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Reworking Potential of Polyvinylpyrrolidone K-25 as a Binder in The Production of Paracetamol Tablets

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Abstract

Binding agents play an important role in maintaining the bond between active and additional ingredients in tablets, especially when subjected to repeated compression. One commonly used binder is polyvinylpyrrolidone (PVP) K-25. However, issues often arise regarding the binder's potential when undergoing multiple compressions. This research, hence, aims to determine the reworking potential of PVP K-25 with different concentration levels as a binder, focusing on the physical properties of the mixtures and the resulting paracetamol tablets. The study follows a pure experimental design with a two-way completely randomized research design. Tablets were compressed and subsequently crashed again twice. Various tests, including flow properties and compressibility for the mixtures, as well as compatibility, hardness, friability, and disintegration time for the tablets, were conducted to assess their physical properties. The obtained data were subjected to statistical analysis, starting with the Shapiro-Wilk normality test, followed by Kruskal-Wallis and Post-Hoc Mann-Whitney tests. The research findings indicate that PVP K-25 can maintain its potential as a binder, as evidenced by the physical properties of both the mixtures and the resulting paracetamol tablets.

Keywords: Reworking potential; tablets; wet granulation; PVP K-25; paracetamol

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INTRODUCTION

Tablets have undergone significant advancements in formulation and offer several advantages. One of the key benefits is their practicality compared to other pharmaceutical forms such as suppositories or injections. Tablets are solid preparations containing a single dose of one or more active ingredients. They consist not only of active ingredients but also of additional components that help maintain the effectiveness of these ingredients during production and use. Common ingredients added to tablet formulations include diluents, disintegrants, binders, lubricants, and glidants.[1] Paracetamol is an analgesic and antipyretic.[2] However, paracetamol has poor flow and compressibility properties, which necessitate forming it into granules using the granulation method.[3] Due to paracetamol's resistance to heat and humidity, wet granulation is the most suitable method.

Wet granulation involves processing a mixture of active substances and excipients into larger particles by adding a binding fluid, forming a moist and easily granulated mass.[4] A binder compatible with the active substance's physical properties and other excipients must ensure the resulting tablet is compact. Polyvinylpyrrolidone (PVP) K-25 is commonly used as a binder in tablets produced using the wet granulation method. PVP K-25 can also enhance the dissolution of substances that are otherwise difficult to separate from the tablet dosage form. In general, PVP K-25 is added at 0.5–5% w/w in tablet formulations.[5]

In the pharmaceutical industry, the tablet compression process is sometimes repeated due to various factors, such as the failure of the tablet to meet predetermined requirements. To avoid material losses, industries often re-compress the tablets, especially for high-value materials. During the re-compression process, particularly in the wet granulation method, the binder plays a crucial role in reuniting the crushed tablets into granules and compressing them back into intact tablets. The binder helps bind granule particles together, preventing the tablets from cracking or breaking easily.[6] This process of crushing and re-compression is known as "reworking potential."

Although reworking potential can be beneficial, it may alter the mixture and physical properties of the tablet. Research[7] found that reworking potential significantly affects the mixture (flow rate, compressibility, and compatibility) and the physical properties of paracetamol tablets (tablet hardness, friability, and disintegration time)7. On the other hand, Gamlen's research[8] suggests that reworking potential does not affect tablet hardness.

Therefore, further research is needed on the impact of binders after repeated compression. The purpose of this study is to determine the reworking potential of PVP K-25 at different concentration levels as a binder, with a focus on the physical properties of the mixture (flow properties and compressibility) and the physical properties of paracetamol tablets (compatibility, hardness, friability, and disintegration time). The mixture in this context refers to a blend of lubricated granules.

METHODS

Materials

Paracetamol pharmaceutical grade (Anqiu Lu'an Pharmaceutical Batch No. 2150096), paracetamol standard USP grade, PVP K-25 pharmaceutical grade (Kollidon® 25 Lot No. 01082147G0), croscarmellose sodium pharmaceutical grade (Primellose® Batch No. 108NS4T), talc pharmaceutical grade (Pingdu Talc Mine Co., LTD Shandong Batch No. YF1-022-201 24 MT), magnesium stearate pharmaceutical grade (Eur Phar Batch No. MGSV1230092), and lactose monohydrate pharmaceutical grade (Brataco Batch No. J 017/23 (23208277)) were used.

Granulation and Mixing Process of Materials

Paracetamol, lactose monohydrate, PVP K-25, and one-third of croscarmellose sodium were weighed according to the

weights determined in Table 1. Subsequently, the three ingredients were mixed using a cube mixer for 15 minutes at a speed of 135 rpm. PVP K-25, which had been previously weighed, was dissolved in distilled water. The ingredients were gradually added to PVP K-25 until a well-formed wet mass was achieved. The wet granules were sieved using a mesh number 12 sieve and then dried at 50°C.

Table 1. Paracetamol Tablet Formula

Material	Formula 1	Formula 2
Paracetamol	300 mg	300 mg
Polyvinylpyrrolidone (PVP) K-25	12 mg	24 mg
Croscarmellose sodium	20 mg	20 mg
Talc	27 mg	27 mg
Mg stearate	3 mg	3 mg
Lactose monohydrate	238 mg	226 mg

Moisture Content Test

A 25-gram amount of granules was placed in a petri dish and then dried in an oven at 60°C. Weighing was carried out daily until a constant weight was obtained. The moisture content of the granules that met the requirements was no more than 3-5%. To calculate moisture content, the following formula 1 was used:

$$\text{MC}\ (\%) = \frac{(\text{Wet Weight} - \text{Dry Weight})}{\text{Dry Weight}} X100\% \quad (1)$$

Lubrication Stage

The dry granules were placed into the cube mixer. Croscarmellose sodium and talc were added to the cube mixer containing the dry granules. The cube mixer was operated for 5 minutes. Subsequently, magnesium stearate was added to the cube mixer and mixed for 5 minutes.

Flow Time Test

The granule flow time test was used to determine the flow properties of granules, which in turn influenced the tableting process. Good granule flow properties will result in a good variety of tablet weights. One hundred grams of granule mixture was placed into the funnel on the flowability tester. Subsequently, the mixture was allowed to flow through the test funnel, and the time it took to pass through the test funnel was recorded as the mixture flow time[9]. The 100-gram good mixture flow time is no more than 10 seconds.

Index Compressibility Test

A total of 40 grams of mixed granules was placed into a 100 mL measuring cup. It was then installed in a volumenometer and tapped 500 times with a test tool until the mixture volume became constant. Changes in the volume of the mixture before and after the tapping process were recorded. The tablet compressibility index value can be calculated using formula 2[10]:

$$Compressibility\ index = 100 \times (\frac{V_o - V_f}{V_o}) \quad (2)$$

Vo = Mixed granules volume before testing (mL)

Vf = Mixed granules volume after testing (mL)

Compatibility Test

The granule mixture was fed into the single-punch tablet machine hopper. The pressure on the machine was regulated by decreasing the lower punch scale by 10 mm, and the upper punch was set in various ways, namely 4 mm, 5 mm, 6 mm, 7 mm, and 8 mm. Compatibility parameters can be observed from tablet hardness.[11]

Tablet Compression Test

The granule mixture was pressed using a single-punch tablet printing machine to form tablets weighing 600 mg per tablet. The mixture was pressed using an upper punch scale of 9 mm and a lower punch scale of 12 mm.

Tablet Organoleptic Test

A physical examination was conducted on the manufactured paracetamol tablets. This inspection includes color, shape, and smell, as well as ensuring that the physical form of the tablet is intact.

Tablet Weigh Uniformity Test

The weight variability test was conducted by weighing up to 10 paracetamol tablets of each formula, one tablet at a time. Then, the average weight value and the values X_1, X_2, ..., X_{10} were used to predict the content of the tested tablet unit. The value can be used in determining the M value, which is a reference value based on the average value of $\overline{X}$. Weight diversity testing can be considered qualified if the acceptability value of the first 10 tablets is not less than or equal to L_1%. If the acceptability value is greater than L_1%, it is necessary to redo the weight diversity test on 20 additional tablets. The following formula 3 can be used to calculate the acceptability value of weight diversity:[10]

$$NP = \left|M - \overline{X}\right| + ks \qquad (3)$$

NP = Acceptance value
M = Reference value
$\overline{x}$ = Average estimated tablet content
k = Acceptance constant (if n=10, then k=2,4; if n=30, then k=2,0)
s = Standard deviation

Tablet Hardness Test

A total of 5 tablets were placed on a digital hardness tester. The tablet's hardness value appeared on the tool, and the results were recorded.[12]

Tablet Friability Test

Tablets were cleaned with fine particles, weighed, and placed in a friability tester. The tool was set for 100 revolutions at a speed of 25 rpm. After testing, the tablets were cleaned again of fine particles, and the paracetamol tablets were weighed. The weight before and after testing was used to calculate the percentage of fragility with the formula 4:[13]

$$\%\ friability = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100\% \qquad (4)$$

Tablet Disintegration Time Test

One dosage unit tablet was placed in each of the six tubes of the basket. The tool was then immersed in a water-filled tube at a temperature of 37°C±2°C. The tube was raised and lowered in the water, and the

time required for the tablet to disintegrate was recorded as the tablet disintegration time.[10]

Data Analysis

The data obtained would be statistically analyzed with a normality test using the Shapiro-Wilk Test. The normality test results indicated that the data were not normally distributed. Subsequently, the data were analyzed using the Kruskal-Wallis and Post Hoc Mann-Whitney tests. A data value of $p<0.05$ indicates a significant difference between the two groups, while a value of $p>0.05$ suggests no significant difference.[14]

RESULTS AND DISCUSSION

Testing the Physical Properties of Mixtures

Testing of the physical properties of the mixture in this study aims to determine the flow properties of the mixtures, including flow time tests and compressibility index tests. Before checking the physical properties of the mixtures, a moisture content test was conducted using the gravimetric method, revealing that the granule moisture content in formulas 1 and 2 was 3.319% and 4.679%, respectively. This result aligns with the requirements, falling within a 3-5% range. The difference in moisture content is influenced by distilled water as a solvent for PVP K-25. Distilled water was chosen as the solvent for PVP K-25 to granulate powder, which is difficult to dissolve.[15]

Testing Flow Time of Mixtures

Table 2. Mixed Flow Properties

Flow Properties	Mixtures					
	Formula 1			Formula 2		
	M1	M2	M3	M1	M2	M3
Flow time (seconds)	1.8±0.1	3.8±0.7	2.1±0.1	2.1±0.0	2.7±0.1	1.6±0.1
Compressibility (%)	4.8±0.1	8.9±1.0	8.9±1.0	6.8±1.4	7.8±0.9	7.9±0.9

Notes:

- Data were collected in $\overline{X} \pm SD$
- Formula 1 : formula with the concentration 2% w/w binder
- Formula 2 : formula with the concentration 4% w/w binder
- M1 : initial mixture
- M2 : the mixture of crushed tablets from the first compression
- M3 : the mixture of crushed tablets from the first re-compression

Flow time measures the time required for granules to flow and is directly associated with their flow properties. Good flow properties in a granule mixture produce tablets with consistent weights. A granule is considered to have a favorable flow time if it flows for no more than 10 seconds for a granule mass of 100 grams[9]. According to the research results presented in Table 2, it was observed that the flow time of the mixture in formulas 1 and 2 met the specified requirements, indicating good flow properties. The data were then subjected to statistical testing using the

Kruskal-Wallis test, and a p-value<0.05 was obtained, signifying a significant difference between compressions and formulas. Based on Table 2, the flow time for the second compression in formulas 1 and 2 was higher than that of the first. Despite the regulation of particle size distribution, the granules from the second compression in formulas 1 and 2 exhibited a smaller size and are in powder form compared to the first and third compressions. Additionally, larger granule sizes can increase specific gravity, resulting in a longer flow time.[9]

Binder concentration also influences the flow properties of the mixture, as evident in the PVP K-25 concentration of 2% w/w in compressions 2 and 3, which exhibited a longer flow time compared to the PVP K-25 concentration of 4% w/w in compressions 2 and 3. This outcome aligns with research conducted by Puspita et al[16], indicating that higher concentrations of added binder lead to improved granule flow properties. In formula 2, the mixture's flow time during the second compression was longer than in the first due to the elevated moisture content, resulting in higher granule cohesiveness[17].

Testing Compressibility Index of Mixtures

A compressibility test can be conducted to determine the granule preparation's compressibility, allowing the assessment of its suitability for compression into tablet preparations.[18] The compressibility index indicates the mixture's flow properties, reflecting the granules' tendency to compress and the particle interactions. A mixture is considered to have good flow properties if the compressibility index value is no more than 15%.[19] This study obtained favorable compressibility index values for formulas 1 and 2, as evident in Table 3. Subsequently, the data were subjected to the Kruskal-Wallis test, revealing a p-value of <0.05, indicating group differences.

In Table 3, repeated compressions led to an increase in the percentage of compressibility index results. This occurrence may be attributed to the more non-uniform size of the mixture in compressions 2 and 3, containing a higher number of fines than the initial mixture in both formulas 1 and 2. The presence of both large and small mixture sizes causes the granules to fill empty spaces, increasing the compressibility index. This is particularly noticeable as granules from compressions 2 and 3 were obtained by manually crushing with a mortar and pestle. Excessive crushing force can yield smaller particles.[20] Additionally, an increase in the concentration of PVP K-25 caused a decrease in the compressibility index, indicating better flow properties. However, in the initial granules, the addition of concentration increased the compressibility index due to higher wetting, leading to reduced compression levels due to the high cohesiveness of the granules.[21]

Testing Compatibility of Mixtures

Table 3. Compatibility Test Results

Upper punch scale	Hardness (Kg)					
	Formula 1			Formula 2		
	1	2	3	1	2	3
4	*	*	*	*	*	*
5	0.08±0.01	0.4±0.04	0.8±0.1	0.01±0.0	0.55±0.1	1.1±0.03
6	0.4±0.1	3.2±0.5	4.6±0.7	0.1±0.0	4.2±0.6	5.9±1.4
7	1.5±0.6	6.8±2.2	7.8±0.4	0.7±0.2	11.3±1.2	12.0±1.2
8	2.0±0.2	#	#	3.92±0.2	#	#

Notes:

* : Granules cannot be tableted yet.

\# : Granules cannot be tableted because the machine could not run normally.

- Data were collected in $\overline{X} \pm SD$
- Formula 1 : formula with the concentration 2% w/w binder
- Formula 2 : formula with the concentration 4% w/w binder
- K1 : tablet for the first compression
- K2 : tablet for the second compression/first recompression
- K3 : tablet for the third compression/second recompression

Compatibility testing was conducted to assess the ability of a mixture to bind together and form a compact mass. This test was performed by placing granule mass into a single-punch tablet pressing machine, with the measured parameter being the tablet hardness.[11] The depth of the upper punch was adjusted and could be observed from the resulting tablet hardness values. The compatibility test results for tablets in formulas 1 and 2 can be seen in Table 3. Subsequently, this data was statistically analyzed using the Kruskal-Wallis test, yielding a p-value of <0.05 for all punch scale reductions, indicating significant differences.

In Table 3, it can be observed that with repeated compression, the compatibility of the mixture improved. This aligns with research conducted by Wunsch et al.[22], suggesting that compatibility increases with a decrease in particle size. In compressions 2 and 3, the number of fines produced also increased. Fines filled the empty spaces between granules, resulting in more compact tablets and increased hardness. Therefore, tablet hardness increased. As the concentration of PVP K-25 added increased, tablets with higher hardness were produced because the mixture became more compact and denser. Additionally, with the same punch scale reduction but a significant difference in PVP concentration, the resulting compatibility also increased.[23]

Testing the Physical Properties of Tablets

Table 4. Tablet Physical Properties Test Results

Tablet Physical Properties ($\bar{X}$±SD)	Tablet					
	Formula 1			Formula 2		
	K1	K2	K3	K1	K2	K3
Average weight (g)	0.618±0.0	0.866±0.0	1.032±0.1	0.628±0.0	0.865±0.0	0.953±0.0
Hardness (kP)	4.3±0.1	5.5±0.1	6.4±0.03	4.7±0.1	8.5±0.3	11.2±0.5
Friability (%)	0.3±0.1	0.4±0.04	1.0±1.0	0.5±0.4	1.4±0.5	1.8±0.3
Disintegration Time (minutes)	0.63±0.1	0.64±0.01	0.66±0.1	2.0±0.2	2.0±0.03	2.4±0.4

Notes:
- Data were collected in $\bar{X}$ ±SD
- Formula 1 : formula with the concentration 2% w/w binder
- Formula 2 : formula with the concentration 4% w/w binder
- K1 : tablet for the first compression
- K2 : tablet for the second compression/first recompression
- K3 : tablet for the third compression/second recompression

The potential of polyvinylpyrrolidone (PVP) K-25 as a binding agent after repeated compression can be observed through its physical properties: hardness, friability, and disintegration time. The results of the examination of the tablet's physical properties can be seen in Table 4. In this study, the compression pressure was maintained with an upper punch scale reduction of 9 mm and a lower punch scale of 12 mm, which can produce tablets with the required hardness. This punch scale reduction was selected based on the results obtained from the first compression of formula 1, considering the desired tablet weight of 600 mg. However, under certain conditions, such as when the mixture is too complex, slight changes in the upper punch scale reduction may occur. However, the difference is insignificant, and the lower punch scale remains.

Testing the Organoleptic of Tablets

Organoleptic testing of the tablets was conducted to determine the shape, odor, and color of the produced tablets. The tablets produced in formula 1 and formula 2, compressions 1, 2, and 3, were round, odorless, and white in color. However, in formula 1, compression 2, and compression 3, some tablets experienced capping. The term "capping" refers to separating some or the entire part of the tablet from its main body. In this study, capping occurred because the amount of binding agent added to formula 1 was less compared to formula 2.[24]

Testing Weigh Uniformity of Tablets

Weight uniformity testing aims to determine whether the produced tablets meet the desired specifications. The weight variation of tablets will affect the uniformity of the content or the active substance. Tablets with uniform weight also contain a uniform amount of active substances. A mixture with good flow

properties will result in uniform weight because it easily flows into the compression space.[25]

All tested tablets exhibited good weight uniformity. However, the weight produced in each compression increased. This could occur because granules require longer flow time than the initial granules. Additionally, differences in particle size and fines also had an impact. Fines filled the empty spaces when the granules were compressed, resulting in a larger tablet weight. According to the Indonesian Pharmacopoeia VI Edition (2020), the parameter for the acceptance of weight variation can be calculated through the acceptance value (NP). The calculation results for the acceptance value (NP) in the tested tablets can be seen in Table 5. Based on this data, all tablets in formulas 1 and 2 for each compression, as shown in Table 5, met the requirements of L1, which was not more than 15.0. The variation in NP values was caused by uneven mixing during repeated compression, increased flow time leading to less favorable flow properties, and the loss of powder during sieving.

Table 5. Tablet Acceptance Value Calculation Results Tablet (NP, %)

Formula	K1	K2	K3
1	7.862	4.567	2.714
2	5.022	2.247	12.870

Notes:
- Formula 1 : formula with the concentration 2% w/w binder
- Formula 2 : formula with the concentration 4% w/w binder
- K1 : tablet for the first compression
- K2 : tablet for the second compression/first recompression
- K3 : tablet for the third compression/second recompression

Testing Hardness of Tablets

Hardness testing on tablets aims to determine the tablet's strength against mechanical pressure during manufacturing, distribution, packaging, and storage.[9] A good tablet should have adequate hardness to withstand shocks, but should not be excessively hard, making it difficult to chew (if intended for chewing) or break by consumers.[14] The optimal tablet hardness ranges from 4-7kP.[26]

The hardness testing results for formulas 1 and 2 in each compression can be seen in Table 4. Based on these results, both formulas in each compression still met the specified requirements, except for formula 2 in compressions 2 and 3, which exceeded 8 kg. If the disintegration time meets the criteria, tablet hardness exceeding the requirements may still be acceptable. Observing Table 4, the tablet disintegration time for formulas 1 and 2 in each compression still met the requirements.

Table 4 shows that tablet hardness increased with repeated compression. This outcome occurred because the compatibility of the granule mixture

improved, and its profile became harder. Thus, with the same compression pressure, there was an increase in tablet hardness in the second and third compressions. Additionally, the formation of fines that filled the empty spaces between particles could make the tablet more compact, leading to increased hardness.[15] The addition of PVP K-25 binding agent concentration also caused an increase in tablet hardness. This is further supported by the Kruskal-Wallis statistical test, which yielded a p-value of <0.05, indicating a significant difference between compression groups and formulas.

Testing Friability of Tablets

Tablet friability aims to determine the edge or surface resistance of tablets against mechanical pressure and to assess the extent of erosion due to friction. The tested parameter is the percentage of tablet friability, which should not exceed 1%.[12] In the test results, formula 1 (first and second compression) and formula 2 (second and third compression) that met the specified requirements are shown in Table 4. Although these results do not align with the theory that tablet friability decreases as hardness increases, it is consistent with the study conducted[9], where adding an extra granular disintegrant can reduce the binding agent's effectiveness, leading to increased tablet friability.

The compressions 2 and 3 mixtures have more fines and an uneven size distribution. A higher number of fines can influence tablet friability. The more fines present, the higher the tablet fragility, especially if the fines are on the tablet's surface and lack binding agents. These fines are more likely to detach, increasing tablet.[27] The percentage of tablet friability in the first compression still met the requirements. Thus, polyvinylpyrrolidone (PVP) K-25 can function as a good binding agent, even though there is no difference between the first compression in formulas 1 and 2. This result is consistent with the Kruskal-Wallis statistical test with a p-value>0.05, indicating no significant difference between groups.

Testing Disintegration of Tablets

Tablet disintegration time is required for a tablet to break down before releasing its active content and being absorbed into the body. The optimal disintegration time for uncoated tablets is no more than 15 minutes.[9] The results of the disintegration time test for formulas 1 and 2 in each compression can be seen in Table 4. From these results, all tablets have met the disintegration time requirement, which is no more than 15 minutes. The produced tablets had a fast disintegration time due to the use of croscarmellose sodium, a super disintegrant. Croscarmellose sodium can absorb water and expand when in direct contact with water. Additionally, croscarmellose sodium employs a swelling mechanism and capillary action that weakens the particle bonds, leading to faster tablet disintegration.[28]

The disintegration time test results were then statistically analyzed using the Kruskal-Wallis test, and a p-value of <0.05 was obtained, indicating a significant difference. Although there was no significant difference between

compression groups, there was a significant difference between formulas. With the increase in added PVP K-25 concentration, the tablet disintegration time also increased. This result is consistent with the hardness test, where the tablet hardness in formula 2 was greater than in formula 1.

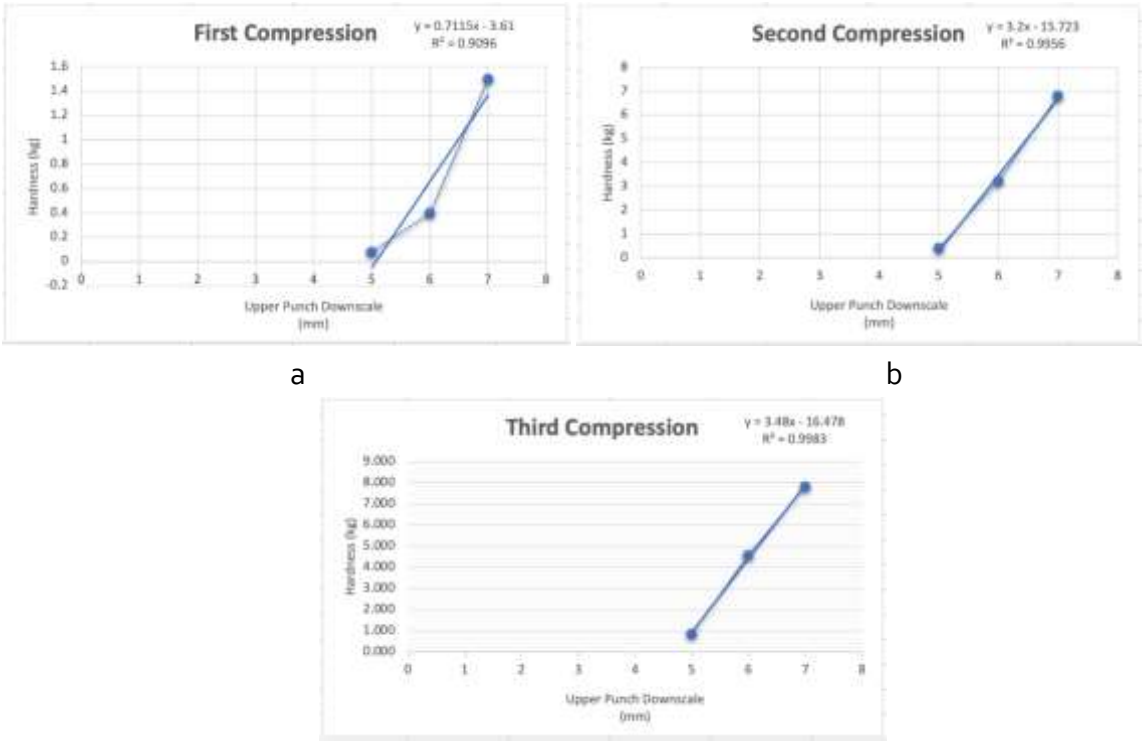
Reworking Potential

Table 7. AUC of Reworking Potential Results

Formula 1			Formula 2		
K1	**K2**	**K3**	**K1**	**K2**	**K3**
1.3	7.0	8.8	0.54	10.5	12.6
-	5.4	6.8	-	19.4	23.3

Notes:

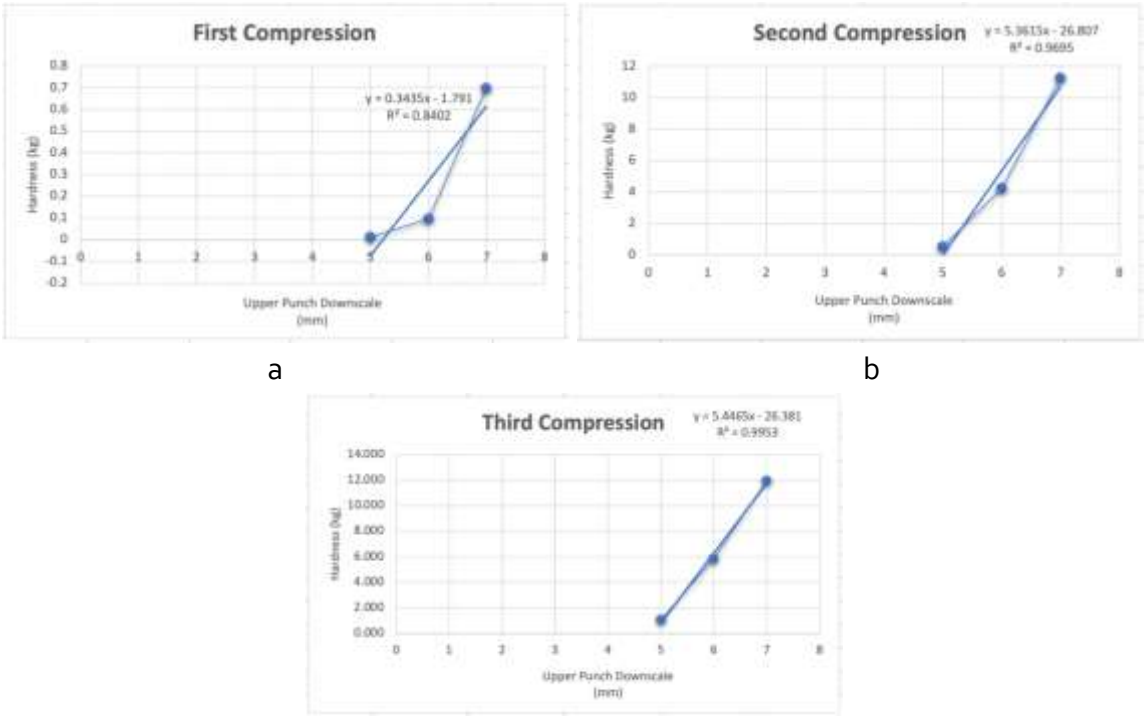
- Formula 1 : formula with the concentration 2% w/w binder
- Formula 2 : formula with the concentration 4% w/w binder
- K1 : tablet for the first compression
- K2 : tablet for the second compression/first recompression
- K3 : tablet for the third compression/second recompression



a b

c

Figure 1. Reworking Potential AUC Curve of Formula 1 Binding Material (a) First Compression; (b) Second Compression 2; (c) Third Compression



a b c

Figure 2. Reworking Potential AUC Curve of Formula 2 Binding Material (a) First Compression; (b) Second Compression 2; (c) Third Compression

Reworking potential can be demonstrated by the ratio of the area under the curve (AUC) of the tablet hardness from the subsequent compression to the first.[29] The AUC values and reworking potential for formulas 1 and 2 with two compressions can be seen in Table 7. Based on the research results, the area under the curve (AUC) for hardness and reworking potential increased with repeated compressions. This can be observed in Figures 1 and 2. Thus, polyvinylpyrrolidone (PVP) K-25 can maintain its role as a binder during repeated compressions, as indicated by the hardness parameter. The larger the AUC, the greater the hardness of the resulting tablet.

CONCLUSION

The reworking potential of PVP K-25 with different concentration levels can maintain its binding effectiveness, as observed from the physical properties of the mixture, which still meet the requirements. The AUC ratio between subsequent and initial compressions in the compressibility test increased, as did the physical properties of tablets, including hardness and disintegration time, which still met the requirements when subjected to repeated compression frequencies. However, with two repeated compressions, there was an increase in friability that caused the tablets to exceed the requirements.

For future research, reducing the initial compression pressure from the optimum compression pressure is recommended.

This ensures that each formula and each repeated compression has the same pressure. Additionally, maintaining the particle size distribution of granules is crucial, and this can be achieved by using sieves with a narrower mesh range.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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