Journal of
Food and Pharmaceutical Sciences

Original Article

The Development of Alternative Dosage Form for Creatine Monohydrate: A Floating Tablet

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Received: 26 May 2023; Revised: 11 August 2023; Accepted: 20 August 2023; Published: 21 December 2023

Abstract: Creatine monohydrate is an ergogenic compound that is widely used to increase sports endurance and muscle mass for bodybuilders. However, its delivery is hampered by its limited capacity of creatine transporter. The floating system is known to increase the residence time of drugs in the stomach; thus, the active substances can be absorbed more optimally. Therefore, this study is aimed to develop creatine monohydrate floating tablets by optimizing the proportion of HPMC K100M and $NaHCO_2$ and evaluating the quality of floating tablets. The formula was designed by Simplex Lattice Design method in Design Expert-13 software. Tablets were prepared by the wet granulation method and evaluated for granule and tablet parameters. The results showed that HPMC K100M significantly increased flow time, absorption rate, hardness, floating time, swelling index; decreased index tap, fragility, and floating lag time. Meanwhile, an increase in $NaHCO_2$ significantly affects an increase in floating lag time. The optimum formula obtained was 18.87% HPMC K100M and 21.12% $NaHCO_2$, with the physicochemical properties of the formula: flow time 6.67 sec/100g, solvent absorption rate 7.61 mg/minute, hardness 7.29 kg, friability 0.172%, floating lag time 9.70 second, floating time 24 hour, swelling index 112.773%. Verification of the optimum formula showed that tablet parameters were not significantly different from the predicted formula. The studies suggest this prototype can be developed to increase creatine residence time in the stomach.

Keywords: floating tablet, creatine monohydrate, HPMC K100M, $NaHCO_2$

1. INTRODUCTION

Creatine is a popular supplement that is widely used to increase endurance and muscle mass for bodybuilders and athletes [1]. However, its delivery encounters several limitations in terms of its enormous doses, physicochemical properties, transport mechanisms, and compound stability. The dose of creatine is relatively large, namely 20 g/day for loading doses, 2-5 g/day for maintenance doses, and 20-30 g/day for neurodegenerative therapy purposes [2,3].

Creatine is a zwitterion compound that bears an issue when being dissolved at physiological pH [4]. In addition, the double charge on creatine excludes creatine from the transcellular passive diffusion route. The main mechanism of creatine transport is through the creatine transporter (CrT) [5]. The rate of absorption of creatine across biological membranes is limited by the capacity of CrT. When the drug dissolution rate exceeds the maximum transporter velocity (Vmax), some creatine is

not absorbed and is excreted via feces. In small doses, the bioavailability of creatine is almost perfect, but in large doses, the bioavailability is 16% [3,6]. An alternate strategy to improve drug bioavailability is by extending the drug's residence time in the digestive tract is floating tablets [7]. This dosage design allows creatine monohydrate to have sufficient absorption time and not cause excessive saturation of the creatine transporter.

A floating mechanism can be achieved through the formulation of the effervescent system in a hydrophilic matrix. HPMC can be used as a hydrophilic polymer in floating tablet formulations because of its good swelling and ability to extend the duration of drug retention in sustained-release preparations [8]. In addition to polymers, the effervescent system also uses an effervescent agent to produce CO_2 bubbles which hasten the floating lag time. $NaHCO_2$ was used as an effervescent agent. This compound reacts with an acidic environment in the gastric and produces CO_2. The gas is trapped in the expanded hydrophilic polymer and causes buoyancy for the tablet [9].

Due to its enormous dose, the formulation of creatine remains a big challenge. Up to now, creatine is sold as a powder to be dissolved by the consumer right before consumption. Thus, studies to provide alternate creatine drug delivery system is imperative. This study aims to develop creatine monohydrate in the form of a floating tablet and evaluate the contributions of HPMC K100M and $NaHCO_2$ on tablet quality. Hopefully, this prototype will increase the efficacy of creatine as an athlete supplement and answer the need for a creatine delivery system to treat neurodegenerative diseases.

2. MATERIALS AND METHODS

2.1. Materials

The materials used were creatine monohydrate (pharmaceutical grade, NOW FOODS Inc., USA), HPMC K100M (pharmaceutical grade, Ashland Specialist Chemicals Indonesia), lactose monohydrate (pharmaceutical grade, Alpavit Inc., Germany), $NaHCO_2$ (pharmaceutical grade, T&T Chemical Co., Ltd., Indonesia), magnesium stearate (pharmaceutical grade, Fagron Inc., Belgia), mucilage starch (pharmaceutical grade, Wujiang Jinyu Lanolin Co., China), and HCl (millipore).

2.2. Methods

2.2.1. Formulation of floating tablets

The design of the creatine monohydrate floating tablet formula was determined by the Simplex Lattice Design method using Design Expert 13 software. The components used are shown in Table 1. Floating tablets are prepared by the wet granulation method. Creatine monohydrate, HPMC K100M, and lactose monohydrate were mixed in a cube mixer for 3 minutes at 30 rpm. Subsequently, 10% mucilage amili binder liquid was added.

Table 1. Formulation of creatine monohydrate floating tablets

Material	Run (mg)							
	1	2	3	4	5	6	7	8
Creatine monohydrate	400.0	400.0	400.0	400.0	400.0	400.0	400.0	400.0
HPMC K100M	187.5	75.0	225.0	150.0	150.0	75.0	225.0	112.5
$NaHCO_2$	112.5	225.0	75.0	150.0	150.0	225.0	75.0	187.5
Lactose monohydrate	64.0	64.0	64.0	64.0	64.0	64.0	64.0	64.0
Magnesium stearate	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Total	**800.0**	**800.0**	**800.0**	**800.0**	**800.0**	**800.0**	**800.0**	**800.0**

The wet granule mass was sieved using a 14-mesh sieve and then dried with a fluid bed dryer for 15 minutes. The dry granules were sifted through a 14-mesh sieve. $NaHCO_2$ and magnesium stearate were added and mixed in a cube mixer for 3 minutes at 30 rpm. The tablet mass was designed to have a diameter of 15 mm, a height of 4 mm, and a weight of 800 mg [10].

2.2.2. Evaluation of granule physical properties

To examine the flow rate, 50.0 g of granules were briefly poured into the flowability tester funnel through the edge of the funnel. The lower funnel cover is opened by pressing the start button. The time it takes for the granules to come out of the funnel is recorded as flow time [10]. For getting the compressibility index, granule mass was measured as much as 100.0 mL using a measuring cylinder tapping device. The measuring cylinder is mounted on the tapping machine and tapped for 4 minutes or 100 beats. The pre-tapping and final volume was recorded, then find out Carr's index by the formula [11]:

$$\text{Index Carr's (\%)} = \frac{Dt - Db}{Dt} \times 100$$

Dt = tapped density

Db = bulk density

To identify the granule absorption rate, a 100.0 mg granule was placed on the surface of the tube for the absorption capacity test. The instrument is connected to a balance that has a vial containing 0.1 N HCl on it. The vial is connected to the capillary which is connected to the granule chamber. The volume of 0.1 N HCl in the vial that was left after 15 minutes due to absorption in the granules is recorded, then evaluated three times for replication[12].

2.2.3. Evaluation of physical characteristics of the tablets.

To test weight uniformity, twenty tablets were sampled randomly and weighed individually. The average weight and standard deviation (SD) of the tablet are calculated. Ideally, no more than 2 tablets deviate by more than 5% of the average weight and no single tablet deviates by more than 10% of the average weight [13]. The hardness of the tablet is evaluated by placing a tablet between two loads on a hardness tester and adjusted by the spindle. The pressures required to break the tablet are recorded. Each run used a minimum of three tablets to evaluate, then averaged. The data is expressed in kg/cm2 unit [14]. For the friability data, a total of 20 tablets were dust-free, then weighed. The tablets that had been weighed were put into the friability tester, then rotated for 4 minutes at 25 rpm for 100 revolutions. The tablets are dust-free again and then the final mass is weighed [11].

2.2.4. Evaluation of floating characteristics.

The floating time was evaluated by placing a tablet into a beaker containing 100 mL of HCl pH 1.2. The time required for the tablet to float on the surface of the dissolution medium is expressed as the floating lag time. The time from the tablet completely floating until it sinks again is expressed as floating time [15]. A tablet from each run was placed into a beaker containing 50.0 mL HCl pH 1.2 at 370 C to identify the swelling index. This experiment was done in three replications for each run. The test was carried out for 6 hours by weighing the tablet mass every hour [11].

2.2.5. Optimum formula determination and verification.

The optimum formula is obtained by analyzing the data obtained from various test parameters using Design Expert 13 software. The response that appears is in the form of a desirability graph that is used to determine the optimum point with precision. The optimum formula has evaluation results within the limits of each parameter and the desirability. The optimum formula has a degree of desirability close to one [16]. The optimum formula physical properties test results were compared with the predicted results using the one-sample T-test method in the IBM SPSS Statistics-26. The goals used in determining the optimum formula for each parameter are: flow time <10 sec/100g, the faster the absorption rate the better, hardness 4-8 kg, brittleness <1%, floating lag time <60 seconds, floating time > 24 hours, the bigger the swelling index the better.

3. RESULTS AND DISCUSSION

3.1. Physical properties of creatine monohydrate's floating tablet

Evaluation of the physical properties of the granules and tablets performed is shown in Table 2.

Table 2. Creatine monohydrate's floating tablets' physical properties evaluation result

Run	**Granule Flowtime (sec/100g)**	**Carr's Index (%)**	**Granule absorption rate (mg/min)**	**Weight uniformity (%CV)**	**Hardness (kg)**	**Friability (%)**	***Floating lag time* (second)**	***Floating time* (hour)**	***Swelling index* (%)**
1	7.07±0.21	7.26±1.18	7.86±1.18	1.087	7.77±0.59	0.21±0.05	10.58±2.22	24	249.44±27.54
2	5.90±0.30	9.00±1.73	7.16±0.61	1.258	6.36±0.45	0.12±0.06	125.58±4.82	5	NA[1]
3	7.50±0.17	6.98±0.04	8.03±0.37	1.382	8.00±0.34	0.25±0.06	9.81±2.26	24	275.35±26.79
4	6.63±0.23	7.67±1.53	7.74±0.78	1.265	7.48±0.24	0.17±0.03	10.91±2.49	24	110.19±20.85
5	6.63±0.23	7.70±0.61	7.77±0.46	1.151	7.61±0.45	0.19±0.06	11.01±1.04	24	144.73±26.71
6	5.83±0.06	9.00±1.73	7.18±0.62	1.198	6.33±0.47	0.11±0.05	119.66±4.28	5	NA[1]
7	7.63±0.29	6.69±0.55	8.27±0.18	1.040	8.12±0.84	0.25±0.09	9.87±0.77	24	282.52±27.72
8	6.43±0.15	8.12±1.83	7.26±0.36	1.141	7.14±0.73	0.15±0.09	15.13±2.64	24	46.29±13.98

[1]NA = not applicable

Flow time testing is carried out to determine the number of granules that can flow per unit of time. This represents the ability of the granules to flow into the compression chamber, thus affecting the uniformity of tablet weights. Various tablet weights can affect the uniformity of the content so that it can provide non-uniform efficacy in the body [17]. Based on Table 2, all granules in each run have good flow properties, namely flow time < 10 seconds/100g [18]. In the design expert graph (Figure 1a), the granules that have the shortest flow time are granules run 2 and 6 with the lowest HPMC K100M concentration and the largest $NaHCO_2$ concentration. This is because HPMC K100M is hygroscopic [19] which results in a great cohesive power. This cohesive power causes the granules to tend to stick to the funnel wall, thereby inhibiting the flow of granules [20]. In addition, according to research from Siswanto [21], $NaHCO_2$ has a greater density than HPMC, so it passes through the funnel faster because its gravitational force is also greater.

Determination compressibility index testing is carried out to determine the compaction of granules during the pressing process. This test is related to the hardness and friability of tablets. The lower the compaction, the lower the tablet hardness and the greater the friability. Based on Table 2, all granules in each run exert a good tap index, which is <10% [22]. The smaller the index tap, the

better the flow properties of the granules. In the design expert graph (Figure 1b), the granules that have the smallest index tap are granules run 2 and 6 with the smallest HPMC K100M concentration and the smallest $NaHCO_2$. These results are per the flow time test, so it can be concluded that the runs with the best flow properties are runs 2 and 6. This is because the HPMC K100M has an irregular shape [23]. Irregular shapes can enlarge the space in the compression chamber so that the reduced volume will be even greater. In addition, the higher density of $NaHCO_2$ also causes the run with more $NaHCO_2$ composition to be more compressed even before setting so that the reduction in volume is not too large.

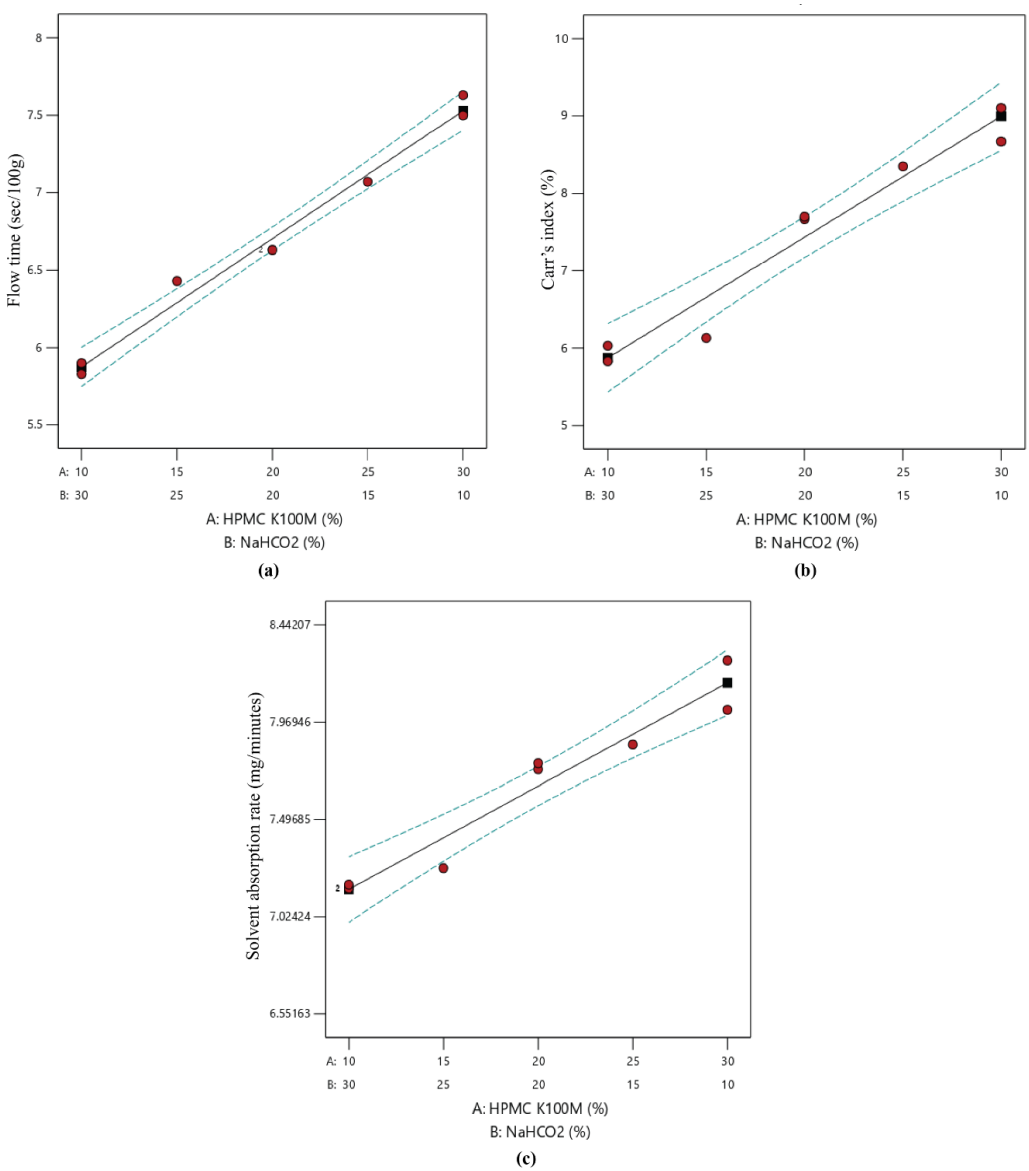

Figure 1. SLD equation graph of creatine monohydrate granules with the optimation of HPMC K100M and $NaHCO_2$ on parameters: (a) flow time, (b) Carr's index, (c) granule absorption rate. Creatine granules were produced using the wet granulation method. The wet granule mass was sieved using a 14-mesh sieve and dried with a fluid bed dryer for 15 minutes.

The granule absorption rate test measures the amount of medium that granules can absorb in a certain time in units of mg/minute [12]. This test is carried out because it is related to disintegration time and swelling index tablets. In the design expert graph of absorption rate (Figure 1c), the granules that have the greatest absorption speed are granules run 3 and 7 with the highest HPMC K100M

concentration ratio of 30% and the smallest $NaHCO_2$ of 10%. This is because HPMC K100M is hydrophilic, so the greater the content of HPMC K100M, the better the ability of the granules to absorb water [24].

Tablet weight uniformity is related to the uniformity of the active substance contained in the tablet. Tablets that have uniform weight are assumed to have uniform levels of the active substance [25]. The results of testing the uniformity of the floating tablet weights from each run are shown in Table 2. All tablets in each run met USP requirements, that is, no tablet deviated by 5% on average by weight and no 1 tablet deviated by 10% on average by weight, and CV < 5%.

Tablet hardness is one of the parameters in support the buoyancy of a tablet. Increasing hardness will increase the floating lag time of the tablet [26]. In addition, an increase in tablet hardness can reduce porosity and prolong the dissolution rate of the drug [27]. All runs have a hardness in the range of 6-9 kg. This value meets the requirements for tablets containing matrix, which is ≥ 5 kg [28]. In the design expert graph (Figure 2a), the granules that have the greatest hardness are granules run 3 and 7 with the highest HPMC K100M concentration and the smallest $NaHCO_2$ concentration. This is due to the hygroscopicity nature of the HPMC. It adsorbs water vapor and results in smaller particle porosity and stronger interparticle particles [29].

The tablet friability test was performed to measure the tablet's resistance to friction and impact on its surface. Based on the data obtained, the friability of floating tablets at all runs meets the requirements, namely <1% [30]. In the design expert graph (Figure 2b), the granules that have the smallest friability are granules run 3 and 7 with the highest concentration ratio of HPMC K100M and the smallest concentration of $NaHCO_2$. This is because HPMC K100M is a polymer that can be used as a binder, so it can reduce the percentage of friability on the tablet surface [31]. These results are by the results of hardness testing, in which the harder the tablet, the smaller the fragility.

Floating lag time is influenced by the swelling ability of the polymer used in the formula. The greater the swelling ability, the faster the floating lag time [20]. In the design expert graphic (Figure 2c), the granules that have the fastest floating lag time are granules run 3 and 7 with the highest $NaHCO_2$ concentration and the smallest HPMC K100M. This is due to the good gelling properties of HPMC K100M that result in a better swelling index [15]. In addition, the production of CO_2 gas result in a reduction in specific gravity and enable the tablet to float [21].

Floating time is the time it takes for the tablet to float until it sinks. In the design expert graph (Figure 2d), only runs 2 and 6 have the shortest floating time with the highest $NaHCO_2$ concentration ratio of 30% and the smallest HPMC K100M, namely 10%. The floating capability reaches 24 hours due to sufficient availability of HPMC K100M that maintains the tablet to be intact for a longer period and remains floating on the surface of the medium [21]. Meanwhile, runs 2 and 6 did not contain sufficient HPMC K100M composition which cause the tablet to sink earlier.

The swelling index affects the floating time tablet. The greater the swelling ability, the longer the floating time. In the expert design chart (Figure 2e), the granules that have the highest swelling index are tablets run 3 and 7 with the highest HPMC K100M concentration and the lowest $NaHCO_2$ concentration. In Table II, some data is indicated as N. A (not applicable), namely runs 2 and 6. This is because the tablets in that run had completely dissolved before 360 minutes and left foam, so there is no swelling hydrogel that could be measured for identification of swelling index. Runs 3 and 7 have the highest swelling values. This is because HPMC K100M can form a hydrophilic polymer matrix that can trap the medium so that the specific gravity of the tablet is reduced because the

volume of the tablet is getting bigger, and the tablet can float for a long time [21]. The longer the tablet floats, the more medium is trapped in the hydrophilic matrix, so the weight of the matrix increases, and the additional weight is calculated as the swelling index.

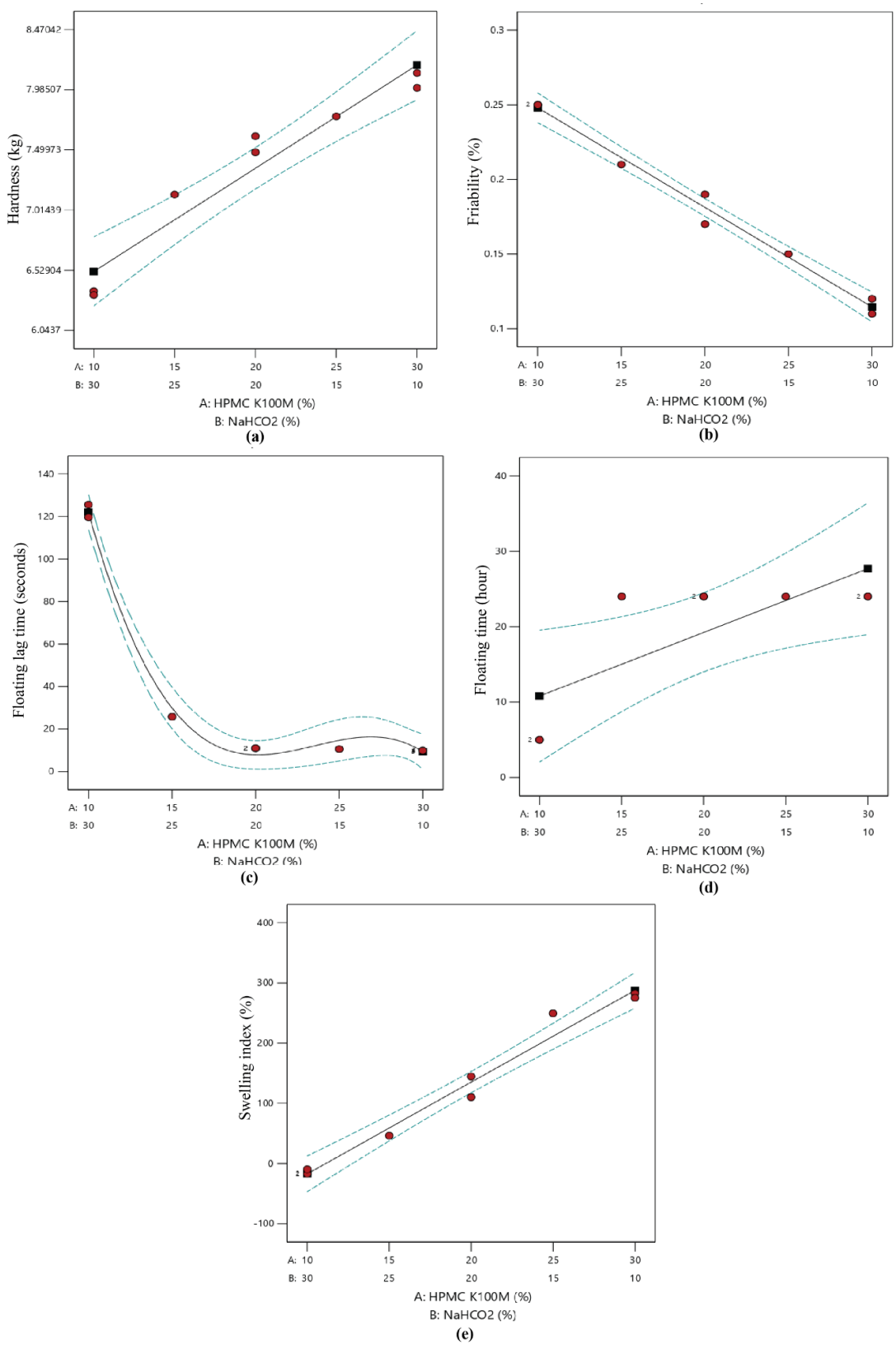

Figure 2. SLD equation graphs of creatine monohydrate granules with the optimation of HPMC K100M and $NaHCO_2$ on parameters: (a) hardness, (b) friability, (c) floating lag time, (d) floating time, (e) swelling index.

The model resulting from ANOVA analysis using Design Expert 13 software is linear and cubic (floating lag time) as shown in Figure 2. The results of the analysis showed that the mixture of the two components gave a significantly different response in the presence of different concentrations (p-value < 0.05). Meanwhile, the lack of fit obtained was not significant with a value of F > 0.05. This shows that the data obtained is not significantly different from the prediction. Meanwhile, the lack of fit of floating time cannot be analyzed because the data is less varied. Almost all runs have a floating time of 24 hours, except for runs 2 and 6. Apart from the linear model, there is no other model that can show the lack of fit results. However, this parameter is still included in the optimization because there are significant differences in the models.

Table 3. Creatine monohydrate's floating tablets SLD equation from each response

Parameter	SLD Equation	*p-value Model*	*Lack of Fit*
Flow time	y = 0.21 A + 0.13 B	< 0.0001	3.23
Carr's Index	y = 0.26 A + 0.11 B	< 0.0001	3.98
Granule absorption rate	y = 0.22 A + 0.17 B	< 0.0001	1.47
Hardness	y = 0.22 A + 0.14 B	< 0.0001	8.24
Friability	y = 0.0079 A + 0.0012 B	< 0.0001	0.15
Floating lag time	y = -5.07 A + 17.04 B – 0.58 AB + 0.03 AB(A - B)	< 0.0001	9.35
Floating time	y = 0.90 A + 0.06 B	0.0255	-
Swelling index	y = 11.00 A – 4.24 B	< 0.0001	2.94

A = component fraction of HPMC K100M

B = component fraction of $NaHCO_2$

3.2 Optimum formula determination and verification

Determination of the optimum formula is carried out by the numerical method using several optimization parameters, namely flow time, absorption rate, hardness, brittleness, floating lag time, floating time, and swelling index. In this study, the highest desirability value was 0.720 with a composition of 18.87% HPMC K100M and 21.13% $NaHCO_2$. The overall composition of the ingredients in the optimum formula for creatine monohydrate floating tablets (weight 800 mg) is creatine monohydrate 400 mg, HPMC 151 mg, $NaHCO_2$ 168 mg, lactose monohydrate 64 mg, and magnesium stearate 16 mg.

The results of the one-sample t-test analysis in Table 4 show that there is no significant difference between the predicted value and the experimental results for all parameters (Sig.2-tailed > 0.05), except for floating time. That means the experimental result has been in accordance with the prediction and the optimum formula has been verified. The floating time value cannot be analyzed for its significance because the resulting data does not vary, namely the floating time of three replications is 24 hours as what the goal criteria have. However, when compared with the prediction, the predicted value is only 18.30 hours. This proves that the experimental floating time value is better than the prediction because the tablet can float longer than expected.

Table 4. Comparison of SLD's Predictive Value with Experimental Value of Optimum Formula Creatine Monohydrate Floating Tablets

Response	Prediction	Research results	p-value (2-tailed)	Significantly different
Flow time (sec/100g)	6.61	6.67	0.806	No
Solvent absorption rate (mg/minute)	7.60	7.61	0.947	No
Hardness (kg)	7.22	7.29	0.706	No
Friability (%)	0.19	0.172	0.512	No
Floating lag time (second)	8.84	9.70	0.421	No
Floating time (hour)	18.30	24	-	Yes
Swelling index (%)	118.00	112.773	0.156	No

4. CONCLUSION

In summary, the creatine monohydrate floating tablet has been formulated with an effervescent system. The increase in HPMC K100M has a significant contribution to increasing flow time, decreasing index determination, increasing absorption rate, increasing hardness, decreasing brittleness, decreasing floating lag time, increasing floating time, and swelling index. While the $NaHCO_2$ has a significant role in reducing floating lag time. The optimum formula obtained has a composition of 18.28% HPMC K100M and 21.72% $NaHCO_2$. This composition provides the optimum physical properties of creatine monohydrate floating tablets.

Funding: This research was funded by the Faculty of Pharmacy through Hibah Berkualitas Prima 2022, University of Gadjah Mada.

Acknowledgments: This research was supported by the Faculty of Pharmacy, University of Gadjah Mada, Hibah Berkualitas Prima 2022.

Conflicts of interest: No potential conflict of interest was reported by the authors.

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