https://doi.org/10.31925/farmacia.2024.6.14 **ORIGINAL ARTICLE**

BILAYER TABLETS FOR THE PURPOSE OF OBTAINING SUITABLE TABLET SUBDIVISIONS

SHADI F. GHARAIBEH [1]*, LINDA TAHAINEH [2]

[1]*Faculty of Pharmacy, Jerash University, Jerash 26150, Jordan*
[2]*Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid, Jordan*

**corresponding author: shadi.gharaibeh@jpu.edu.jo*

Manuscript received: October 2024

Abstract

Tablets can be subdivided by patients for several reasons. However, these subdivisions are not guaranteed to produce acceptable splits using the known subdivision techniques. The main objective of this study is to evaluate the use of bilayer tablets to obtain suitable tablet subdivisions. Bilayer tablets of two formulations were evaluated. The bilayer tablets were produced by compaction of 250 mg of powder at 43 MPa followed by compaction of an additional 250 mg of the same powder at 43 MPa. Each of the evaluated bilayer tablets was either composed of microcrystalline cellulose (MCC) or a mixture of MCC and caffeine. Subdivisions were performed by pressing the metal tip of a lancet on the edge of the bilayer tablet at the interface between the layers. Properties of the bilayer tablets and the subdivided layers were determined. Furthermore, the friability of the bilayer tablets was tested. It was found that the produced bilayer tablets lost less than 1% of their weight and did not delaminate during the friability test. Moreover, it was found that two almost intact tablets were subdivided from each bilayer tablet. The weight of each subdivision was close to 50% of the weight of the whole bilayer tablet. The standard deviations of the percentage weights of the subdivisions were less than or equal to 0.15%. Therefore, it was possible to subdivide bilayer tablets to produce tablet splits with relatively high accuracy and precision.

Rezumat

Obiectivul principal al acestui studiu a fost de a evalua utilizarea comprimatelor bistratificate pentru a obține subdiviziuni adecvate. Au fost evaluate tablete bistrat din două formulări farmaceutice. Tabletele cu două straturi au fost produse prin compactarea a 250 mg de pulbere la 43 MPa urmată de compactarea a încă 250 mg din aceeași pulbere la 43 MPa. Fiecare dintre comprimatele cu două straturi evaluate a fost compus fie din celuloză microcristalină (MCC), fie dintr-un amestec de MCC și cafeină. Subdiviziunile au fost efectuate prin apăsarea vârfului metalic al lancetei pe marginea tabletei, la interfața dintre straturi. Au fost determinate atât proprietățile comprimatelor bi-strat cât și ale straturilor subdivizate. În urma determinării friabilității, s-a concluzionat că aceste comprimate bistratificate obținute au pierdut mai puțin de 1% din greutate și nu s-au delaminat. Greutatea fiecărei subdiviziuni a fost aproape de 50% din greutatea întregului comprimat. Abaterile standard ale ponderilor procentuale ale subdiviziunilor au fost mai mici sau egale cu 0,15%.

Keywords: bilayer tablets, tablet subdivision, microcrystalline cellulose, caffeine

Introduction

Bilayer tablets have been used in the market for several years [1]. Bilayer tablets are manufactured for several purposes which include combining more than one drug in the bilayer tablet to improve patient compliance, separation of two incompatible ingredients in the formulation and preparation of a controlled release dosage form where the two layers are formulated for different release profiles of the drug [2-5]. A bilayer tablet compression machine which has two different feed hoppers is used for their production [1]. The production involves compaction (tamping) of a powder or granule mixture in a die cavity to produce the first (lower) layer followed by a second compaction of a powder or granule mixture filled on top of the first layer to produce the second (upper) layer. The formed bi-layer tablet is then ejected from the die cavity. After each powder filling in the die cavity, the powder or granule mixture is compressed to a pre-set compression force. The compression force applied after the first fill (lower layer) and that applied after the second fill (upper layer) should be optimised according to the formulation ingredients in order to facilitate adhesion between the layers and to prevent the delamination between the layers [6, 7]. Therefore, it is important to optimize both the formulation and the compaction process to ensure sufficient strength of the bilayer tablet and sufficient adhesion between the layers of the tablet. Patients tend to subdivide tablets for different reasons which include obtaining a smaller dose that is not available in the market, easing swallowing and/or saving on cost [8-10]. Several techniques can be applied to obtain tablet subdivisions. These techniques include subdivision by hand, teeth, knife or tablet splitters [10-12]. Nevertheless, none of these techniques can be guaranteed to produce suitable subdivisions. Several

factors affect the accuracy and precision of the tablet subdivision. These factors include tablet size, shape, strength, formulation and presence of a score line [13-16]. The variability in the subdivided portions of a tablet can be large and could affect the suitability of administration even if the manufacturer provides a score line on the tablet [17, 18]. It has also been reported that the subdivision process depends on both the porosity (packing) and the strength of the tablet [19, 20]. Therefore, it is difficult to assure a uniform breakage (fracture) of the tablet along its diameter even if a knife or a tablet splitter is used [21].

According to the authors' best knowledge, the use of bilayer or multilayer tablets for the purpose of obtaining suitable tablet subdivisions has not been reported. Therefore, the aim of this study was to evaluate the use of bilayer tablets to obtain suitable tablet subdivisions by splitting the tablets at the interface between the layers. Two tablet formulations were investigated. The first formulation was of tablets that had two layers of microcrystalline cellulose (MCC). The second formulation was of tablets that had two identically formulated layers of a mixture of MCC and caffeine. MCC is a commonly used excipient for the direct compression operations [22]. Caffeine is a chemical that can be used for migraine, headaches and as a stimulant. It is usually administered orally in doses between 50 mg and 260 mg for adults [23]. Caffeine tablets of 100 mg or 200 mg can be found in the market.

Materials and Methods

Materials

MCC powder (Avicel® PH-101 NF) was obtained from DuPont Nutrition USA, Inc. (Wilmington, DE, USA). Caffeine powder (Emprove® Essential, Ph. Eur, BP, USP) was obtained from Merck KGaA (Darmstadt, Germany).

Preparation of MCC/caffeine powder mixture

The mixture was prepared by manual tumbling of 15.0 g of MCC powder with 10.0 g of caffeine powder in a 500 mL reagent bottle for 5 minutes. All weights in this work were measured using a digital balance (Phoenix Instrument-ASN324, Garbsen, Germany).

Preparation of bilayer tablets

Bilayer tablets were prepared using a stainless-steel punch and die set. The punches were cylindrical with flat faces and the die cavity had a diameter of 14 mm. The powders were compressed by utilizing a manual hydraulic press model 15 T (SCO Tech, Dingelstädt, Germany). The first layer (lower layer) was prepared by compressing 250 mg of the powder in the die cavity. The applied compression pressure was 43 MPa with a dwell time of 10 seconds. The second layer (upper layer) was prepared by adding an additional 250 mg of the same powder on top of the first compacted layer. Then both layers were subjected to an applied compression pressure of 43 MPa with a dwell time of 10 seconds. The upper layer of each tablet was lightly marked with a pen before the bilayer tablet was ejected from the die cavity. Bilayer tablets of MCC and of MCC/ caffeine were produced.

Determination of tablets properties

The dimensions of the bilayer tablets and tablet subdivisions were determined using a digital (electronic) calliper model WT 4171 (Worksite Tools and Equipment, Guangzhou, Guangdong, China). The density of each tablet was calculated by dividing the weight of the tablet by its volume. The force required to break each tablet was determined utilizing a Biobase hardness tester model YD-3 (Biobase Group, Jinan, Shandong, China). It was noted that placing bilayer tablets on their faces on the testing area of the immobile bar during the test produced failure (breakage) of the tablets only along the diameter of the upper layer (relative to the testing area). This was due to the clearance between the moving bar and the testing area of the immobile bar which was close to the thickness of the individual layers of the produced tablets. Therefore, the tablets were placed on their edges on the testing area of the immobile bar during the test (Figure 1). Accordingly, the tested tablets were pressed along their diameters between the moving bar and the immobile bar facilitating force application on both layers of the tablets during the test. The subdivided layers of the tablets were also tested in a similar manner. The distribution of forces in a tablet during the test is expected to be affected by the placement of the tablet on one of its faces or on its edge. Therefore, the force required to break the tablets in this work was termed apparent crushing strength (F'). In addition, the values of the apparent tensile strength (TS') of the tablets were calculated using the equation

$$TS' = 2F'/\pi tD\ , \qquad (1)$$

where, t is the thickness and D is the diameter of the tested tablet. The aforementioned properties were determined for the bilayer tablets and for the subdivided tablets. A total of 5 bilayer tablets or tablet subdivisions were used to determine the mean and standard deviation of each property.

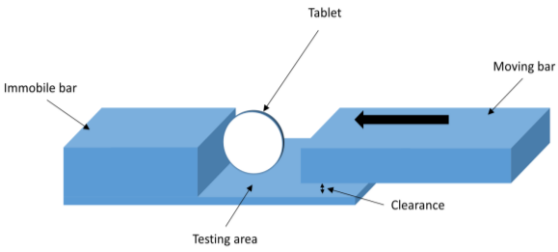

Figure 1.
A diagram showing the placement of tablets in the testing area of the hardness tester during the test

Friability test

Friability of the bilayer tablets was tested using a CS-1 Tablet Friability Tester (Biobase Group, Jinan,

Shandong, China). A sample of 20 bilayer tablets of each formulation was produced. The weight of the tablet sample was recorded. The tablets were placed in the drum of the tester which had an internal diameter of 28.5 cm and a depth of 3.9 cm. The tester was operated at a speed of 25 revolutions *per* minute for 4 minutes. At the end of the test, the tablets were collected, examined for any apparent separation between the layers and weighed. The percentage weight loss (*%F*) was calculated using the equation

$$\%F = \frac{Wb-Wa}{Wb} \times 100, \qquad (2)$$

where, Wb is the weight of the tablets before the test and Wa is the weight of the tablets after the test. The test was performed for MCC and MCC/caffeine bilayer tablets.

Subdivision of bilayer tablets

A 30-year-old male pharmacist volunteered to perform the subdivisions. A lancet that accompanies a digital glucometer was used to subdivide the bilayer tablets. The metal tip of the lancet was pressed in the middle of the edge of each bilayer tablet to produce two subdivided tablets. A total of 10 bilayer tablets of each formulation were produced and subdivided. The weight of each bilayer tablet and its corresponding subdivisions were recorded. The percentage weights of the lower (% $weight_l$) and upper (% $weight_u$) layers of the subdivided tablets were calculated using the equations:

$$\% \, weight_l = \frac{W_l}{W_t} \times 100, \qquad (3)$$

$$\% \, weight_u = \frac{W_u}{W_t} \times 100, \qquad (4)$$

where, W_l is the weight of the lower layer of the subdivided bilayer tablet, W_u is the weight of the upper layer of the subdivided bilayer tablet and W_t is the weight of the subdivided bilayer tablet.

Statistical analyses

The independent t-test assuming equal variances was used to compare the mean values of the densities and apparent tensile strengths of the subdivided layers to those of the corresponding bilayer tablets. In addition, the independent t-test assuming equal variances was used to compare the mean values of the densities and apparent tensile strengths of the lower subdivided layers to those of the upper subdivided layers of each formulation of the bilayer tablets. A significant difference between the means was considered if the *p*-value was less than 0.05.

Results and Discussion

Both MCC powder and MCC/caffeine powder mixture were compacted into bilayer tablets that had sufficient strength to withstand further analyses. Table I shows the properties of the bilayer tablets of MCC and MCC/caffeine. It can be seen that MCC bilayer tablets had slightly lower mean tablet density compared to that of MCC/caffeine bilayer tablets. However, MCC bilayer tablets had a higher mean apparent crushing strength and mean apparent tensile strength. This is indicative of a higher magnitude of inter-particulate bonding in the MCC tablets. During tablet subdivisions, a clear separation between the lower and upper layers was achieved when the lancet tip was pressed in the middle (interface) of the edges of the bilayer tablets. Therefore, it was possible to produce two almost intact tablets from each bilayer tablet that was subdivided.

Table I

Properties of the bilayer tablets and the subdivided layers

Property	**MCC**	**MCC/ caffeine**
Bilayer tablet density (g/cm^3)	1.015 (0.007)	1.066 (0.005)
Bilayer tablet apparent crushing strength (N)	150.6 (2.67)	88.0 (5.61)
Bilayer tablet apparent tensile strength (MPa)	2.19 (0.041)	1.34 (0.084)
Lower layer tablet density (g/cm^3)	1.018 (0.038)	1.049 (0.015)
Lower layer tablet apparent crushing strength (N)	77.8 (2.02)	38.9 (6.03)
Lower layer tablet apparent tensile strength (MPa)	2.28 (0.143)	1.18 (0.182)
Upper layer tablet density (g/cm^3)	1.018 (0.018)	1.026 (0.018)
Upper layer tablet apparent crushing strength (N)	74.2 (3.94)	34.9 (3.65)
Upper layer tablet apparent tensile strength (MPa)	2.15 (0.147)	1.02 (0.093)

Note: Numbers represent values of the means while standard deviations are presented between brackets, n = 5.

Table I also shows the values of the mean density, mean apparent crushing strength and mean apparent tensile strength of the lower and upper layers of the subdivided tablets. It can be seen that both the lower and upper layers of the subdivided tablets of MCC had similar mean tablet densities compared to that of the bilayer tablets of MCC ($p > 0.05$). In addition, both the lower and upper layers of the subdivided tablets of MCC had similar mean apparent tensile strengths compared to that of the bilayer tablets of MCC ($p > 0.05$).

Table I also shows that the lower layers of the subdivided tablets of MCC/caffeine had similar mean tablet density and mean apparent tensile strength compared to those of the bilayer tablets of MCC/caffeine ($p > 0.05$). However, the upper layers of the subdivided tablets had significantly different values of mean tablet density and mean apparent tensile strength compared to those of the bilayer tablets of MCC/caffeine ($p < 0.05$). Accordingly, the mean tablet density and the mean apparent tensile strength of the upper layers were 4%

and 24%, respectively, lower than those of the bilayer tablets. Moreover, there was no statistically significant difference ($p > 0.05$) between the mean density and the mean apparent tensile strength of the lower layers compared to those of the upper layers of the subdivided tablets of MCC. Similarly, there was no statistically significant difference ($p > 0.05$) between the mean density and the mean apparent tensile strength of the lower layers compared to those of the upper layers of the subdivided tablets of MCC/caffeine.

The weights of the 20 bilayer tablets of MCC before and after the friability test were 9.92 g and 9.90 g, respectively. Therefore, the percentage weight loss after the friability test (%*F*) was 0.2% for the bilayer tablets of MCC. In addition, the weights of the 20 bilayer tablets of MCC/caffeine tablets before and after the friability test were 9.98 g and 9.90 g, respectively. Therefore, the percentage weight loss after the friability test (%*F*) was 0.8%. In both cases the %*F* values were less than 1%. Moreover, none of the tested bilayer tablets delaminated, split, or broke during the test. Friability testing of bilayer tablets provides an indication of the risk of layer separation [24]. Therefore, these results suggest that the produced bilayer tablets had sufficient strength to withstand possible mechanical stresses of packaging, storage, shipping and handling. MCC is a binder used in directly compressible tablet formulations. It predominantly deforms by plastic flow under pressure which brings the surfaces of the particles to close proximity leading to strong inter-particulate bonding [22]. Therefore, the compacts of MCC were strong and had low friability. In addition, MCC enhanced bonding between the layers. It was reported that the compacted layers that are excessively hard would not bond sufficiently [25]. Thus, the plasticity of MCC and the relatively low applied compression pressure used in this study led to sufficient bonding between the layers. Furthermore, the layers of each of the produced bilayer tablets were similar in composition and compacted at the same compression pressure. This reduced the variation between the layers especially in terms of elasticity and therefore reduced the risk of delamination [26]. Caffeine powder can be mixed with excipients and compacted by direct compression [27]. It was also reported that a mixture of caffeine with MCC could be directly compressed to form compacts at a relatively low applied compression pressure of 40 MPa [28]. In this study, each layer of the bilayer tablets of caffeine was composed of 100 mg (40%) caffeine and 150 mg (60%) MCC. Therefore, it would be expected that the particle properties of MCC had a major contribution on the mechanical properties of the mixture. This facilitated the production of bilayer tablets of caffeine that had sufficient strength and bonding between the layers to withstand the friability test.

Figure 2 and Figure 3 show the percentage weights of the subdivided lower and upper layers of the bilayer tablets of MCC and MCC/caffeine. It can be seen that the percentage weights of the subdivisions were close to 50% of the weights of the whole bilayer tablets. The means ± standard deviations of percentage weights of the lower- and upper-layer subdivisions of MCC bilayer tablets were 49.73 ± 0.15% and 50.23 ± 0.10%, respectively. Moreover, the means ± standard deviations of percentage weights of the lower- and upper-layer subdivisions of MCC/caffeine bilayer tablets were 49.71 ± 0.14% and 50.17 ± 0.10%, respectively. These findings show a high degree of accuracy and a low degree of variability in the weights of the subdivided tablets.

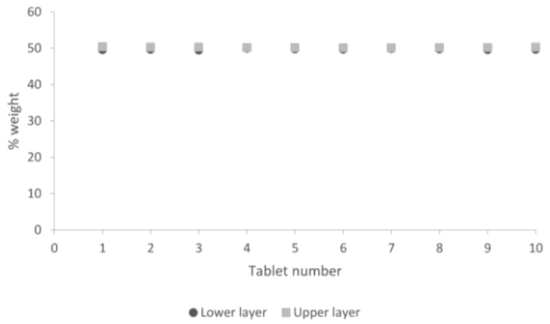

Figure 2.
A representation of the % weight of subdivided layers of the bilayer tablets of MCC

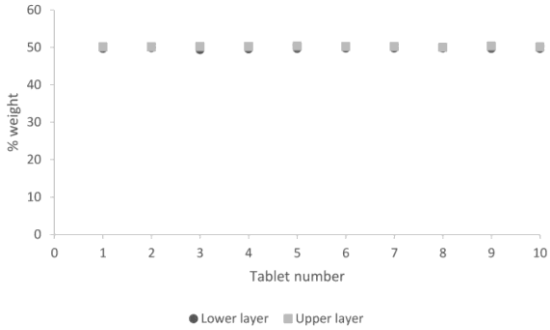

Figure 3.
A representation of the % weight of subdivided layers of the bilayer tablets of MCC/caffeine

As mentioned in the introduction section, it is important to optimize the compression pressure applied during compaction of the lower and upper layers to facilitate strong interfacial bonding between the layers of bilayer tablets [6, 7]. In this study, the applied compression pressure during the compaction of the lower layer was larger than what is required for tamping the powder. Furthermore, the applied compression pressure on the upper layer was similar to that applied during the compaction of the lower layer. Thus, there was limited mixing of the powder between the upper layer and the lower layer during compaction. This facilitated a suitable subdivision at the interface between the layers. Nevertheless, both the used formulations and the applied compression pressure were suitable to produce strong bilayer tablets with a magnitude of interfacial bonding between the layers that made the bilayer tablets

withstand the friability test. Therefore, optimization of the formulation and applied compression pressure during compaction of the layers is also necessary to ensure the production of bilayer tablets for the purpose of tablet subdivision.

The produced bilayer tablets along with the suggested method of subdivision resulted in tablet subdivisions that were with high accuracy and low variability. This could be utilised to produce bilayer tablets on an industrial scale that can be split without compromising safety and/or efficacy of the medication. For example, it could be possible to produce bilayer tablets that can be subdivided into almost equal halves of a higher strength bilayer tablet. This could replace the need to produce tablet medications in two strengths where one strength is double the other. This would have an economic advantage in terms of production and consequently cost saving for the patients.

Conclusions

Bilayer tablets of different compositions were produced with sufficient strength and adhesion between the layers to withstand the friability test. Subdivision of these tablets at the bilayer interface produced subdivisions of almost equal weights and with low variability. Therefore, bilayer tablets could be produced for the purpose of obtaining suitable tablet subdivisions.

Conflict of interest

The authors declare no conflict of interest.

References

1. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM, Review of bilayer tablet technology. *Int J Pharm.*, 2014; 461(1): 549-558.
2. Efentakis M, Peponaki C, Formulation study and evaluation of matrix and three-layer tablet sustained drug delivery systems based on carbopols with isosorbite mononitrate. *AAPS PharmSciTech.*, 2008; 9(3): 917-923.
3. Vaithiyalingam SR, Sayeed VA, Critical factors in manufacturing multi-layer tablets – Assessing material attributes, in-process controls, manufacturing process and product performance. *Int J Pharm.*, 2010; 398(1): 9-13.
4. Donea C, Ciobanu AM, Cristian DA, Popa DE, Burcea-Dragomiroiu GTA, Hîrjău M, Drăgănescu D, Crăciun P, Lupuliasa D, Determination of the impact of the compression force by evaluating the mechanical and release properties of mesalazine tablets. *Farmacia*, 2022; 70(5): 964-975.
5. Shiyani B, Gattani S, Surana S, Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. *AAPS PharmSciTech.*, 2008; 9(3): 818-827.
6. Li SP, Karth MG, Feld KM, Di Paolo LC, Pendharkar CM, Williams RO, Evaluation of bilayer tablet machines – A case study. *Drug Dev Ind Pharm.*, 1995; 21(5): 571-590.
7. Inman SJ, Briscoe BJ, Pitt KG, Topographic characterization of cellulose bi-layered tablets interfaces. *Chem Eng Res Des.*, 2007; 85(7): 1005-1012.
8. Fischbach MS, Gold JL, Lee M, Dergal JM, Litner GM, Rochon PA, Pill-splitting in a long-term care facility. *CMAJ Can Med Assoc J.*, 2001; 164(6): 785-786.
9. Marriott JL, Nation RL, Splitting tablets. *Aust Prescr.*, 2002; 25(6): 133-135.
10. Gharaibeh SF, Tahaineh LM, Khasawneh AH, Tablet splitting practice in Jordan. *J Pharm Health Serv Res.*, 2018; 9(4): 373-379.
11. Olgac S, Yilmaz Usta D, Incecayir T, Comparison of tablet splitting techniques for dosing accuracy of nebivolol tablets: Hand splitting *versus* tablet cutter and knife. *Saudi Pharm J.*, 2021; 29(12): 1486-1491.
12. Melo VV, Pereira GR, Soares AQ, Silva IC, Taveira SF, Cunha-Filho M, Marreto RN, Prevalence of tablet splitting in a Brazilian tertiary care hospital. *Pharm Pract Granada.*, 2020; 18(2): 1910.
13. Tahaineh LM, Gharaibeh SF, Tablet splitting and weight uniformity of half-tablets of 4 medications in pharmacy practice. *J Pharm Pract.*, 2012; 25(4): 471-476.
14. Somogyi O, Meskó A, Csorba L, Szabó P, Zelkó R, Pharmaceutical counselling about different types of tablet-splitting methods based on the results of weighing tests and mechanical development of splitting devices. *Eur J Pharm Sci.*, 2017; 106: 262-273.
15. Son KB, Recent trends in tablet subdivision and factors affecting subdivision in South Korea. *Medicine (Baltimore)*, 2020; 99(18): e19990.
16. Gharaibeh SF, Tahaineh L, Effect of different splitting techniques on the characteristics of divided tablets of five commonly split drug products in Jordan. *Pharm Pract Granada.*, 2020; 18(2): 1776.
17. Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, The frequency of inappropriate tablet splitting in primary care. *Eur J Clin Pharmacol.*, 2006; 62(12): 1065-1073.
18. Arnet I, Hersberger KE, Misleading score-lines on tablets: facilitated intake or fractional dosing?. *Swiss Med Wkly.*, 2010; 140(7-8): 105-110.
19. Teixeira MT, Sa-Barreto LL, Silva IC, Gratieri T, Gelfuso GM, Marreto RN, Landin M, Cunha-Filho M, The influence of porosity on tablet subdivision. *Particuology*, 2020; 53: 192-196.
20. Cunha-Filho M, Teixeira MT, Santos-Rosales V, Sa-Barreto LL, Marreto RN, Martin-Pastor M, García-González CA, Landin M, The subdivision behaviour of polymeric tablets. *Int J Pharm.*, 2019; 568: 118554.
21. Gharaibeh SF, Tahaineh L, Effect of strength and porosity of tablets on the magnitudes of subdivision forces. *Pharm Dev Technol.*, 2023; 28(1): 138-142.
22. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B, Microcrystalline cellulose, a direct compression binder in a quality by design environment – A review. *Int J Pharm.*, 2014; 473(1): 64-72.
23. CAFFEINE: Overview, Uses, Side Effects, Precautions, Interactions, Dosing and Reviews. www.webmd.com/vitamins/ai/ingredientmono-979/caffeine.
24. Niwa M, Hiraishi Y, Iwasaki N, Terada K, Quantitative analysis of the layer separation risk in bilayer tablets

using terahertz pulsed imaging. *Int J Pharm.*, 2013; 452(1-2): 249-256.
25. Akhtar M, Jamshaid M, Zaman M, Mirza AZ, Bilayer tablets: A developing novel drug delivery system. *J Drug Deliv Sci Technol.*, 2020; 60: 102079.
26. Podczeck F, Theoretical and experimental investigations into the delamination tendencies of bilayer tablets. *Int J Pharm.*, 2011; 408(1): 102-112.
27. Alam K, Shareef H, Bushra R, Formulation development and evaluation of caffeine tablets (200 mg) by direct compression. *Int J Drug Dev Res.*, 2013; 5: 371-376.
28. Wray P, Chan KLA, Kimber J, Kazarian SG, Compaction of pharmaceutical tablets with different polymer matrices studied by FTIR imaging and X-ray microtomography. *J Pharm Sci.*, 2008; 97(10): 4269-4277.