DEVELOPMENT AND IN VITRO EVALUATION OF TABLET IN CAPSULE DRUG DELIVERY SYSTEM FOR SIMULTANEOUS ADMINISTRATION OF TWO ANTI-PLATELET DRUGS

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Abstract: Large number of elderly population suffers from heart stroke and secondary symptoms associated with it. To treat this condition, a novel tablet in capsule approach was developed wherein the combination of two antiplatelet drugs was used. Clopidogrel bisulphate was used as an immediate release blend incorporated in hard gelatin capsule which shows quicker onset of action while enteric coated aspirin tablet incorporated in capsule shows pulsatile release after predetermined lag time of about 4 h. The immediate release blend completely dissolved in 0.1 N HCl (1.2 pH) within 120 min. The enteric coating polymers, Eudragit L100 and Eudragit S 100 having pH dependent solubility, were used for coating of aspirin tablet for achieving desired lag time before rapid and complete drug release. The lag time and drug release depends upon coating level of pH dependent polymers.

Keywords: Pulsatile, clopidogrel, aspirin, heart stroke, tablet in capsule drug delivery
INTRODUCTION

Circadian rhythms have been well established for almost all body function. e.g., heart rate, stroke volume, blood pressure, blood flow, peripheral resistance, blood viscosity, body temperature, gastric pH and plasma concentration of various substances such as hormones, c-AMP, protein, enzyme, glucose etc. In addition various organs’ function varies with the time of the day. Researchers have recognized onset and symptoms of certain disease which shows predictable variations within the 24 h of the day. Diseases like cardiovascular disease (ischemic heart stroke, platelet aggregation, and hypertension), asthma, arthritis, duodenal ulcer and cancer show different circadian rhythms during 24 h of the day (Gohel et al. 2002). In peptic ulcer patients, gastric acid secretion is highest during the night. Cardiovascular disease shows capillary resistance and vascular reactivity higher in morning and decreases latter in the day. The circadian and reactive changes in adrenergic activity are the driving factor in the day-night variation in platelet function. Platelet agreeability was low in midnight at 12 a.m. and start increases thereafter. In the early morning, platelet activity was quite higher and remains up to 8 a.m. This could lead to a state of relative hyper coagulability of the blood and produces chances of heart stroke (Haus et al., 2007). Stroke is the third leading cause of death worldwide. As age is an important non modifiable risk factor, the incidence of stroke is expected to rise as individuals are now living longer. After having suffered a stroke, victims are more likely to experience another stroke or transient ischemic attack (TIA) than a subsequent heart attack. More than 7,80,000 cases of stroke occur each year. Secondary stroke prevention is of vital concern because 25% of strokes each year are recurrent. Antiplatelet therapy is the most effective strategy for preventing recurrent stroke in patients with a history of minor stroke or transient ischemic attack (TIA) of non cardio embolic origin, which account for 80% of all strokes. Clinicians have 3 choices of predominant antiplatelet therapy for secondary stroke prevention: acetylsalicylic acid (ASA), ASA + extended release dipyridamole, and clopidogrel and extended release aspirin (Chaturvedi et al.). In the treatment of platelet aggregation two drugs are mostly used in combination for
management of patients with heart stroke and secondary events associated with it. The risk of secondary events after stroke or acute myocardial infarction (AMI) is high and thus reducing this risk by administering aspirin and clopidogrelbisulphate in combination is very effective (Aino et al 2009).

For this purpose, we have developed new tablet in capsule formulation containing two antiplatelet drugs. The main object of this study is to prevent heart stroke and release the drug at right time. Hard gelatin capsule consist of clopidogrelbisulphate blend and enteric coated aspirin tablet. Clopidogrelbisulphate release immediately from blend after disintegration of hard gelatin capsule shell and enteric coated aspirin tablet releases drug after predetermined lag time.

Clopidogrelbisulphate releases immediately from blend and provide pharmacological action between midnight to early morning, the period during which platelet activity increases. The enteric coated aspirin tablet release drug in the intestine after predetermined lag time of 4 h i.e. early in the morning, when platelet activity was quite higher and give an effective therapeutic drug concentration. Eudragit L100 and Eudragit S100, pH dependent polymers, which only dissolved at or above pH 6, were selected as the coating material to fit the mentioned purpose. The combination has been shown to provide better cardiovascular protection.

**MATERIALS AND METHODS**

**Material**

Aspirin and clopidogrelbisulphate were received as a gift sample from Cadila Pharmaceuticals Ltd, Ahmadabad, India. Microcrystalline cellulose (Avicel 102) was supplied as a gift sample by Research lab, Mumbai, India. Croscarmellose sodium, stearic acid, talc, lactose monohydrate, Sodium hydroxide, Potassium dihydrognorthophosphophate, Potassium chloride were supplied by Loba chemie, Mumbai, India. Eudragit L 100 and Eudragit S 100 supplied gratis sample by Evonik Degussa Pvt Ltd, Mumbai, India. Diethyl phthalate (Loba chemie, Mumbai, India.) was use as a plasticizer. All other chemicals used were of analytical grade.

**Method**

**Preparation of ClopidogrelBisulphate Blend**

Clopidogrelbisulphate blend was prepared for immediate release of drug. Lactose monohydrate was used as a diluent and
castor oil as a solvent. Accurately weighed clopidogrelbisulphate (75mg), lactose monohydrate and castor oil were mixed together in mortar and pestle, mixture was passed through #20 sieve followed by drying in hot air oven at 50°C for 15 min. Different formulation batches of clopidogrelbisulphate blend are shown in table 1.

**Preparation of Pulsatile Release Aspirin Tablet**

**Selection of polymer**
The polymers which gave minimum swelling in acidic buffer and maximum swelling in basic media were selected for this study. Polymers like Eudragit L100 and Eudragit S100 were used for preparation of pulsatile release aspirin tablets.

**Preparation of core tablets**
The core tablets of aspirin were prepared by direct compression method. For the preparation of core tablets, microcrystalline cellulose was used as a binder and croscarmellose sodium was used as superdisintegrant, stearic acid was used as a lubricant and purified talc as a glidant. All these ingredient were mixed together in mortar and pestle. A theoretical weight of about 105 mg powder was fed manually in to die of 10 stations(Rimek minipress-1, Ahmadabad, India)and compressed by using 6 mm flat faced punch by direct compression method(Yan et.al2004).

**Enteric coating of aspirin tablets**
5% (w/w) solutions of polymethacrylates (Eudragit L100 and Eudragit S100) were prepared in isopropyl alcohol: dichloromethane mixture. The ratio of Eudragit L100: Eudragit S100 selected was 1:2. The solution was plasticized with diethyl phthalate (5%, w/w, with respect to dry polymer), core tablets were coated by dipping method, and tablets were removed from the coating solution when the coating loads have been reached 5% (w/w). The tablets were kept in an oven for 2 h at 50°C.Different formulation batches of enteric coated tablets are shown table 2.

**Preparation of tablet in capsule formulation**
The first step in the formulation of tablet in capsule approach was to select the appropriate capsule size that can accommodate optimized batches of enteric coated tablet and immediate release blend. For the purpose, capsule size “1” was selected according to specifications given by USP. Size “1”capsule can accommodate enteric coated aspirin tablet weighing 105 mg and immediate release
Characterization of clopidogrel blend and enteric coated aspirin tablet

Determination of flow properties

The method used by Lachman (1987) was followed. Flow properties were determined by calculating angle of repose and compressibility index. The angle of repose clopidogrel blend and powder aspirin core tablets was calculated from the equation:

\[ \tan \theta = \frac{h}{r} \]

Where \( h \) is the height of the cone and \( r \) is the radius of cylinder.

Compressibility index (CI) values of the clopidogrel blend and powder of aspirin core tablets were determined by measuring the initial volume \( (V_0) \) and final volume \( (V) \) after subjecting to 100 tapings in graduated measuring cylinder using the equation:

\[ I = [1 - (V/V_0)] \times 100 \]

Such measurements revealed a qualitative assessment of internal cohesive and frictional effects under low level of external loading.

Determination of physical characteristic of core aspirin tablets

The prepared core tablets of aspirin were characterized as per the official monographs for weight variation \( (n=20) \), hardness \( (n=6) \), thickness \( (n=20) \), diameter and friability. Hardness of tablet was determined by using monsanto tablet hardness tester (Campbell electronics, Mumbai, India), Friability test was performed using roche friabilator, thickness & diameter of the tablets was measured by digital vernier caliper.

In vitro release of clopidogrel blend

Prepared blend of clopidogrel was kept in hard gelatin capsule and dissolution studies were performed using a USP XXIII dissolution apparatus I basket type (TD]TT-08L plus, Electro lab, Mumbai, India) in 900 ml medium at 37±0.5°C at a rotation speed of 50 rpm. In vitro release study was carried out in acidic media at pH 1.2 for 2 h. Five milliliters sample was withdrawn at specific time intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter. The concentration of samples was analyzed using UV spectrophotometer (1700, Shimadzu, Japan) at \( \lambda_{max} \) 235 nm.

In vitro release of enteric coated aspirin tablets
Dissolution studies were performed using USP XXIII dissolution apparatus II paddle type (Electro lab TDT- 08L plus, Mumbai, India) in 900 ml medium at 37.0±0.5°C, at a rotation speed of 50 rpm. Dissolution media selected were 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8). Dissolution test was performed for 2 h in 0.1N HCl (pH 1.2) and for 6 h in phosphate buffer (pH 6.8). Five milliliters sample was withdrawn at specific intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter (Fan et al. 2001). The concentration of samples was analyzed using UV spectrophotometer (UV-1700, Shimadzu, Japan) at 226 nm.

Water uptake study
Water uptake by the pulsatile release aspirin tablets was examined at the condition of drug release test. The media was a solution of phosphate buffer (pH 6.8). Tablet was kept in beaker and weight of sample was measured at the intervals of 1 h. The weight of the pulsatile tablets was measured with elapsed of time until the coating of the film burst (Fan et al. 2001).

In vitro release of tablet in capsule formulation
Dissolution studies were carried out in a USP XXIII dissolution apparatus I basket type (TDT- 08L plus, Electro lab, Mumbai, India)) in 900 ml medium at 37±0.5°C at a rotation speed of 50 rpm. Hard gelatin capsule (500mg) contains optimized batches of clopidogrelbisulphate blend and enteric coated aspirin tablet were transferred to the basket. For simulating conditions of the GI tract dissolution test was performed for 2 h in acidic stage (pH 1.2) and for 6 h in the 6.8 pH phosphate buffer. 5 ml sample was withdrawn at predetermined time intervals and replaced with fresh dissolution media (Gohelet al 2002). The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by UV spectrophotometer (1700, Shimadzu, Japan) using validated multi component method for first 2 h at $\lambda_{max}$ 226 and 235 nm respectively. After 2 h dissolution sample were analyzed using by UV spectrophotometer (1700, Shimadzu, Japan) at $\lambda_{max}$ 226 nm.

Study of similarity factor (F2) of test batch and marketed batch
For the determination of similarity factor, marketed batch Clopitab-A 75 (Lupinpvt. Ltd, India) was taken as an innovator product and in vitro drug release of optimized tablet in capsule formulation was compared with innovators product, which is
an important aspect in studying in vitro release behavior of formulation under investigation. Comparison between innovators product and test batches was done using statistical factors called similarity factor (F2). The similarity factor (F2) was defined by CDER and FDA as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference products. This was calculated to compare the test with reference release profiles. In vitro release study of the marketed Clopitab-A75 was performed under similar condition as used for in vitro release testing of the test product for the release of clopidogrel blend and aspirin tablet. The similarity factor between the two formulations was determined using the data obtained from drug release studies. The data were analyzed by the formula as shown in below

\[ F_2 = 50 \times \log \left[ \left( \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right] \]

(3)

\( n \) = number of time points

\( R_t \) = the reference profile at the time point \( t \)

\( T_t \) = the test profile at the same points

**Differential Scanning Calorimetry**

The possibility of any interaction between clopidogrel, aspirin, physical mixture and polymer (Eudragit L100 & Eudragit S 100) used in the formulation of clopidogrel blend and enteric coated aspirin tablet was assessed by carrying out the thermal analysis method. The thermal behavior of plain drugs, Eudragit L 100 and Eudragit S100 and physical mixture were determined using differential scanning calorimeter (DSC60, Shimadzu, Japan) at heating rate of 5\(^\circ\)C/min. The measurements were performed at a heating range of 40 to 420\(^\circ\)C under nitrogen atmosphere.

**Stability Studies**

Accelerated stability study of an optimized batch of clopidogrel bisulphate and enteric coated aspirin tablets in hard gelatin capsule shell was carried out as per ICH guidelines. Capsule were kept for stability studies at 40 ± 2\(^\circ\)C and 75 ± 5 % RH in an environmental test chamber (CHM 10S, REMI Instruments Ltd, India) for a period of 3 months. These samples were kept in glass vials without rubber plugs. After 90 days, the samples were analyzed for the in vitro drug release (Omaimah et al 1999).
RESULTS AND DISCUSSION

Flow properties
The values of angle of repose and compressibility for clopidogrel blend and powder of aspirin core tablets are shown in Table 3. Angle of repose for all the clopidogrel blend and powder of aspirin core tablets batches was found to be 27.32-29.21° dictating good free flowing nature. The compressibility index of the clopidogrel blend was between 13.02-15.78% suggesting good flow property where as aspirin blend was between 12.78-14.62% indicating suitability of aspirin core powder for direct compression in to tablet.

Physical characteristic of aspirin tablets
The result of the uniformity of weight, hardness, thickness, diameter and friability of the core aspirin tablets are given in Table 4. All the tablets of the test product complied with the official requirement. The friability indicates that the tablets are compact and hard.

In vitro release of clopidogrel blend
Dissolution profile of clopidogrel is shown in Fig. 1. It shows that clopidogrel blend releases immediately after capsule was ruptured. More than 75% drug was released within 15 min and complete dissolution was achieved in 120 min. From release profile of all the formulations we concluded that batch A3 shows suitable immediate release profile as compared to other batches. Therefore, batch A3 was optimized for further study.

In vitro release of enteric coated aspirin tablets
Eudragit L100 and Eudragit S 100 are water insoluble and pH dependent polymer. Aspirin tablets can be coated with 1:2 w/w ratios of these polymers to provide pulsatile drug release in the intestine.

Effect of pH on the drug release behavior
Drug release behavior under different batches is shown in Fig. 2. EudragitL 100 and EudragitS 100 are soluble at pH 6 and pH 7 respectively. These polymers suppress release of the drug in the stomach and only 5-10% drug get released at pH 1.2 while drug get rapidly released at pH 6.8 due to solubility of these polymers in phosphate buffer. Polymers create pores in the coating film. Penetration of water molecules from the surrounding through the pores into the aspirin core tablet causes expansion of the croscarmellose sodium which is used as swelling agent and expansion of swelling agent causes bursting of enteric coated film of Eudragit at pH 6.8 and releasing the drug.
with a single pulse. After bursting the enteric coated film, it shows more than 75% release rapidly after 4 h of lag time. Remaining drug gets released over a period of 8 h. From Fig.2 which showed the drug release profiles of all formulations batches, we concluded that batch F5 shows suitable pulsatile release as compared to other batches. Therefore batch F5 was optimized for further study.

**Water uptake study**

Fig. 3 shows the amount of water uptake by enteric coated aspirin tablet with time at 5% thickness of coating film. Water penetrated through the film and caused the water uptake and expansion of swelling agent until the internal forces of the film caused tablet to burst, thereby, releasing drug.

**Effect of swelling behavior**

The relationship between the tablets expansion and its effect on release behavior of aspirin is shown in Fig.4. From swelling studies it was concluded that tablet without croscarmellose sodium, Eudragit L 100 and Eudragit S100 layer do not show any swelling but the tablet containing croscarmellose sodium in the core of aspirin tablet and coated with EudragitL100 and Eudragit S100 exhibit significant swelling. Therefore, it dictates that, the swelling agent and enteric coating agent are both crucial for the fast release phase. Swelling volume of croscarmellose sodium also affect lag time of the aspirin tablets. Swelling volume was constant in the pH range 1.2 but increased in the pH range 6.8 and shows swelling energy was higher in phosphate buffer at pH 6.8 and lower in acidic buffer at pH 1.2. This could be attributed to the presence of carboxylic groups in croscarmellose sodium, which are unionized in an acidic environment thus resulting in a lower water uptake and lower expansion of swelling layer of croscarmellose sodium. Whereas, in phosphate buffer (pH 6.8), carboxylic groups get ionized and shows greater water uptake and larger swelling resulting in rupture of film of Eudragit L 100 and Eudragit S100 subsequently rapid drug release.

**In vitro release of tablet in capsule formulation**

Dissolution profile of hard gelatin capsule containing optimized batch of clopidogrel blend (A3) and enteric coated aspirin tablet (F5) is shown in Fig.5. Hard gelatin capsule ruptured in acidic media. After rupture of capsule, clopidogrel blend get released immediately and shows more than 75% drug release within 15 min and complete dissolution occurred in 120 min. Whereas, aspirin tablets remains
intact in acidic media (pH 1.2). It shows that only 5% drug release in acidic media and remaining amount of drug released rapidly after predetermined lag time of about 4 hr phosphate buffer (pH 6.8) and complete dissolution was occurred in 8 h.

**Similarity factor**

The principal purposes of dissolution testing are 3-fold: 1) for quality control, to ensure the uniformity of product from batch to batch; 2) to help predict bioavailability for formulation development; and 3) as a measure of change when formulation changes are made to an existing formulation. The so-called f2 method can be used to compare two dissolution profiles. Similarity factor analysis between the prepared capsule which contain optimize batches of clopidogrel blend and enteric coated aspirin tablet with marketed capsule Clopitab-A75. The release of clopidogrelbisulphate and aspirin showed f2 factor of 53.29 and 52.47 respectively. It proved that the release of clopidogrel and aspirin from the prepared capsule was similar to that of the marketed tablet.

**Differential Scanning Calorimetry**

Fig.6 shows the DSC thermogram of aspirin, clopidogrel, mixture of both drugs, mixture of both drugs and polymer, lastly physical mixture of formulation. From the Fig.6 it was concluded that melting point of aspirin is 144.15°C and melting point of clopidogrel is 165.04°C respectively. It is evident that DSC peaks of both drugs are slightly shifted (from 145 to 143.10°C) for aspirin and (160 to 166.12°C) for clopidogrel. From the analysis of thermogram, it was revealed that no drug-drug interaction between aspirin and clopidogrel physical mixture was observed. It also suggests no drug excipient interactions. It can be concluded that aspirin and clopidogrel are compatible with each other, while the individual drugs in combination with excipients are also compatible with each other.

**Stability study of optimized batch**

The effect of temperature and time on the physical and chemical characteristic of the capsule was evaluated for assessing the stability of the formulated capsule. Dissolution profile of the stability batch is shown in Fig.7, and the results indicate that there wasn’t significant changes in the in vitro drug release of clopidogrelbisulphate and aspirin respectively.

In conclusion, the formulated tablet in capsule drug delivery for the simultaneous administration of two anti-platelet drugs...
may be promising alternative for better management of heart stroke and prevention of recurrent attacks in susceptible individual. The comparison made with marketed formulation (Clopitab-A 75) also suggests its suitability for this purpose.

**ACKNOWLEDGMENTS**

Authors are thankful Cadila Pharmaceuticals Ltd, Ahmadabad, India for providing gift samples of Aspirin and clopidogrelbisulphate. Authors are also grateful to Evonic Degussa India Pvt. Ltd., Mumbai, India for providing gift samples of Eudragit L100 and Eudragit S 100. The authors would also like to thank Principal (R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur) for providing necessary infrastructure and facilities to carry out this work.

**Figure 1** Dissolution profile of clopidogrel blend batches.
Figure 2: Dissolution profile of enteric coated aspirin tablets.

Figure 3: Relationship between the amount of water uptake and time of coating film. Weight increased for pulsatile release tablet.

Figure 4: Comparative dissolution profile of tablet containing swelling agent and enteric coating film (x) and tablet containing without swelling agent and enteric coating film (y).
Figure 5 Dissolution profile of tablet in capsule formulation

Figure 6 DSC curve of aspirin, clopidogrel, mixture of aspirin & clopidogrel, aspirin & polymer and physical mixture.

Figure 7 In vitro release profile of tablet in capsule formulation of optimized batch after stability study
Table 1
Formulation composition of clopidogrel blend

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation batches (Quantity in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td>Clopidogrel bisulphate</td>
<td>75</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>300</td>
</tr>
<tr>
<td>Castor oil</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

Table 2
Formulation composition of enteric coated Aspirin tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation batches (Quantity in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>75</td>
</tr>
<tr>
<td>Microcrystalline cellulose (avicel 102)</td>
<td>11</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>1</td>
</tr>
<tr>
<td>Talc</td>
<td>16</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>2</td>
</tr>
<tr>
<td>Eudragit L100:</td>
<td>5%</td>
</tr>
<tr>
<td>Eudragit S 100 (1:2)</td>
<td></td>
</tr>
<tr>
<td>Diehyl phthalate</td>
<td>3</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>q.s.</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>q.s.</td>
</tr>
</tbody>
</table>
### Table 3

Flow properties of clopidogrel and aspirin tablet blend

<table>
<thead>
<tr>
<th>Batches</th>
<th>Angle of repose*</th>
<th>Compressibility Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>28.38±0.41</td>
<td>15.78±0.88</td>
</tr>
<tr>
<td>A2</td>
<td>27.32±0.21</td>
<td>13.18±0.42</td>
</tr>
<tr>
<td>A3</td>
<td>28.29±0.18</td>
<td>14.02±0.62</td>
</tr>
<tr>
<td>F1</td>
<td>28.38±0.41</td>
<td>12.78±0.88</td>
</tr>
<tr>
<td>F2</td>
<td>27.32±0.21</td>
<td>14.18±0.42</td>
</tr>
<tr>
<td>F3</td>
<td>28.29±0.18</td>
<td>13.02±0.62</td>
</tr>
<tr>
<td>F4</td>
<td>29.21±0.24</td>
<td>14.52±0.44</td>
</tr>
<tr>
<td>F5</td>
<td>28.42±0.32</td>
<td>14.62±0.41</td>
</tr>
<tr>
<td>F6</td>
<td>29.33±0.40</td>
<td>14.55±0.62</td>
</tr>
</tbody>
</table>

* Results are the mean of three observations± SD (n=3)

A1-A3 shows flow properties of clopidogrel blend batches.

F1-F5 shows flow properties of powder aspirin core tablets.
## Table 4
Physical properties of aspirin tablets

<table>
<thead>
<tr>
<th>Test</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight uniformity (mg)</td>
<td>103±1.2</td>
<td>104±1.4</td>
<td>104±1.3</td>
<td>105±1.1</td>
<td>105±1.2</td>
<td>106±1.1</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>2.1±0.4</td>
<td>2.1±0.5</td>
<td>2.3±0.3</td>
<td>2.4±0.5</td>
<td>2.5±0.4</td>
<td>2.5±0.6</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>1.56±0.03</td>
<td>1.58±0.02</td>
<td>1.57±0.05</td>
<td>1.54±0.04</td>
<td>1.56±0.02</td>
<td>1.57±0.03</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>6.73±0.043</td>
<td>6.74±0.03</td>
<td>6.79±0.03</td>
<td>6.81±0.05</td>
<td>6.82±0.04</td>
<td>6.83±0.05</td>
</tr>
<tr>
<td>Friability</td>
<td>0.86±0.1</td>
<td>0.82±0.2</td>
<td>0.79±0.5</td>
<td>0.72±0.4</td>
<td>0.66±0.3</td>
<td>0.65±0.6</td>
</tr>
</tbody>
</table>
REFERENCES


