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Development and Characterization of Halal Excipient Co-Processed Jackfruit Seed Starch (Artocarpus Heterophyllus Lam.) and HPMC K15

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ABSTRACT

Direct compression is a tablet manufacturing method known for the simple and economical process, but it requires excipient with good flow properties and hardness. Based on 2022 data from Indonesian Ministry of Health, about 95% of excipient raw materials are imported from countries with Muslim minorities or non-Muslim populations, raising concerns about halal status. Partial pregelatinization of jackfruit seed starch (PPJFSS) can enhance flowability and reduce compressibility, angle of repose, and moisture content, although the compactibility remains low. Co-processing through wet granulation by combining PPJFSS with HPMC K15, a material with good compactibility, offers a potential halal excipient alternative. Therefore, this study aims to develop and characterize an optimal combination of co-processed excipient (PPJFSS–HPMC K15) with favorable physical and mechanical properties. Preparation started with JFSS production and formulation optimization using Design Expert 13, varying PPJFSS and HPMC K15 ratios. Responses examined include moisture content, flowability, angle of repose, compressibility, and compactibility. The optimum formula was subjected to organoleptic, microscopic, flow property, FTIR (Fourier Transform Infrared), SEM (Scanning Electron Microscope), XRD (X-ray diffraction), and particle size analyses. The results showed that the optimal PPJFSS–HPMC K15 ratio of 95.75:4.25% met all physical evaluation criteria except particle size distribution. It demonstrated the functional groups of JFSS and HPMC K15, amorphous polymer characteristics, and granulated morphology. In conclusion, the optimum co-processed excipient (95.75:4.25%) showed good physical and mechanical properties. The structural characteristics are in line with previous literature, making it a promising halal excipient alternative.

Keywords: Tablet, PPJFSS, Hydroxypropyl methylcellulose K15, co-process, Design Expert.

Introduction

Indonesia imports more than 95% of pharmaceutical excipient, making the country vulnerable to disruptions in domestic drug production, specifically in crises such as a pandemic.[1,2] Furthermore, most of the exporting countries have Muslim minorities or even non-Muslim populations, which may not pay attention to halal status of medicines. Indonesia is a predominantly Muslim country, where halal aspect of ingredients is essential. Government Regulation Number 42 of 2024 concerning Halal Product Assurance Sector implementation mandates that all products entering, circulating, and traded in the territory of Indonesia must be halal certified.[2] In general, halal is defined as permitted or allowed, and a basic understanding of this concept is essential for every Muslim.[3] The Ministry of Religious Affairs of Indonesia confirmed Hydroxypropyl Methylcellulose (HPMC) as halal-certified ingredient because it is a chemical compound from organic synthesis. Jackfruit seed starch (JFSS) is a plant-based ingredient, and aquadest is natural water processed physically through distillation without adding other substances, thereby retaining the natural chemical structure, H_2O, and safe for consumption.[4,5]

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Tablets have become the most commonly used pharmaceutical form due to the practicality and stability, with the direct compression method as the preferred process due to the cost and energy efficiency.[6] Excipient from waste, such as JFSS, have the potential to reduce import dependence, address environmental issues, and are halal certified because it is derived from plant-based materials. However, natural JFSS has less than optimal mechanical properties.[7] Jackfruit seeds contain a significant amount of starch, reaching approximately 20%.[8]

Two types of pregelatinization methods can be distinguished, namely partial and complete. More specifically, complete pregelatinization is carried out by heating the starch suspension above the gelatinization temperature, while in partial pregelatinization, the starch suspension is heated below the gelatinization temperature.[9] Physical modifications, such as partial pregelatinization, can improve flowability and compressibility, but still require enhancement of functional properties.[10] In general, partially pregelatinised starch has brittleness and a poor disintegration time.[11]

Previous studies have shown that co-processing of pregelatinised starch and HPMC improves flow properties, compressibility, and good binding strength, similar to the study using ofada rice starch.[12] Combined with HPMC K15, the co-processing method was selected based on the proven ability to enhance flowability, compressibility, and binding capacity, critical characteristics for direct compression tablet manufacturing. Simplex Lattice Design (SLD) has proven effective for optimization, ensuring systematic, data-driven formulation[13], while validation and verification steps ensure reliability

and reproducibility. Comprehensive characterization using standard pharmacopeial methods and analytical tools (FTIR, SEM, XRD) provides a strong understanding of excipient functionality and structural properties. The co-process method with materials such as HPMC can produce superior excipient for direct compression tablets, and formula optimisation using Design Expert has proven effective.[13] However, the combination of partially pre-gelatinised JFSS with HPMC K15 has not been studied using the approach. Therefore, this study aims to develop halal and environmentally friendly excipient alternatives based on partially PPJFSS and HPMC K15 with optimal flow and compressibility properties.

Materials and Methods

Materials

The materials used in this study included jackfruit seed flour produced from Bantul Regency (7°44′04″–08° 00′ 27″ N, 110°12′34″–110°31′08″ E), DI Yogyakarta, Indonesia, which has been registered with the Indonesian health department (P-IRT No. 2063402010662-26), and on the production date of March 1, 2024. HPMC K15 was obtained from PT. Dipa Prasada Husada, Tasikmalaya, Indonesia, while Aquadest was obtained from Bratachem, Surabaya, Indonesia. All materials were of analytical grade. The instruments used include a single punch tablet press, FTIR (Agilent Technologies Cary 630 FTIR, Santa Carla, USA), SEM (FEI Inspect S50, Hillsboro, USA), XRD (X'Pert PRO PANalytical, Netherlands), Binocular Microscope (Yazumi Microscope XSZ-107BN, China), hardness tester (TBH 125 Erweka, Germany), moisture analyzer (Mettler Toledo, Germany), analytical balance (Shimadzu, Kyoto, Japan), oven (Memmert UF110, Germany). The Design Expert software version 13.0 was released in January 2021.

Methods

Jackfruit Seed Starch (JFSS) Extraction

JFSS was obtained by dispersing jackfruit seed flour in cold aquades, squeezing, and letting the liquid sit for 24 hours to precipitate the starch. The precipitate was dried in an oven (Memmert UF110, Germany) at 40°C for 24 hours, then ground and sieved with a 100 mesh.

Formula Optimization

Optimization was carried out using Design Expert 13.0 with SLD method to determine the best PPFJSS (X1) and HPMC K15 combination (X2). The measured responses included moisture content (Mettler Toledo, Germany), flow properties, angle of repose, compressibility, and compactibility (TBH 125 Erweka, Germany), with optimal results determined based on desirability values.

Validation and Verification

Validation was carried out by creating an optimal formula with three repetitions, while verification was performed by comparing the results of the excipient tests with the software predictions. The formula was declared valid when the results fell in the acceptance range.[14]

Co-process Excipient Manufacturing

PPJFSS was produced by heating JFSS in hot aquadest (42% w/w) at a temperature of 70°C for 60 minutes. HPMC K15 solution was mixed with JFSS suspension, homogenized, sieved (mesh 18), dried at a temperature of 40°C for 3 hours, and sieved using mesh 20.[7]

Characterization of Excipient

Organoleptic Test

Co-processed excipient was observed with human senses to determine smell, taste, texture, shape, and colour.[1]

Microscopic Test

A small sample was placed on a glass slide, glycerol was added, and observed under a binocular microscope (Yazumi Microscope XSZ-107BN, China) with a magnification of 40–1000 times to observe the shape and size of the particles.[15]

Moisture Content Test

A moisture analyzer (Mettler Toledo, Germany) was used at 105°C with a sample weight of 500 mg.

Flow and Angle of Repose Test

The flow property was measured using a granule flow tester, while the angle of repose was calculated (*equations 1 and 2*) based on the height and diameter of the fallen powder.[16]

$$\text{Powder flow rate} = \frac{\text{Wight (Grams)}}{\text{Time (Second)}} \quad (1)$$

$$\text{Tan } \alpha = \frac{2h}{d} \quad (2)$$

Where, h is the height of the granules, and d is the diameter of the granules.

Compactibility Test:

The sample was compressed at a pressure of 1 ton for 3 seconds, and then the tablet hardness was measured with a hardness tester (TBH 125 Erweka, Germany).

Compressibility Test:

The sample was placed into a 100 ml measuring glass to measure the volume before and after tapping using a tap density apparatus, and then the compressibility index was calculated (*equation 3*).

$$100\left(\frac{V_0 - V_F}{V_0}\right) \quad (3)$$

Where, V_0 is volume before compression and V_F = volume after compression.

Particle Size Distribution

The sample was sieved using a sieve shaker (Benchtop Octagon, London, UK) with tiered meshes (20, 40, 60, 80, and 100), then weighed, and the weight percentage of each fraction was calculated (*equation 4*).[16]

$$\%\ \text{powder weight} = \frac{b-a}{sample\ weigt}\ x\ 100\% \quad (4)$$

Where, a is the empty sieve weight and b is the weight of the sieve with powder

Fourier Transform Infrared (FTIR) Analysis

This test was conducted by taking several samples placed on a clean crystal plate. Each sample was analyzed at mid-IR frequencies (Agilent Technologies Cary 630 FTIR, Santa Clara, USA), specifically from 400 to 4000 cm^{-1}.[12]

Morphology

The analysis was conducted using SEM (*FEI Inspect S50*, Hillsboro, USA). The samples in dry condition were attached to carbon tape and sputter-coated with AuPd for 30 seconds under vacuum.[12]

X-ray diffraction (XRD) Analysis

XRD pattern was recorded using X-ray diffractometer (*X''Pert PRO PANalytical*, X'Pert PRO PANalytical, Netherlands). The scanning region of the diffraction angle (2) was from 5° to 90° at a step size count of 2 s.[12]

Statistical Analysis

Data modeling was carried out using the Design Expert software with four types of mathematical models, namely linear, quadratic, cubic, and special cubic. Model selection was based on criteria such as model significance, lack of fit significance, adjusted R-squared, and predicted R-squared obtained from Analysis of Variance (ANOVA) analysis. A model was considered appropriate when both the model p-value and lack of fit p-value were below the alpha level (5%), indicating a statistically significant influence on the response at the 5% significance level.[13]

Results and Discussion

Formula Optimization Results

The contour plot of moisture content (Figure 1) and equation results (Table 1) shows that coefficient A (PPJFSS) is more dominant in increasing the moisture content response than coefficient B (HPMC K15). Coefficient AB shows a negative value (-1.314), indicating that the interaction can reduce the moisture content response. Meanwhile, coefficient AB(A-B) shows a positive value, suggesting that doubling the addition of both components increases the moisture content response. Coefficient $AB(A-B)^2$ shows a negative value, meaning that tripling and adding both components reduces the moisture content

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response.[17] The mathematical equation of flow properties (Table 1) indicates that coefficient B (HPMC K15) has a stronger impact on enhancing flow property responses compared to coefficient A (PPJFSS).

Table 1: Equation results for each response

Response	Equation
Moisture content	$Y = +4.79A +4.09B -1.14AB +2.35AB(A-B) -4.08AB(A-B)^2$
Flow properties	$Y = +8.13A +12.73B$
Angle of repose	$Y = +30.93A +25.75B$
Compressibility	$Y = +8.11A +2.81B -4.22AB$
Compactibility	$Y = +3.28A +3.78B + 2.15AB -3.09AB(A-B)$

Table 2: Comparison of the prediction formula results with the experimental formula

Analysis	Predicted Mean	Predicted Median	Std. Dev	N	SE Pred	95% PI Low	Data Mean	95% PI High	*p-value*
Moisture content (%)	3.63	3.63	0.012	3	0.0141	3.593	3.67	3.683	0.001
Flow properties (g/s)	11.58	11.58	0.571	3	0.4099	10.584	11.68	12.590	0.000
Angle of repose (°)	27.04	27.04	0.593	3	0.4256	26.000	26.19	28.083	0.000
Compressibility (%)	3.34	3.34	0.511	3	0.3880	2.342	3.56	4.337	0.009
Compactibility (Kg)	4.30	4.30	0.100	3	0.1012	4.063	4.163	4.625	0.276

Table 3: Results of testing the characteristics of the optimal combination of co-processed excipient

Type of Testing	Requirements	Optimal Combination PPJFSS – HPMC K15 ($\bar{X}$ ±SD)
Moisture content (%)	2-5[4]	3.67 ±0.18
Flow properties (g/s)	>4[20]	11.68 ± 0.32
Angle of repose (°)	25-40[20]	26.19 ± 0.74
Compressibility (%)	≤20[20]	3.56 ± 0.57
Compactibility (Kg)	4-8[21,22]	4.26 ± 1.15

The contour plot (Figure 1) and mathematical equation of the angle of repose (Table 1) indicate that coefficient A (PPJFSS) has a greater influence on increasing the repose response angle than coefficient B (HPMC K15).[17] According to a previous study,[18] pre-gelatinized starch tends to show a good angle of repose value. The results of PPJFSS also indicated a decrease in the angle of repose, but in combination with HPMC K15, HPMC K15 was more dominant in reducing the angle of repose for the excipient. As shown by the contour plot (Figure 1) and equation results (Table 1), coefficient A (PPJFSS) has a more dominant effect in increasing the compressibility response than coefficient B (HPMC K15). Coefficient AB shows a negative value (-4.22), indicating that the interaction can reduce the compressibility response.[17]

The contour plot (Figure 1) and mathematical (Table 1) of compactibility show that coefficient B (HPMC K15) has a more dominant influence in improving the compatibility response than coefficient A (PPJFSS). The positive AB coefficient (+2.15) indicates that their interaction can enhance the compatibility response. Meanwhile, AB(A-B) coefficient shows a negative value, meaning that doubling the addition of both components decreases the compatibility response.[17] Compared to native starch, co-process excipient indicates an improvement in moisture content, compressibility, flow property, angle of repose, and compactibility.[18,19]

Optimum Formula Results

Figure 2 shows that the higher and closer the desirability value is to 1, the better the performance of the optimal formula to produce a response value close to the desired target. This optimal formula value was obtained by considering responses or evaluation results, including moisture content test, flow properties, angle of repose, compressibility, and compactibility. Each response has a specific target value as a reference to determine the optimal formula.[17] The optimal combination identified in this study consisted of 95.75% PPJFSS and 4.25% HPMC.

Validation and Verification

Based on the confirmation results in Table 2, the mean data of each response were recorded. A good mean data is indicated when the value is above the 95% PI low and below the 95% PI high. Meanwhile, the prediction interval is the range of values that describes the estimate of the following measurement result under the same conditions.[17] The comparison results between predictions and experiments after statistical analysis show no significant difference in the compactibility response, indicated by a p-value >0.05. However, there are significant differences in the flow rate, angle of repose, and compressibility responses, evidenced by a p-value <0.05.

Characteristic Test Results

Organoleptic

The organoleptic test results of the co-processed excipient of the optimum formula (Figure 3), replicated three times, showed the same characteristics, namely brown, with a distinctive smell, a bland taste,

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and in the form of granule particles. Due to the dominant presence of starch, the same colour, smell, and taste were present. However, the shape of the excipient produced changed from the original material, taking the form of granule particles.

Microscopic

The results show changes in shape, specifically in JFSS subjected to partial pregelatinization, where the starch structure has broken into irregular shapes. Meanwhile, after the wet granulation process, HPMC

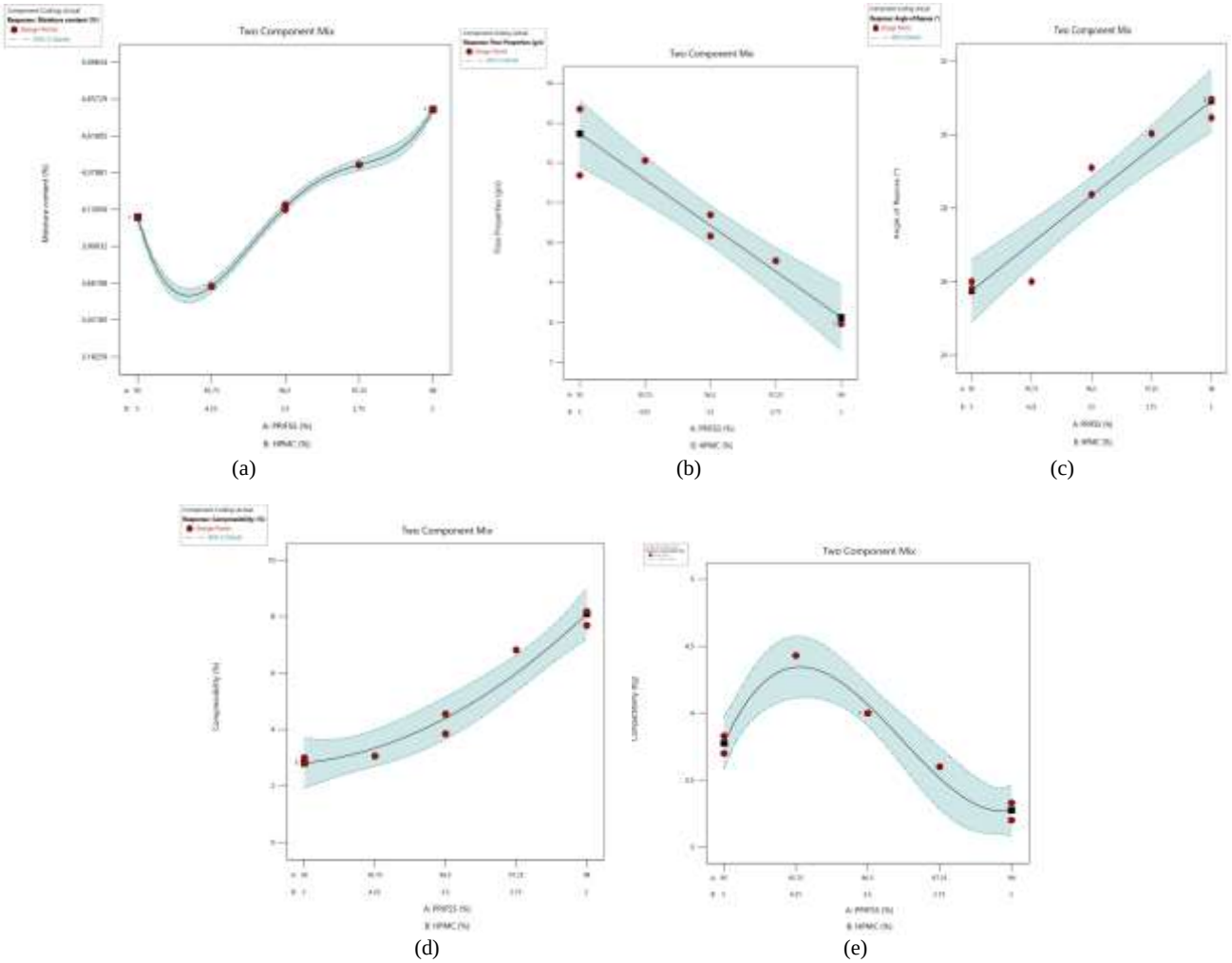

Figure 1: Contour plot graph, moisture content (a), flowability (b), angle of repose (c), compressibility (d), compactibility (e) of the optimum combination of co-processed excipient

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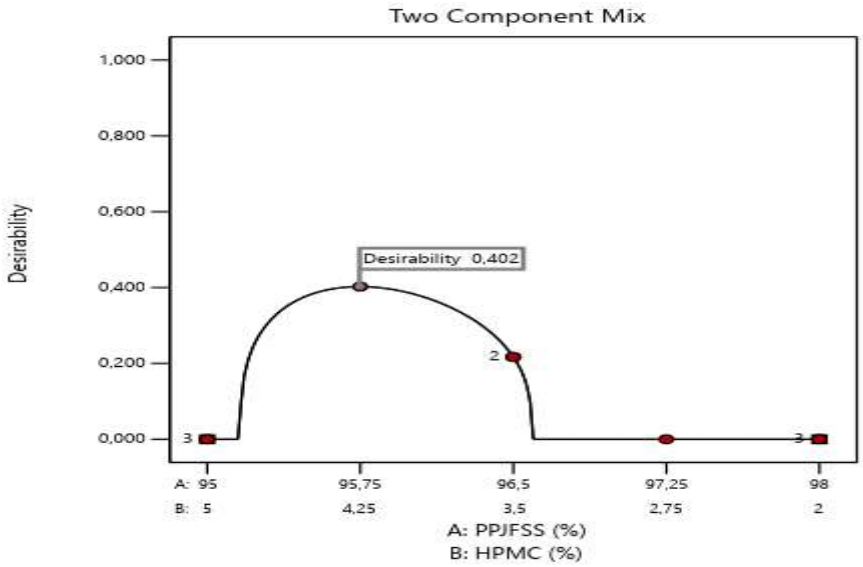

Figure 2: Desirability value of HPMC K15 and PPJFSS formula optimization

(a) (b)

Figure 3: Results of (a) organoleptic and (b) microscopic test of the optimum combination of co-processed excipient

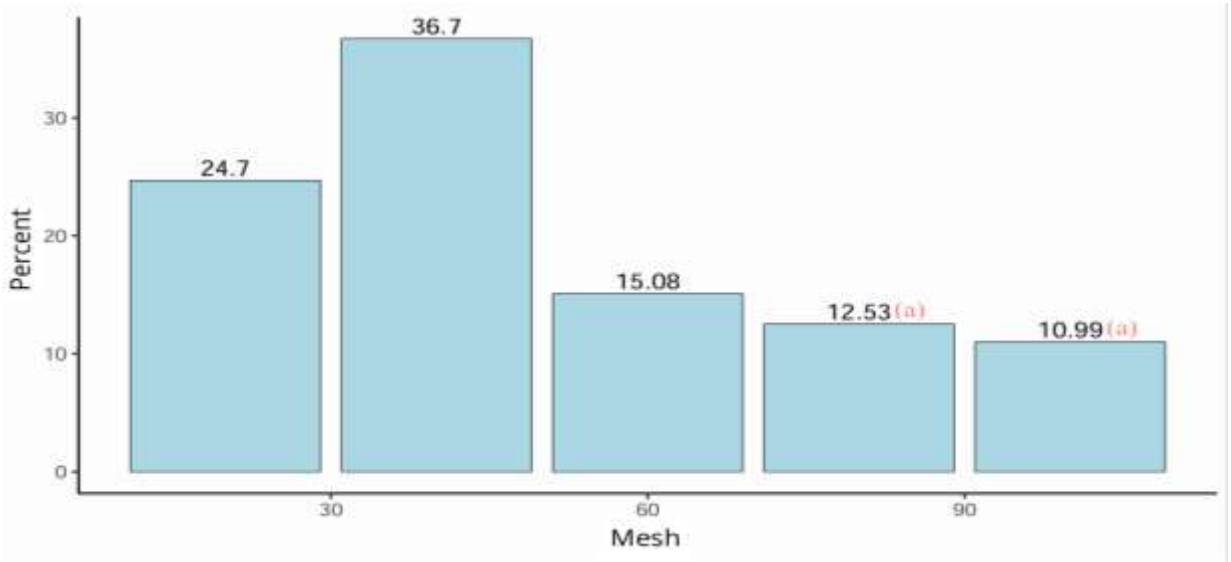

Figure 4: Particle size distribution results of co-processed excipient, symbol (a) indicates %fines

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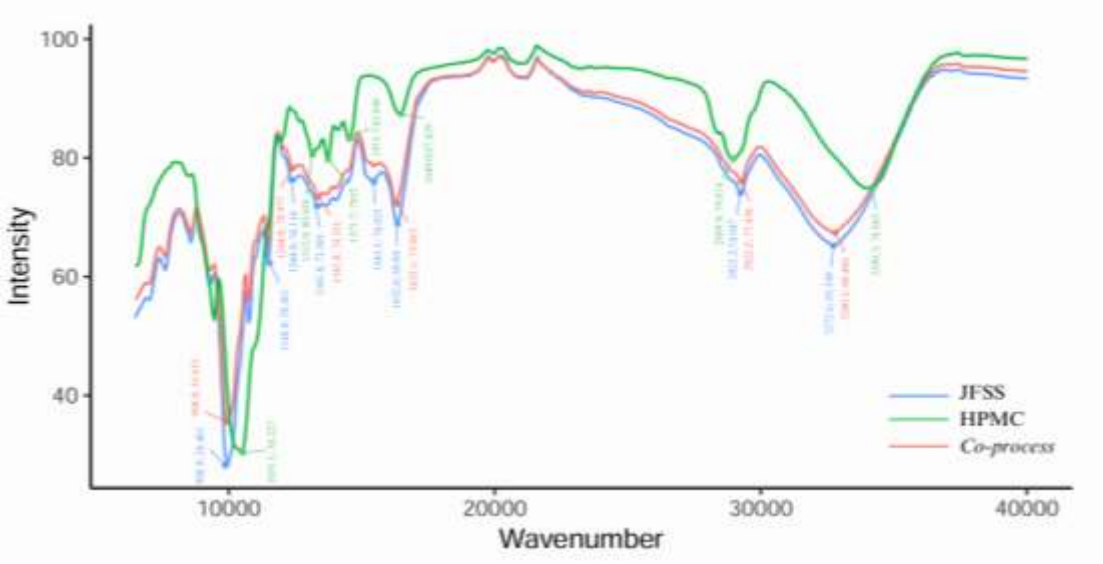
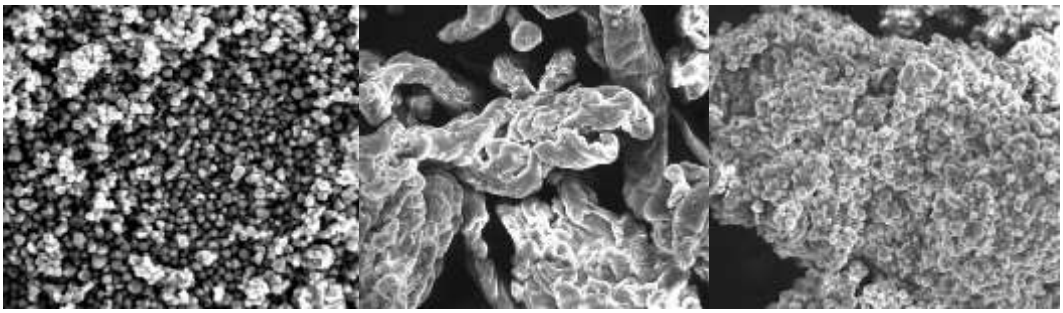


Figure 5: FTIR Analysis of co-processed excipient, JFSS, and HPMC K15



(a) (b) (c)

Figure 6: SEM results of JFSS (a), HPMC K15 (b), an optimal co-processed excipient combination of PPJFSS – HPMC K15 (c) at a scale of 100 µm

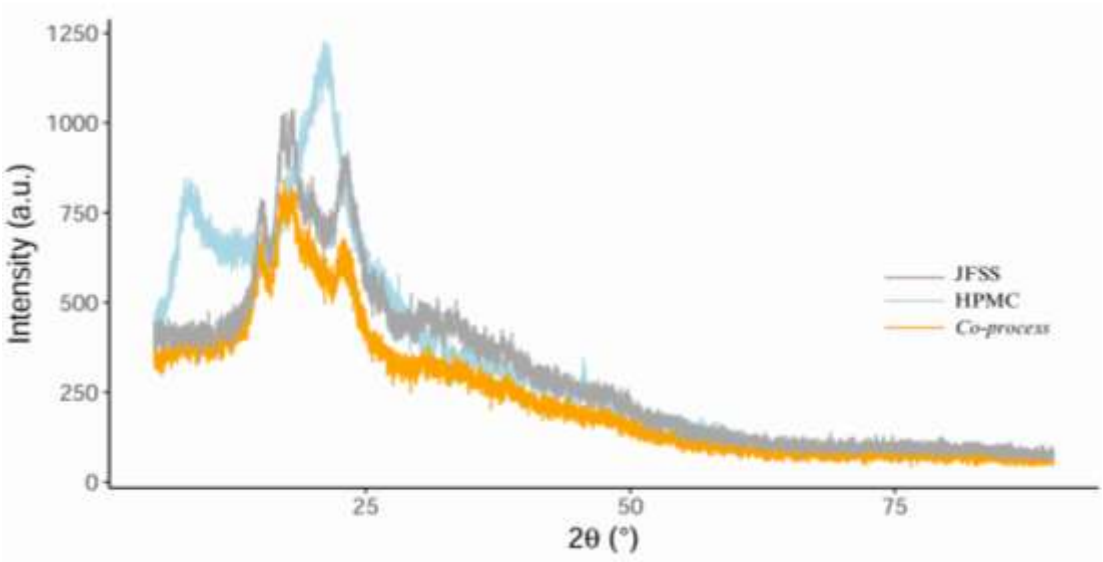


Figure 7: XRD Analysis of co-processed excipient, JFSS, and HPMC K15

K15 binds the starch together, forming pregelatinised granules (Figure 3).[23]

Moisture Content

The moisture content test was conducted on the three replications of the optimum formula, which met the required range between 2% and 5%, as shown in Table 3. The co-processed excipient results show

good outcomes where the low moisture content can facilitate the flow of granules. The friction between particles increases with the rising moisture content. This stronger friction reduces the mobility of the granules, resulting in a longer flow time. According to reports, extremely dry granules cause the tablets to become brittle.[24]

Flow Properties and Angle of Repose

Flow properties and angle of repose tests of the co-processed excipient are shown in Table 3. The test results of the co-processed excipient PPJFSS–HPMC K15 show an improvement in flow properties and angle of repose compared to the material before co-processing. The flow properties and angle of repose can be classified in the very good category because there is an increase in particle size from the base material and a change in particle shape to round granules. The increase in HPMC shows a significant (p<0.05) rise in flow rate due to the larger particle size.[12] The larger the size of the granules, the lower the cohesive force, hence, the granules tend to flow and not clump together.[25] The angle of repose test also illustrates the flowability of an excipient, where a smaller angle indicates a higher flowability. This study observed a significant difference (p<0.05) in the static angle values with the

combination of HPMC and PPJFSS (Table 2).[12] Aside from flow properties, the angle of repose test results are also influenced by various factors, including granule shape and size, moisture content, inter-granular friction, cohesiveness, bulk density, and the arrangement of particles.[26,27,30] This indicates that the co-processed excipient has stronger cohesive properties than the original material, as reflected by a lower angle of repose and an improved flow rate.[12]

Compactibility

Table 3 shows that the optimum formula has a compactibility value of 4.26 kg, which falls in the normal range of 4-8 kg. As shown in Table 1, the co-processing results between formulas indicate a rise in HPMC concentration, suggesting an increase in binding power, but the difference was not significant (p>0.05).[12,30] In this study, the incorporation of HPMC K15 aided plastic deformation, where particles change shape and become rigid following the compaction process. Tablet hardness can be influenced by the mechanical properties of the binder. In general, binders with high deformability (plastic) tend to improve tablet strength better due to the ability to fill voids between particles and create more bonding points. Pre-gelatinized starch also has good tablet ability properties due to the higher level of plastic deformation during compression, indicating good binding properties. The mechanical properties of the binder influence the hardness of the tablet, the distribution of the binder, and the compaction pressure.[18,31]

Compressibility

According to U.S. Pharmacopeia, the result falls into the perfect classification in the range of ≤10% (Table 3). This study had significant (p<0.05) differences between formulas regarding compressibility values, indicating that an increase in HPMC concentration causes a decrease in compressibility. The degree of compressibility is influenced by the size and shape of the granules, the angle of repose, as well as density. The smaller the bulk density obtained, the better the flow properties.[28] With larger particle sizes, the frictional and attractive forces between particles are smaller, resulting in denser granules that experience smaller volume changes during compaction.[19]

Particle Size Distribution

The results from the optimal combination of co-processed excipient (Figure 4) show particle sizes <850 µm, with most granules stopping at mesh 40. However, many are also retained on mesh 80 and 100 as fine powder. Good granules have an acceptable powder percentage of less than 15%, and the flow properties of the granules are reduced above this value.[29] The results indicate that a fine powder value of 23.52% suggests a suboptimal granule distribution. The high content can be caused by an overly aggressive granulation process, leading to the granules breaking into smaller particles or inadequate inter-particle bonding.

Fourier Transform Infrared (FTIR) Analysis

Figure 5 shows FTIR test result of the optimum co-processed excipient combination, with several absorptions. The spectrum produced from the combination of PPJFSS and HPMC K15 shows no change in functional groups or chemical alteration. The presence of–OH group is indicated at a wavenumber of 3280.1 cm^{-1}, and C-H alkane group is indicated at a wavenumber of 2922.2 cm^{-1}. The ether group corresponds to wavenumbers of 1148, 1244.9, and 1341.8 cm^{-1}, while a wavenumber of 1625.1 indicates the presence of hydrogen bonding.

Morphology

SEM analysis results show that JFSS is semi-spherical due to the presence of indentations, densely overlapping with a size of 1-9 µm. Figure 6 shows SEM analysis of the optimal co-processed combination of PPJFSS and HPMC K15. Based on the results, the excipient are in the form of irregular granules and nearly spherical with a size of 100 µm, larger than the unmodified JFSS. Furthermore, the shape of the modified starch and the unmodified JFSS was also observed. HPMC K15 appears to bind the starch together, filling the gaps between the granules.[23]

X-ray diffraction (XRD) Analysis

XRD results (Figure 7) show that the optimum co-process formula produced has peaks at 15.1108°, 17.0222°, 18.1069°, and 22.8913°. The excipient demonstrates clear crystalline structures, marked by several peaks but with moderate intensity. These results show that the starch has partially gelatinized, and only some crystalline amylopectin structures have been broken down. High crystallinity indicates that the mass will be easy to compress and improve tablet compactibility. Meanwhile, in the dissolution rate, the solubility rate decreases as the crystallinity of the material increases.[18]

Conclusion

In conclusion, the optimum composition of PPJFSS was 95.75%, with HPMC K15 at 4.25%, resulting in a desirability value of 0.402. The optimum co-process formula PPJFSS – HPMC K15 predicted by SLD for responses such as moisture content, flow properties, angle of repose, and compressibility showed significant differences. In contrast, the compactibility response did not show significant differences. All responses were in the range of high PI and low PI requirements. The particle size characteristics in the optimum formula produced granules still had high fine powder. The resulting spectrum showed the presence of OH, C-H, and ether groups. The particle morphology produced by HPMC K15 appeared to bind the modified starch to each other, and the crystal properties indicated an amorphous nature. This excipient combination demonstrates favorable properties, fulfills the necessary criteria, and is suitable for direct compression tablet formulations.

Conflict of Interest

The author`s declare no conflict of interest

Authors Declaration

The authors declare that the work presented in this article is original and any liability for claims relating to the content will be borne accordingly.

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