Sains Malaysiana 51(10)(2022): 3347-3357
http://doi.org/10.17576/jsm-2022-5110-19

Formulation and Hardness Evaluation of Tablets Containing *Citrus limon* and *Hylocereus polyrhizus* Powder using D-Optimal Mixture Design

(Formulasi dan Penilaian Kekerasan Tablet yang Mengandungi *Citrus limon* dan Serbuk *Hylocereus polyrhizus* menggunakan Reka Bentuk Campuran D-Optimum)

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Received: 10 February 2022/Accepted: 18 May 2022

ABSTRACT

The powder of mixed fruits that are Lemon (*Citrus limon)* and Red Pitaya (*Hylocereus polyrhizus)* was used as a nutritional supplement in tablet form for nutraceutical application. D-optimal mixture experimental design (D-Optimal MED) was employed to investigate the influence of different components on the response hardness of the tablet. For tablet formulation, magnesium stearate, A (0.2-1.0% w/w), menthol, B (0.2-1.0% w/w), lemon powder, C (1.0-10.0 w/w), maltodextrin, D (5.0 -10.0) and glucose, E (37.5-53.1%) are the variables while red pitaya powder and preservative are fixed components. The experimental data were used to analyze analysis of variance (ANOVA) and to develop a polynomial regression model for tablet hardness in terms of the five design factors considered in this study. D-Optimal MED predicted the hardness of the tablet at 8.5 kg/cm^2. The results showed that the best mixture was the formulation that included 0.66% A, 0.74% B, 6.15% C, 7.61% D and 44.34% E, with the actual hardness of the optimized tablet recorded at 8.581 kg/cm^2 (R^2 = 0.9925). The study demonstrated the potentiality of mixed fruit tablets as a nutritional supplement with therapeutic properties for general consumers well-being.

Keywords: *Citrus limon;* D-Optimal mixture experimental design; *Hylocereus polyrhizus;* nutraceutical; tablet hardness

ABSTRAK

Serbuk buah Lemon (*Citrus limon)* dan Pitaya Merah (*Hylocereus polyrhizus)* telah dibangunkan sebagai makanan tambahan dalam bentuk tablet untuk aplikasi nutraseutikal. *D*- reka bentuk uji kaji campuran optimum (D-Optimal MED) digunakan untuk mengkaji pengaruh komponen yang berbeza terhadap kekerasan tablet. Untuk formulasi tablet, magnesium stearat, A (0.2-1.0% b/b), mentol, B (0.2-1.0% b/b), serbuk lemon, C (1.0-10.0 % b/b), maltodekstrin, D (5.0 -10.0 % b/b) dan glukosa, E (37.5-53.1% b/b) adalah pemboleh ubah manakala serbuk pitaya merah dan pengawet adalah komponen tetap. Keputusan uji kaji telah digunakan untuk menganalisis analisis varians (ANOVA) dan membangunkan model regresi polinomial untuk kekerasan tablet dari segi lima komponen berbeza yang dipertimbangkan dalam kajian ini. D-Optimal MED meramalkan kekerasan tablet pada 8.5 kg/cm^2. Keputusan menunjukkan bahawa campuran terbaik adalah formulasi yang mengandungi 0.66% A, 0.74% B, 6.15% C, 7.61% D dan 44.34% E, dengan kekerasan sebenar tablet yang optimum direkodkan pada 8.581 kg/cm^2 (R^2 = 0.9925). Kajian ini menunjukkan potensi tablet buah-buahan campuran sebagai makanan tambahan yang bersifat terapeutik untuk kesejahteraan pengguna secara umum.

Kata kunci: *Citrus limon*; *Hylocereus polyrhizus;* kekerasan tablet; nutraseutik; reka bentuk uji kaji campuran optimum

Introduction

The knowledge of plants having therapeutic effects and able to cure numerous diseases and health issues has already existed since the dawn of time (Islam et al. 2020). It has been widely known that the potentials are largely due to a rich pool of bioactive phytochemicals contained within the different parts of plant organs such as leaves, stems, roots, flowers, fruits, and seeds (Santana & Macedo 2019). Polyphenols such as flavonoids, stiblins, phenolic alcohols, phenolic acids and lignan are some examples of bioactive phytochemicals. These compounds provide natural antioxidants, have the potential to optimize human body functions and help boost and support general human well-being (Joshi & Prabhakar 2020).

Comprehensive clinical studies on the health benefits of bioactive phytochemicals have increased in many parts of the world. Among the more frequently mentioned are Lemon (*Citrus limon* (L.) Burm. f.) and Red Pitaya (*Hylocereus polyrhizus* (Haw) Britton et Rose)) (Leporini et al. 2021; Putthawan et al. 2021). *C. limon* (Rutaceae) and *H. polyrhizus* (Cactaceae) are considered as superfruits because they are rich in antioxidants (Abd Manan et al. 2019; Park et al. 2021), vitamins and dietary fibre (Abobatta 2019; Joshi & Prabhakar 2020), as well as showing antimicrobial (Hendra et al. 2019; Muhammed & Mohammed 2020), antidiabetic (Den Hartogh & Tsiani 2019; Panjaitan 2021), anticancer (Koolaji et al. 2020; Safira et al. 2021), and antiviral (Battistini et al. 2019; Chang et al. 2020) properties.

Beneficial phytochemicals isolated from plants are sensitive, have poor stability, and are easily degraded by oxidation, which are unavoidable reactions in food systems. Therefore, encapsulation of bioactive phytochemicals to protect against oxidation and increase their chemical/biological stability is vital (Rezvankhah et al. 2020). Industries such as food and pharmaceutical used spray drying technology to encapsulate valuable compounds isolated from plants. This technique utilizes a hot drying gas medium to convert material from liquid to a dried powder, granules or agglomerates (Li et al. 2018). During spray drying of fruit juices, substances like maltodextrin are often used as carrier agents so that the valuable compounds are trapped inside and, hence, are protected from being damaged (Stavra et al. 2021).

In recent years, the demand for nutritional supplements that are food products incorporated with bioactive phytochemicals has increased drastically. They have gained much interest among the public, who take the products to maintain optimal physical and mental conditions to have a better quality of life (Siddiqui & Moghadasian 2020). There are many forms of nutritional supplements, but the most popular form is tablets. Tablets are generally easy to handle and carry around due to their small size and lightweight. They are also not difficult to swallow hence helping patients to practice self-administration. From manufacturers' perspectives, tablets are generally low-cost and more suitable to be produced on a large scale than other forms (Hassan et al. 2020).

One of the most common issues during tableting of fruit powders is punch sticking. During compression of active ingredients and excipients, the powders begin to adhere to the tablet punches due to film formation on the punch face. With subsequent compressions, more particle adheres to the tablet punch, causing the powders to build up. Eventually, the accumulation of powders produces defective tablets. This phenomenon greatly affects the efficiency of the tableting process and tablet quality. The addition of excipient like lubricants and adjusting the temperature and/or humidity may help reduce the problem (Simmons 2019).

The development of a new formulation of tablets is very intricate work. One way to simultaneously assess the effect of multiple input factors (excipients) and their interactions on output (response) is by using statistical techniques called D-Optimal Mixture Experimental Design (MED) (Al-Hagbani et al. 2018). D-Optimal MED is a response surface experiment that involves linear optimization based on a chosen optimality criterion and the best model that fits. The range of maximum and minimum percentages of independent variables affects the experiments whereby the levels of each variable are restricted and dependent on each other since the level of a single component cannot be changed independently. Hence, the amount of each variable in the mixture should total 100% (Shu et al. 2020).

To preserve the integrity of tablets, assessment of tablet properties in terms of physical, chemical, and biological are crucial. The physical quality of tablets such as hardness is essential to prevent the tablet from crumbling or breaking due to shock and abrasion during manufacturing, handling, packaging, and transporting processes. Tablets also require sufficient resistance against force to withstand the stress that occurs during the use of the tablets by patients or consumers (Prada et al. 2020; Sabri et al. 2018).

In this study, powders of lemon and red pitaya were selected as active ingredients in tablet formulation using computed-generated D-Optimal MED. The

hardness of tablets produced was studied to ensure they comply with the pharmacopeia standard. The effect of different excipients on the hardness of tablets was also investigated.

Materials and Methods

Materials

Fresh fruits of red pitaya were supplied by a local grower in Sepang, Selangor. The fruits selected were Grade B (278.2g – 305.4g), fully ripe, blemished, and diseased-free (Zainudin 2014). Fruit pulp was separated from the peels and placed in a juice extractor (Tefal ZC255B Juice Extractor Infiny) to draw out the juice. Mucilage and insoluble particles from the previous process were separated using a centrifuge (Eppendorf 5810 R, 4 °C, 10 min) (Abd Manan et al. 2019). After that, 300 g of maltodextrin was added to 1 L of juice to achieve a maltodextrin concentration of 30% (w/v) (Lee et al. 2013). The mixture was homogenized using an overhead stirrer (RW20; IKA, Guangzhao, China) at 500 r.p.m. for 15 min. The mixture was then spray-dried in a laboratory spray dryer, model GEA FSD Minor Spray Dryer (GEA Process Engineering A/S, Soeborg, Denmark) at inlet air temperatures of 160 °C with an outlet temperature preset at 90 °C and feed flow rate of 250 mL h^{-1}. Food grade magnesium stearate, menthol, lemon powder, maltodextrin, and glucose were purchased from Take It Global Sdn. Bhd., Penang, Malaysia. Menthol crystal was grind using a grinder (A 11 Basic Analytical Mills; IKA, Selangor, Malaysia) prior tableting because the size is not suitable for tableting. All materials were carefully packed in an airtight polyethylene bag and stored in the dark at room temperature for tablet formulation.

Experimental Design

D-Optimal MED operated by Design-Expert 12 software (Stat-Ease Inc., Minneapolis, MN, USA) was performed to identify the optimal formulation of mixed fruit tablets with five independent variables (control factors) and two dependent variables (fixed factors). The excipients chosen for tablet formulation were based on ingredients used in commercial tablets sold in the market. Red pitaya spray-dried powder and preservatives are fixed factors. The excipients of tablets were magnesium stearate (A) as a lubricant, menthol (B) and lemon powder (C) as active ingredients and flavouring agents, maltodextrin (D) as a binding agent and glucose (E) as an energy-contain sweetener (Cabiscol et al. 2018; Hartel et al. 2018; Paul & Sun 2018). Preliminary formulations were made according to the previous work of Arora et al. (2011), Chatuvedi et al. (2017) and Venugopal et al. (2014) to obtain the lowest and highest limits for the components to be added in the D-Optimal MED. Therefore, a total of 24 runs was performed by means of D-optimal design with restrictions for variables to be A (0.2-1.0%), B (0.2-1.0%), C (1.0-10.0%), D (5.0-10.0%) and E (37.5-53.1%), as shown in Table 1.

Preparation of Tablet

Tablets were prepared by mixing fruit powder with other materials in the Glas-Col Dry Powder Rocking Shaker (Glas-Col, LLC, Terre Haute, IN, USA) (Mohamad Zen et al. 2015) and then compressed in a single punch tablet press machine (THDP-3, ShangHai Tian He Machinery Equipment Co., Ltd, Shanghai, China), using the 12 mm mold. The tablets have a round shape, 8 mm diameter, 3 mm thickness and light purple colour. The fraction of each food-grade excipients, namely, magnesium stearate, menthol, lemon powder, maltodextrin and glucose were varied according to the mixture design provided by the software and presented in Table 1.

Determination of Hardness

To measure tablet hardness, the method by Sabri et al. (2018) was used with minor modifications. Texture analyzer (TA·XT plus Stable MicroSystems, UK) was equipped with a 5 kg load cell were used to test the hardness of the tablet. The individual tablets were compressed using a stainless probe with a diameter of 10 mm (P/10). Hardness was reported as the maximum penetrating force (kg/cm^2) required for the probe to obtain statistically reliable results, a sufficiently large number of granules (20) were tested per experiment.

Optimization of Models

The optimum hardness for tablet formulation provided by The United States Pharmacopeia-National Formulary (USP-NF) ranged from 4 kg-10 kg (USP-NF 2009). In the present study, investigation and visualization of the interaction between independent variables using D-Optimal surface and contour plots yielding the desirability function was carried out to acquire an optimized tablet formulation as presented in Table 1. Based on the preliminary studies, the optimum tablet formulation was prepared with 0.66% magnesium

TABLE 1. The experimental design and results of D-optimal mixture experiment

Run	A, %	B, %	C, %	D, %	E, %	Actual hardness, kg/cm^2	Predicted hardness, kg/cm^2	Relative standard error, %
1	1.00	1.00	5.42	5.00	47.08	9.464492	9.54489	-0.84231
2	0.60	0.60	5.50	7.50	45.30	8.918925	8.52626	4.60536
3	1.00	0.51	10.00	10.00	37.99	6.146622	6.17294	-0.42634
4	1.00	1.00	7.57	5.00	44.93	10.2703	10.6247	-3.33567
5	0.60	0.60	5.50	7.50	45.30	8.143843	8.52626	-4.48517
6	1.00	1.00	7.84	7.18	42.48	10.26884	10.3047	-0.34796
7	1.00	1.00	1.00	10.00	46.50	11.65071	11.2837	3.252524
8	1.00	1.00	10.00	7.47	40.03	10.10164	10.6522	-5.16849
9	0.20	1.00	1.00	7.46	49.84	8.713369	8.80742	-1.06786
10	0.20	0.92	3.59	10.00	44.79	9.729778	9.67204	0.596958
11	0.20	0.51	1.00	10.00	47.79	9.781664	9.84838	-0.67743
12	0.85	0.21	3.29	7.40	47.75	11.26358	11.8633	-5.05525
13	1.00	0.20	10.00	5.00	43.30	15.53208	15.9833	-2.82306
14	0.20	0.20	3.91	5.00	50.19	9.985432	9.28823	7.506296
15	0.56	0.20	1.00	10.00	47.74	15.8825	14.6634	8.313863
16	0.63	1.00	1.00	5.00	51.87	9.363216	9.11873	2.681141
17	1.00	0.20	5.61	10.00	42.69	9.608395	9.6502	-0.4332
18	0.20	1.00	10.00	5.00	43.30	3.150016	3.41959	-7.88323
19	0.60	0.60	5.50	7.50	45.30	8.193476	8.52626	-3.90305
20	0.20	0.20	10.00	9.06	40.04	8.191429	8.2401	-0.59066
21	0.20	0.20	1.00	5.00	53.10	9.556342	9.17378	4.170168
22	1.00	0.39	1.00	6.25	50.86	6.06129	6.46479	-6.2415
23	0.20	0.20	10.00	9.06	40.04	8.109251	8.2401	-1.58795
24	0.20	1.00	10.00	10.00	38.30	6.059562	5.55157	9.150421

A – Magnesium stearate; B – Menthol; C – *C. limon* powder; D – Maltodextrin; E – Glucose

stearate, 0.74% menthol, 6.15%, lemon powder, 7.61% maltodextrin and 44.34% glucose and the predicted value of the hardness was 8.5 kg/cm^2. The resulting responses obtained from the evaluation of optimization constraints were compared with the predicted one by quantifying the relative standard error (RSE), as shown

in Equation (1) (Kamairudin et al. 2014; Mohamad Zen et al. 2015).

$$\text{RSE},\% = (\text{Experimental value} - \text{Predicted value})/(\text{Predicted value}) \times 100 \quad (1)$$

Results and Discussion

Mixture optimal design and results

D-optimal MED was used to evaluate the effect of changes in compositions of independent variables, namely magnesium stearate, menthol, lemon powder, maltodextrin and glucose on tablet hardness. In Table 1, 24 experimental runs were presented, including high and low levels of constraint for each independent variable. Statistics were used to find the best-fitted model for five independent variables and the significance of the coefficient of the quadratic polynomial models was evaluated by using a one-way analysis of variance (ANOVA) (Al-Hagbani et al. 2018; Faridatul Ain et al. 2016; Mohamad Zen et al. 2015). The actual and predicted data set of the tablet hardness test are presented in Table 1. The results were established by calculating relative standard error (RSE) in terms of percentage (Equation 1).

Analysis of variance

Table 2 shows the analysis of variance (ANOVA), a basic method used to evaluate the regression model by regression model significance test and lack-of-fit test for the model. To select the best model for the hardness of the tablet, five components were considered: sum of squares, degree of freedom, mean square, F-value and *P*-value (Faridatul Ain et al. 2016). The statistical analysis from Design Expert Version 12.0 software suggested the quadratic model as the best model. The F-value of 85.03 indicated that the model was significant, with less than 0.01% chance that a large model F-value could occur due to noise. When the value of 'probability > F' was less than 0.05, this implied that the model terms were significant (Kamairudin et al. 2014). The F-value of lack of fit test from the quadratic model of 1.18 showed no significance relative to pure error, indicating the model is fit and suitable. There was a 48.22% chance that a lack of fit F–value this large could occur due to noise. The coefficient of determination (R^2), adjusted coefficient of determination (Adj-R^2), predicted coefficient of determination (Pre-R^2), regression (*P*-value) and F-value

TABLE 2. Data from analysis of variance (ANOVA) for hardness of tablets

Source	F-value	*P*-value	Significant
Model	84.53	< 0.0001	***
AB	0.016	0.9015	
AC	204.12	< 0.0001	***
AD	173.79	< 0.0001	***
AE	191.50	< 0.0001	***
BC	308.39	< 0.0001	***
BD	285.33	< 0.0001	***
BE	302.20	< 0.0001	***
CD	47.99	< 0.0001	***
CE	0.100	0.7592	
DE	8.35	0.0179	**
R^2		0.9925	
Adjusted R^2		0.9807	
Predicted R^2		0.8553	
Coefficient of Variation, %		4.04	
Lack-of-fit		Not Significant	
Standard Deviation		0.38	
PRESS		24.53	

Notes: ***p<0.01, **p<0.05, *p<0.1; PRESS: Predicted Residual Sum of Squares

are also shown in Table 2. In this study, the D-Optimal analysis demonstrated that the second-order polynomial used for tablet hardness determination is $R^2 = 0.9925$. The resultant coefficient showed 99.25% of the response variation of tablet hardness could be described by D-Optimal mixture design models as the main tablet formulation function. The slight difference between the adjusted coefficient of determination ($adjR^2 = 0.9807$) and R^2 indicates that the equation is well-fitted. The ANOVA table shows that the linear mixture components, AC, AD, AE, BC, BD, BE and CD ($P_{AC,AD,AE,BC,BD,BE,CD} < 0.0001$) are significant model terms, indicating that the interaction between magnesium stearate with lemon powder, maltodextrin, and glucose; menthol with lemon powder, maltodextrin, and glucose, as well as lemon powder and maltodextrin, have the most significant impact on hardness. In addition, the interaction between D and E also has a notable effect on hardness, as its *P*-value is less than 0.5 ($P_{DE} = 0.0179$).

EFFECT OF COMPONENTS VARIABLES ON THE HARDNESS OF TABLETS

The interactions between AC, AD, AE, BC, BD, BE, CD and DE were significant ($p < 0.05$) model terms (Table 2). From Table 3, linear coefficient and quadratic coefficient were obtained. It was observed that four of the linear coefficients (B, C, D, E) and four quadratic coefficients (A and B, A and C, A and D, A and E) of the model had a positive effect. The final model to predict the hardness of the tablet formulation is shown in regression Equation (2).

$$Y = -1242.35\ A + 1466.29\ B + 0.8822C + 5.1788\ D + 0.1963\ E \quad (2)$$

where Y is the predicted hardness values in mixed fruit tablets; and A, B, C, D, and E are the fraction of magnesium stearate, menthol, lemon powder, maltodextrin, and glucose, respectively.

Many factors can influence the hardness of tablets, such as compaction force and speed, relative humidity of surrounding air, temperature, physical or mechanical properties of input materials (excipients) and others (Hartel et al. 2018). According to Charoo (2019), material properties can be divided into three levels. The first level is the constituent of molecules (chemical species). The second level is how these molecules/atoms are arranged (i.e., structure in the condensed states such as non-crystalline and crystalline structures, including polymorphs). The last level includes particle morphology, particle size, as well as other particle characteristics such as moisture sorption, pore structure (e.g., granule structure), consolidation, and density.

Figure 1 and Equation (2) show that menthol, lemon powder, maltodextrin, and glucose positively affected tablet hardness. Among the excipients, menthol has larger size than others. A study by Skelbæk-Pedersen et al. (2020) found that larger initial particle sizes fragment more extensively than smaller initial particle sizes. As the menthol particles fragment during tableting, the contact sites for interparticulate bonding also increase. The process culminates incoherent mass formation with reduced interparticle spaces between granules. This resulted in stronger compressibility of the mixtures and consequently increased tablet hardness (Charoo 2019).

The use of maltodextrin as a binder and diluents in tablet formulation also significantly affected tablet hardness. An amorphous material such as maltodextrin goes through a change from a 'glass-like' to a 'rubber-like' state when the temperature of glass transition of that material is reduced. As a result, the material becomes sticky on the surface providing cohesiveness to the particles (Foster et al. 2006; Takeiti et al. 2010). Therefore, the addition of maltodextrin improved the compressibility and compactability of particles during tabletting as it helped all the excipients to adhere to each other (Thapa et al. 2017). During compression of mixtures into tablet form, maltodextrin was forced into the inter particulate spaces resulting in more solid bonds between granules hence, contributing to the hardness of tablets (Gunatilake et al. 2016). A study by Elnaggar et al. (2010) reported that maltodextrin exhibited a hardening effect on the tablet as the concentration in the formulation increased. Mohamad Zen et al. (2015) studied the effect of maltodextrin addition on the hardness of the okara tablet. They found that increasing the percentage of maltodextrin increases tablet hardness. In addition, results obtained by Naji-Tabasi et al. (2021) showed that the hardness of barberry effervescent tablets increased by the increment of maltodextrin concentration.

Glucose which is used as functional excipients (excipients that possess multiple roles in a dosage form or drug delivery system) in tablet formulation also classified as amorphous material (Van de Merwe et al. 2020). When exposed to room temperature, glucose particles adsorb water vapour in the surrounding air, leading to powder caking. This interaction causes the particles to aggregate thus transforming a readily free-flowing powder into a

coherent solid, contributing to tablet hardness. In a study conducted by Danki (2021), Lornoxicam immediate-release tablets containing sucrose (glucose) exhibit the highest hardness among other formulations that do not contain sucrose. Their research shows that sugars do influence tablet hardness.

In contrast, magnesium stearate had an adverse effect on tablet hardness (Figure 2 & Equation 2). The negative effect of magnesium stearate on tablet strength is widely known (Paul & Sun 2018; Rajani et al. 2017). According to Li and Wu (2014) and Perrault et al. (2011), boundary lubricants such as magnesium stearate created a hydrophobic film or layers between sur-faces and prevented further contact between powder particles, hence altering interactions at the particle-particle bonding interface. This resulted in a low compact strength as well as tablet hardness. Study by Paul and Sun (2018) observed that a high amount of magnesium stearate in tablet formulation led to a serious deterioration in tablet strength as a higher concentration created a thicker lubricant layer which weakened adhesion between compacts.

TABLE 3. Regression coefficient values for final reduced model

Source	Coefficient estimate
A-Magnesium stearate	-1242.35435
B-Menthol	+1466.28803
C-C. limon powder	+0.88222
D-Maltodextrin	+5.17875
E-Glucose	+0.19626
AB	+0.25267
AC	+22.18688
AD	+20.24077
AE	+21.36820
BC	-25.57896
BD	-24.37756
BE	-25.35658
CD	-0.22402
CE	-3.00420×10^{-003}
DE	-0.089580

VERIFICATION OF EXPERIMENT

To validate the D-Optimal surface equation, a comparison was made between experimental and theoretical predicted values (Kamairudin et al. 2014). The experiments were formulated under the suggested conditions, and the resulting responses were compared to the predicted ones by computing the relative standard error (Equation 1). The optimized tablet formulation has a hardness of 8.581 kg/cm^2. As stated in Table 4, no significant difference was observed between the theoretical predicted and experimental value under optimal conditions. Therefore, the finalized equation for hardness generated by Design-Expert software was acceptable to be used in mixed fruit tablet formulation. The optimal formula obtained by software optimization are 0.66% magnesium stearate, 0.736% menthol,

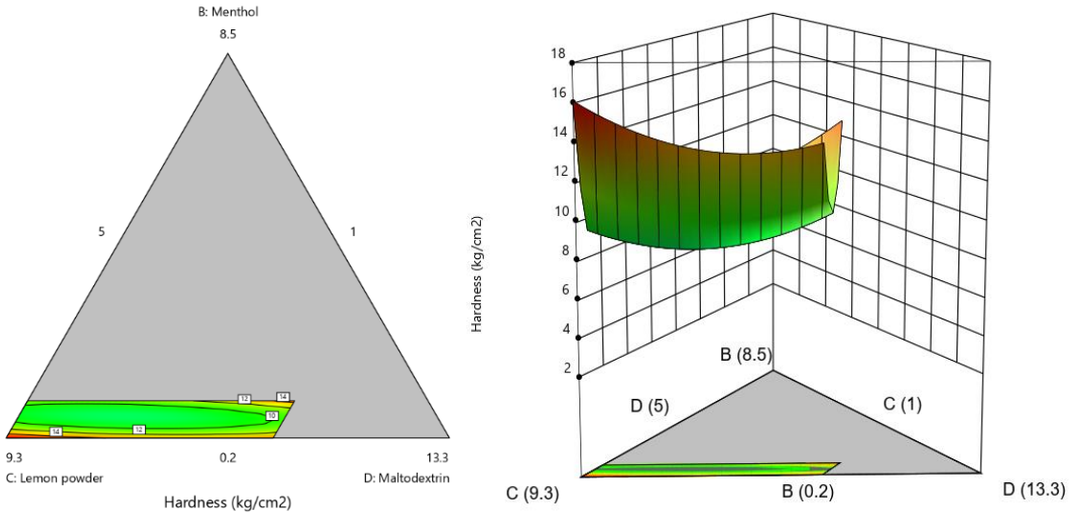

FIGURE 1. Contour plot (two-dimensional) and three-dimensional surface plots showing the interaction effect between three variables: B - Percentage of menthol, C – Lemon powder, D - Maltodextrin and with actual component of Magnesium stearate (A=0.6%) and Glucose (E=45.3%) to the hardness of the tablet

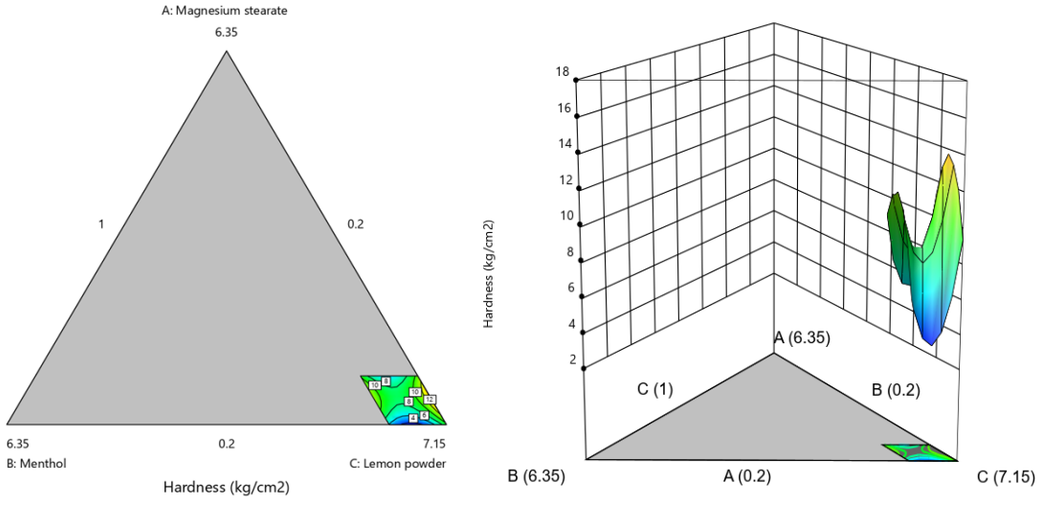

FIGURE 2. Contour plot (two-dimensional) and three-dimensional surface plots showing the interaction effect between three variables: A - Percentage of Magnesium stearate, B - Menthol, C – Lemon powder with actual component of Maltodextrin (D =7.5%) and Glucose (E=45.3%) to the hardness of the tablet

6.154% *C. limon* powder, 7.61% maltodextrin and 44.34% glucose. The predicted response value under this formulation for tablet hardness is 8.5 kg/cm^2. Three confirmatory experiments were carried out to obtain hard-ness value of 8.5 ± 0.5 kg/cm^2. There was no significant difference from the predicted values

calculated using RSE ($p<0.05$), indicating that the optimal formulation of tablets can be accurately predicted by using D-Optimal MED.

TABLE 4. Predicted and observed values for optimal formulation of tablet

Independent variables					Hardness (kg/cm^2)		
A (%)	B (%)	C (%)	D (%)	E (%)	Predicted	Experimental	RSE (%)
0.66	0.736	6.154	7.61	44.34	8.5	8.581	0.9529

Note: A – Magnesium stearate; B – Menthol; C – *C. limon* powder; D – Maltodextrin; E – Glucose, RSE - Relative standard error

Conclusion

The formulation of mixed fruit tablets was successfully conducted using D-Optimal Mixture Experimental Design (MED) by combining the independent variables: magnesium stearate, menthol, Lemon powder, maltodextrin, and glucose. The optimum components for the natural tablet formulation were established and the effects of the mixture components on tablet hardness have been successfully investigated using D-Optimal MED. The result showed that menthol, lemon powder, maltodextrin and glucose had positive effects on tablet hardness, while magnesium stearate had negative effects. The optimal inputs determined by D- Optimal MED was established at magnesium stearate (0.66 % w/w), menthol (0.74 % w/w), lemon powder (6.15 % w/w), maltodextrin (7.61 % w/w) and glucose (44.34 % w/w), with the actual hardness of the optimized tablet at 8.581 kg/cm^2. The analysis of variance stated that the accuracy of the model, using F-value (84.53) and a very low *P*-value (<0.0001) with a non-significant lack of fit, and $R^2 = 0.9925$. The establishment of an optimized protocol for preparing a successful mixed fruit tablet contributes to the body of knowledge in preparing plant-based nutraceutical tablet. Therefore, the proposal in making lemon and red pitaya as nutritional supplements (nutraceuticals) used to promote health status and prevent certain diseases presented a promising undertaking.

Acknowledgements

The authors gratefully acknowledge the financial assistance grant by Universiti Putra Malaysia Graduate Research Fellowship (GRF) and Geran Putra Berimpak of Universiti Putra Malaysia (UPM) (Grant No. 9688800).

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