20.

3.3. Mixing

The granules of clopidogrel were mixed for 45 min with its excipients (MCC, croscarmellose, lactulose monohydrate to uniformity powder size.

3.4. Lubricated

Add talc and castor oil lubricant for 5 min, after that, the mixture was loaded into a double cone blender and samples were collected and uniformity was achieved. All this was done in the dark and lightness lab.

3.5. Sieving

Aspirin powder sifts through mesh # 20 then is loaded into a double cone blender and also stirred for 5 minutes to prevent powder particles from clumping.

3.6. Mixing

loaded MCC, croscarmellose, lactulose monohydrate after that through mesh # 20.

3.7. Lubricants

Then, talc and castor oil lubricant were used for 5 minutes, with uniformity also achieved in the dark and lightness lab.

4. Physical study of Powder

Bulk density (Table 2): That is the ratio of the mass, m, of an amount of bulk solid to its volume, V, $\rho B = M/V_B$. **Tap density:** the density of a powder after it has been mechanically tapped, which reduces the air spaces between particles, resulting in a higher density than the initial bulk density, $\rho T = M/V_T$. **Hausner ratio:** is a measure of a material's flowability, specifically how easily a powder or granular material can be compressed and how well it flows, $HR = \rho T/\rho B$. **Carr's index (%):** measure of a powder's compressibility, indicating how much it can be compacted under pressure, $CI = (\rho T - \rho B)/\rho T * 100$. **Angel of repose (˚):** derived from the relationship between the coefficient of friction and the angle of friction. $\theta = \tan^{-1}$ (h/r), where θ is the angle of repose, h is the height of the pile, and r is the radius of the base of the pile.

Table 2. Bi-layer tablets aspirin/clopidogrel powder characterization.

Sample	Bulk density g/cm^3	Tap density g/cm^3	Hausner ratio	Carr's index %	Angel of repose (˚)
Asp 1	0.51 ± 0.01	0.55 ± 0.011	1.078	7.272	21.088
Asp 2	0.51 ± 0.02	0.54 ± 0.014	1.058	5.555	16.102

Continued

Asp 3	0.49 ± 0.02	0.56 ± 0.012	1.143	12.5	36.233
Asp 4	0.54 ± 0.03	0.55 ± 0.01	1.018	1.818	5.269
Clo 1	0.49 ± 0.02	0.52 ± 0.01	1.061	5.769	16.722
Clo 2	0.52 ± 0.01	0.54 ± 0.014	1.038	3.703	10.733
Clo 3	0.49 ± 0.02	0.53 ± 0.012	1.081	7.547	21.876
Clo 4	0.49 ± 0.03	0.52 ± 0.01	1.061	5.769	16.722

5. Bi-Layer Tablets Pharmaceutical Formulation of Aspirin/Clopidogrel

It includes multistep, where the active ingredients are mixed with their excipients that ensure physical and chemical stability that eudragit L100 (methacrylic acid - methyl methacrylate copolymer (1:1) powder (Mw = 125,000) g/mol [11], within the constitutional limits and becomes the final beneficial medicinal product [12]. Currently multiple medication formulations are available on the market to prescribe and for patients to utilize. Each of these pharmaceutical formulations has had a significant amount of time and money put into the production of the combination of medications to understand how they work and to test their efficacy with chemical and physical stability [13].

Compression: Aspirin was loaded in the first funnel and clopidogrel in the second one on the bi-layer machine compression that was done at speed of 25 ± 2 RPM, where the lubricated powders were transferred into bilayer tablet compression machine with 15 mm punches with Aspirin as first layer and Clopidogrel as second layer with accepted bi-layer tablets wight, shape, thickness and hardness. **Table 3** summarizes physical properties of bilayer film-coated tablets aspirin/clopidogrel.

Table 3. Physical stability study of bi-layer film-coated tablets.

Bilayer tablets	Thickness (mm) n = 25	Hardness (kp) n = 25	Friability (%) n = 25	Deviation weight variation (mg) n = 25	Disintegration (min)	Dissolution (min)
Asp-Clo 1	2.5 - 2.8	6.8 - 8.8	0.99	0.04 - 0.045	28 ± 0.5	15 ± 1
Asp-Clo 2	2.7 - 2.8	8.5 - 9.5	0.98	0.03 - 0.04	27 ± 0.5	16 ± 1
Asp-Clo 3	2.4 - 2.7	8.9 - 9.5	0.97	0.04 - 0.045	28 ± 0.5	11 ± 1
Asp-Clo 4	2.4 - 2.9	6.9 - 9.7	0.98	0.025 - 0.035	29 ± 0.5	14 ± 1
Asp-Clo 5	2.6 - 2.8	8.7 - 8.9	0.98	0.025 - 0.03	28 ± 0.5	14 ± 1

6. Film Coating

Tablets coated with HPMC, PEG and lactose monohydrate that were weighted and dissolved in water, then loaded into a coating funnel, PVP water soluble polymer used as binder, titanium dioxide water insoluble making suspension, and iron oxide as a colorant cl 77,491.

7. Stability Study [14]

Performed to evaluate biopharmaceutical products under various environmental conditions (temperature, humidity, light, etc.) by time; randomly 20 bi-layer film coated tablets packets at an accelerated stability predictions of stability over a much longer period than the stability study can be defended, were taken for 3 months were studied at 40˚C, 60% RH for 10 pockets (Table 4), and at 50˚C, 75% RH for another 10 pockets (Table 5).

Table 4. Stability study of bilayer film-coated tablets for 1st and 2nd 10 pockets.

Stability study for first 5 pockets (first study)	API contents %
Asp-Clo, 1 month 40˚C, 60% RH	A = 98, C = 96
Asp-Clo, 2 month 40˚C, 60% RH	A = 96, C = 95
Asp-Clo, 3 month 40˚C, 60% RH	A = 94, C = 92
Stability study for second 5 pockets (second study)	
Asp-Clo, 1 month 40˚C, 60% RH	A = 99, C = 98
Asp-Clo, 2 month 40˚C, 60% RH	A = 97, C = 96
Asp-Clo, 3 month 40˚C, 60% RH	A = 93, C = 95

Table 5. Stability study of bilayer film-coated tablets for 3rd and final 10 pockets.

Stability study for another 5 pockets (third study)	API contents%
Asp-Clo, 1 month 50˚C, 75% RH	A = 97, C = 94
Asp-Clo, 2 month 50˚C, 75% RH	A = 94, C = 92
Asp-Clo, 3 month 50˚C, 75% RH	A = 90, C = 91
Stability study for final 5 pockets (final study)	
Asp-Clo, 1 month 50˚C, 75% RH	A = 98, C = 94
Asp-Clo, 2 month 50˚C, 75% RH	A = 94, C = 92
Asp-Clo, 3 month 50˚C, 75% RH	A = 92, C = 90

8. Dissolution and Analysis Assay

8.1. Dissolution Test

Clopidogrel/aspirin, acid buffer medium pH 2, volume 1000 ml, temperature 37˚C ± 0.5˚C, RPM 100, time 25 min. Aspirin, acetate buffer medium pH 4.5 - 5, volume 1000 ml, temperature 37˚C ± 0.5˚C, time 25 min using RC-6 dissolution tester [15].

8.2. HPLC Assay [6]

Randomly taken, weighted and titrated 6 tablets. The tablet triturate equivalent to

10 mg of the drug was weighed accurately and dissolved in suitable ethanol. The solution was filtered and diluted suitably. Further dilutions were done suitably to get a concentration of 10 µg/ml with buffer pH 6.8. The drug content was analysed by HPLC at 235 nm.

8.3. pH 6.8 Buffer

In purified water, adjust 4.52 g of sodium acetate and 14 mL of 2 N acetic acid in 1000 mL and pH to 6.8 with 2 N acetic acid (17.1 mL of acetic acid in 1000 mL).

8.4. Standard Stock

Weigh and transfer about 50 mg of clopidogrel working standard into 50 mL flask, dissolve the mobile phase and make up the volume with mobile phase.

8.5. Standard Preparation

5 mL of stock into 25 mL volumetric flask and make up the final volume with mobile phase.

8.6. Disintegration Results

At an acid medium HCl 0.1N was studied using BJ-3 disintegration tester, the results are shown in Table 3.

9. Evolution of Bilayer Pharmaceutical Dosage Form

By HPLC analysis, the pure aspirin/clopidogrel drugs and their excipient mixture were analyzed. From the graphs based on peaks and wave numbers the specific functional group of aspirin (ester) and clopidogrel (binding chloride), no additional peaks were obtained which indicates that there is no significant interaction between drug and excipients in this way. And the results of bilayer tablets of (40˚C, 60% RH), which ensured the stability of the active pharmaceutical ingredients 98% (Asp) and 96% (Clo) for 1st study, are clear evidence that HPLC results under applicable conditions and preparation method had acceptable stability results. After 3 months at accelerated stability and 94% (Asp), and 92% (Clo) for the final study after 3 months at accelerated stability (Table 4 APIs contents, for the first 5 pockets (first study)), with these results, we ensured the chemical stability. These results confirm the stability of the pharmaceutical preparation by reducing the contact surface between aspirin/clopidogrel by wet granulation of clopidogrel particles that are coated with Eduragit L100, thus by fully coating clopidogrel powder particles, we have preserved the chlorine binding and using suitable excipients that are chemically compatible with aspirin as well. Finally, results study with other conditions (50˚C, 75% RH) that ensured the stability of active ingredients 97% (Asp) and 94% (Clo), and after 3 months at accelerated stability 92% (Asp) and 90% (Clo) (Table 5 APIs contents, for final 5 pockets (final study)).

10. Tablets Evaluation

Weight variation: 25 tablets were randomly selected, weighed individually and all together to evaluate weight variation where the smallest bi-layer tablets weight was 272 mg and the largest weight was 294 mg, ***hardness*** of the tablet in a diametric compression YD-1A tablets hardness tester. (expressed in kg/cm^2) was within accepted range, ***thickness*** of 25 tablets were randomly selected and measured by using Vernier Caliper also within acceptable limits then collected to be coated with film and that the packaging is done in a systematic manner, ***friability (F)*** to evaluate the tablet's mechanical strength of the tablet determined using CS-1 tablets friability tester in a plastic chamber revolving at 50 rpm and pre weighed sample of tablets was placed in the friabilator subjected to the 250 revolutions (film coated tablets) (Table 5).

Figure 1 shows the percentage stability of the first 5 pockets at a stability accelerated study with (40˚C, 60% RH) of aspirin/clopidogrel as 98% - 94% for aspirin and 96% - 92% for clopidogrel so that the aspirin/clopidogrel percentage is acceptable and effective. Whereas Figure 2 also shows the same acceptable and effective at percentage stability accelerated study for 2nd pockets with 99% - 95% for aspirin and 98% - 95% for clopidogrel percentage, which is considered acceptable according to US Pharmacopoeia 90% - 110% [14].

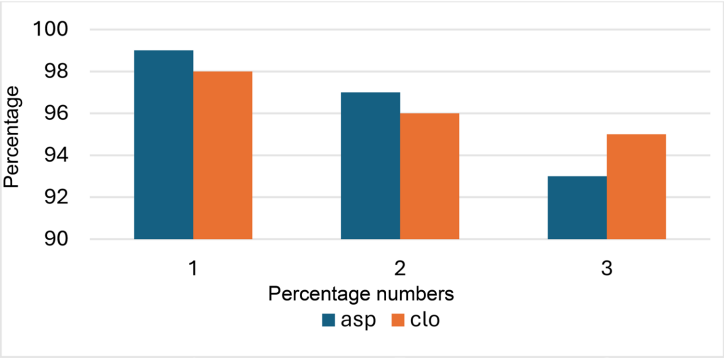

Figure 1. Percentage stability accelerated study for 1st pockets.

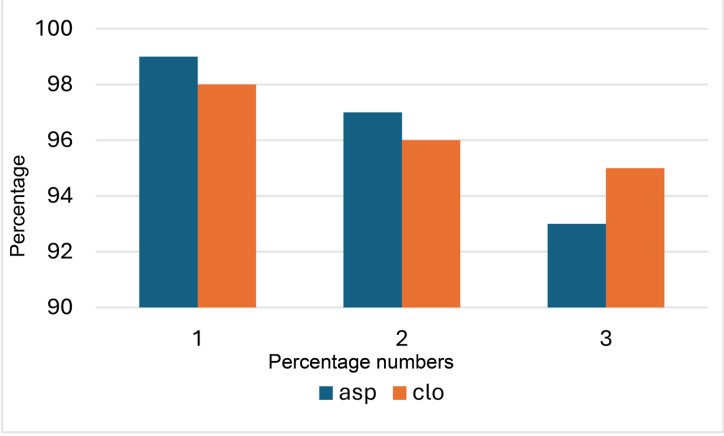

Figure 2. Percentage stability accelerated study for 2nd 5 pockets.

Whereas Figure 3 shows the percentage stability of 3rd study of 5 pockets at a stability accelerated study with another condition (50˚C, 75% RH) of aspirin/clopidogrel the results were 97% - 90% for aspirin and 94% - 91% for clopidogrel so that the aspirin/clopidogrel percentage is constitutionally acceptable. And Figure 4 also shows the same acceptable and effective at percentage stability accelerated study with the same condition for final 5 pockets with 98% - 92% for aspirin and 94% - 90% for clopidogrel percentage.

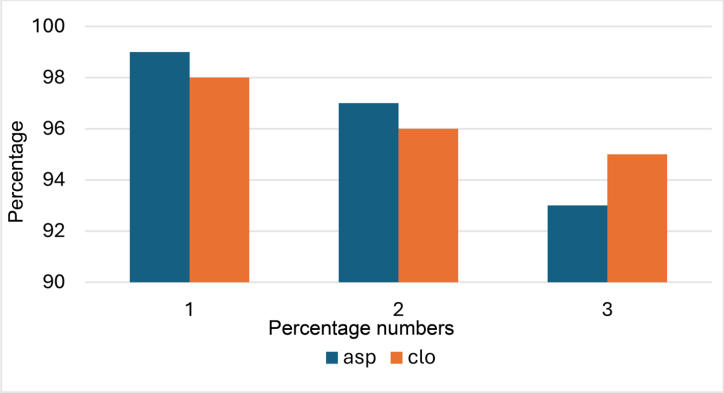

Figure 3. Percentage stability accelerated study for 3rd 5 pockets.

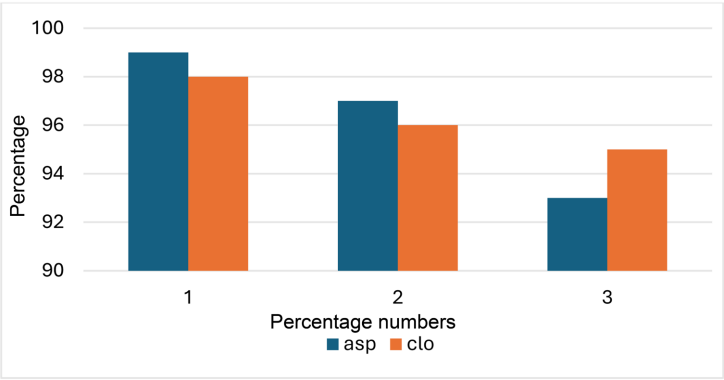

Figure 4. Percentage stability accelerated study for final 5 pockets.

11. Conclusion

In this research, we proposed a pharmaceutical formulation to develop a stable combination of tablets aspirin and clopidogrel, ensuring compatibility and chemical stability between them over physical stability. The reason for the chemical incompatibility between aspirin and clopidogrel is the ester and carboxyl groups in aspirin and the chlorine binding to the ring of clopidogrel a resulting in a smell similar to acetic acid. Necessarily, it must suggest a pharmaceutical form that ensures the compatibility between them. The results showed that clopidogrel was prepared by wet granules with eudragit L100, manufactured in a darkness, moisture-free lab, and applied a bilayer film-coated tablet, whereas we used eudragit as a polymer that coats clopidogrel molecules internally. This resulted in a significant

reduction in the contact area between the functional group of two compounds, and by using bi-layer film coated tablets significantly reduced the interaction rate by reducing the contact surface between them, ensuring the compatibility and chemical stability. Based on the results we obtained, as shown in Table 4 and Table 5, which showed constitutionally acceptable results, the proportions of the active ingredients of both substances must be 90% - 110% according to the US Pharmacopoeia, which confirms acceptable physical properties reflects chemical stability of aspirin/clopidogrel.

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Conflicts of Interest

The authors declare no conflicts of interest.

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