

Optimization of Dispersible Diclofenac Potassium Tablet Formula with a Combination of Explotab and Avicel PH-101

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Abstract

Diclofenac potassium is a nonsteroidal anti-inflammatory drug (NSAID) frequently employed as an analgesic therapy for inflammatory conditions and pain associated with osteoarthritis and rheumatoid arthritis. It is formulated as a dispersible tablet, requiring dispersion in solution prior to administration to expedite onset and facilitate use, particularly for patients with difficulty swallowing intact tablets. This study aims to investigate the effects of the optimal combination and proportion of explotab and avicel pH-101 in the formulation of diclofenac potassium dispersible tablets using the Simplex Lattice Design (SLD) method with two factors. The tablet formulations, based on the SLD method with explotab (A) and avicel pH-101 (B) as excipients, are as follows: Formula I (100% A), Formula II (75% A:25% B), Formula III (50% A:50% B), Formula IV (25% A:75% B), and Formula V (100% B). The tablets were prepared via direct compression and subsequently evaluated for their physical properties, including hardness, friability, size uniformity, weight uniformity, disintegration time, dispersion time, wetting time, and content determination. The study's findings indicated that the combination of explotab and avicel pH-101 affected the physical properties of the tablets, notably decreasing weight uniformity, enhancing tablet hardness, reducing friability, and prolonging both disintegration and dispersion times of the diclofenac potassium dispersible tablets. The optimal formula was identified as comprising 40% explotab and 60% avicel pH-101. This optimal formulation was determined based on the highest total response value calculated using the SLD with two factors.

Keywords: Avicel pH-101, diclofenac potassium, dispersible tablets, explotab, Simplex Lattice Design.

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Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that is widely used to treat inflammatory conditions and degenerative rheumatic diseases. The potassium salt form of diclofenac shows greater solubility in water and is more easily absorbed than its sodium salt. As a result, diclofenac potassium is often indicated to achieve rapid and effective onset in the management of acute and chronic pain conditions. However, diclofenac potassium powder has a bitter taste, requiring further formulation development to produce patient-friendly and pleasant-to-drink tablets [1][2]. The development of preparations to overcome this is to make dispersible preparations.

Dispersible tablets are pharmaceutical formulations that are first dispersed in solution before being administered. This method is expected to accelerate the onset of action and increase drug efficacy. The mechanism underlying these benefits lies in the tablets that go through the process of disintegration and deaggregation in the body. Dispersible tablets have advantages in ease of manufacture and transportation, good physical and chemical stability, precise dosage and ease of administration so that they can be given to elderly patients and children who have difficulty swallowing. Dispersible tablets differ from conventional disintegrating tablets, where these tablets are dissolved in water before being given to patients. This indicates that dispersible tablets combine the ease of use as in liquid preparations with the advantages of stability possessed by conventional tablets [2][3].

In contrast, the drug is dissolved directly in the solution medium, allowing immediate absorption [4]. The development of dispersible tablets has emerged as a preferred method in the reformulation of diclofenac potassium

tablets due to their superior stability compared to liquid formulations. This advancement facilitates administration, especially for patients who have difficulty swallowing whole tablets. To obtain a sodium diclofenac dispersible tablet formula that meets the requirements, the formula optimization of the constituent materials was carried out by combining explotab as a disintegrant and avicel pH-101 as a binder using the mixture design method. One of the data models in mixture design is simplex lattice design, where the criteria used are model significance, lack of fit significance, adjusted r-square, and predicted r-square during ANOVA analysis.

Materials and Methods

Materials

The materials employed in this study include Diclofenac potassium (Dexa Medica, Indonesia), Avicel® PH-101 (microcrystalline cellulose, Dexa Medica, Indonesia), Explotab® (sodium starch glycolate, Kalbe Farma, Indonesia), PEG 6000 (Dexa Medica, Indonesia), magnesium stearate (Dexa Medica, Indonesia), sorbitol (Dexa Medica, Indonesia), eosin yellowish, and distilled water. The apparatus utilized in this research encompasses a set of glassware, a digital balance, a single-punch tablet press machine, a cube mixer, a tapping test apparatus, a hardness tester, a friability tester, a disintegration tester, a caliper, a UV-vis spectrophotometer, a centrifuge, filter paper, petri dishes, a 40-mesh sieve, and a stopwatch.

Methods

Determination of the dispersible tablet formulation of diclofenac potassium using the Simplex Lattice Design method

The formulation determination was conducted utilizing variations of excipients, specifically explotab (component A) and avicel pH-101 (component B), in specified proportions. This study will encompass five experimental trials, with each tablet formulation (total weight = 200 mg) being as follows: FI: 100% explotab; FII: 75% explotab + 25% avicel pH-101; FIII: 50% explotab + 50% avicel pH-101; FIV: 25% explotab + 75% avicel pH-101; FV: 100% Avicel PH-101. The composition of the diclofenac potassium dispersible tablet formulations prepared using the Simplex Lattice Design is presented in Table 1.

Table 1. Formula of dispersible potassium diclofenac tablet using Simplex Lattice Design.

Formula	Materials (mg)						Tablet weight
	Diclofenac potassium	Explotab	Avicel	Sorbitol	PEG 6000	Mg Stearat	
F I	50	105	0	37,5	6	1.5	200 mg
F II	50	78.75	26.25	37,5	6	1.5	200 mg
F III	50	52.5	52.5	37,5	6	1.5	200 mg
F IV	50	26.25	78.75	37,5	6	1.5	200 mg
F V	50	0	105	37,5	6	1.5	200 mg

Mixing

Each component of the materials was weighed according to the specified formulation design and subsequently sieved using a 40-mesh sieve. Diclofenac potassium was blended with the excipients explotab, avicel, and sorbitol to achieve homogeneity in a cube mixer for 10 minutes at a rotational speed of 30 rpm. Following this, PEG 6000 and magnesium stearate were added, each being mixed for 2 minutes at the same rotational speed [5][6].

Tablet compression

The formulated dispersible potassium diclofenac tablets are introduced into the hopper and compressed by the coordinated movement of the upper and lower punches. The tablet mass is compressed at a machine rotation speed of 20 rpm. During the compression process, certain parameters are maintained consistently, including the total weight of each tablet at 200 mg and the tablet hardness, which is regulated to remain within the range of 2 to 5 Kg [7][8].

Evaluation of the physical properties of potassium diclofenac dispersible tablets

Size uniformity

A sample of 20 tablets was extracted from the production batch for analysis. The diameter and thickness of the tablets were measured using a caliper. Unless otherwise specified, the diameter of the tablets does not exceed three times nor fall below one and one-third times their thickness [9][10].

Weight uniformity

The uniformity of weight can be quantified by calculating the coefficient of variation (CV). The weight uniformity of a tablet formulation is deemed satisfactory when the CV value is less than 5% [11].

Tablet hardness

The measurement of tablet hardness was conducted by positioning the tablet centrally and perpendicularly on a hardness tester. Initially set at the zero position, the apparatus was gradually rotated until the tablet fractured. The scale reading corresponding to the point at which the tablet broke or disintegrated was recorded [10][12].

Tablet friability

Amount of 20 tablets was initially dedusted and subsequently weighed, recorded as M1. These tablets were then introduced into a friabilator, which was operated for a duration of 4 minutes at a rotational speed of 25 rpm. Upon completion of the 4-minute interval, equating to 100 rotations, the tablets were extracted from the apparatus, subjected to a secondary dedusting process, and reweighed, documented as M2. The friability of the tablets is determined by calculating the difference in weight, stipulating that the mass of the tablets post-testing must not diminish by more than 1% of their initial weight prior to testing [13][14].

Evaluation of disintegration time

The disintegration test apparatus comprises a basket rack equipped with six vertically aligned tubes positioned above a mesh sieve of size 10. Each tube in the basket accommodates six tablets. Subsequently, the basket undergoes vertical reciprocation in a clear solution at a frequency ranging from 29 to 32 cycles per minute. Optimal dispersible tablets exhibit a disintegration time of less than 3 minutes, with the medium employed being water maintained at a temperature between 15°C and 25°C [15].

Evaluation of wetting time

A tablet was positioned on a filter paper with a diameter of 10 cm, which was placed in a Petri dish with a diameter of 6.5 cm containing 6 mL of a dye solution (eosin). The time required for the liquid to reach the upper surface of the tablet is referred to as the wetting time [16].

Disperses time testing

Three tablets from each selected formula were randomly sampled and subsequently immersed in 10 mL of water. The time required for the tablets to achieve complete dispersion was recorded as the dispersion time [17].

Quantitative determination assay

The quantitative analysis of diclofenac potassium in the dispersible tablet formulations was carried out using a UV-visible spectrophotometric method. The procedure included the preparation of the diclofenac potassium standard solution, determination of the maximum wavelength of diclofenac potassium, development of the diclofenac potassium standard curve, and the quantitative determination test of diclofenac potassium dispersible tablets [18].

Optimization of the formula of dispersible diclofenac potassium tablet

The optimal formulas of dispersible diclofenac potassium tablets is determined through the Simplex Lattice Design approach, predicated on the equation: $Y = B1(A) + B2(B) + B12(A)(B)$. The obtained data are integrated into the equation to derive coefficient values, which enable the theoretical profiling of mixture properties using various proportions of explotab and avicel. Subsequently, the aggregate response, derived from the cumulative physical tablet responses, is sought. The total response can be calculated via the formula: $R_{total} = R1 + R2 + R3 \dots + Rn$. Given the variability in individual responses, standardization of response evaluation is necessary. Thus, R can be computed by multiplying the value N by the predetermined weight. Consequently, the calculation of the total response becomes: $R_{total} = (R1 \times N_{response1}) + (R2 \times N_{response2}) + (R3 \times N_{response3}) \dots + (Rn \times N_{response-n})$. The optimization response parameters employed include weight uniformity, hardness, disintegration time test, and dispersion time test. Based on the Simplex Lattice Design method, equations pertinent to each of these parameters were established.

Data analysis

The data acquired from testing various physical properties of tablets were analyzed through a theoretical approach by comparing the criteria outlined in the Indonesian Pharmacopoeia and other authoritative sources such as the British Pharmacopoeia and the United States Pharmacopoeia. The selection of the optimal formula was conducted using the Simplex Lattice Design, a two-factorial method, to evaluate the response of the tablets' physical characteristics.

Results and Discussion

Results of the physical property testing of diclofenac potassium dispersible tablets

The evaluation of the physical properties of the tablets encompassed assessments of weight uniformity, size uniformity, hardness, friability, disintegration time, dispersion time, wetting time, and content determination. The results pertaining to the physical characteristics of the dispersible diclofenac potassium tablets are presented in Table 2.

Table 2. Results of the physical property evaluation of dispersible diclofenac potassium tablets.

Evaluation	Formula				
	Formula I	Formula II	Formula III	Formula IV	Formula V
Tablet weight average (mg) $\bar{x} \pm SD$	189.5 $\pm$ 10.26	197.3 $\pm$ 3.13	203.3 $\pm$ 2.31	199.3 $\pm$ 2.15	199.2 $\pm$ 3.16
Weight uniformity / CV (%)	5.42	1.58	1.13	1.08	1.58
Size uniformity (cm)					
Diameter	0.91 $\pm$ 0.05	0.91 $\pm$ 0.03	0.90 $\pm$ 0.02	0.90 $\pm$ 0.02	0.90 $\pm$ 0.02
Thickness	0.37 $\pm$ 0.04	0.34 $\pm$ 0.04	0.36 $\pm$ 0.03	0.38 $\pm$ 0.01	0.39 $\pm$ 0.05
Friability (%)	100	1.27	0.73	0.63	0.25
Hardness (kg) $\bar{x} \pm SD$	1.67 $\pm$ 0.49	2.56 $\pm$ 0.55	3.27 $\pm$ 0.46	3.09 $\pm$ 0.42	3.85 $\pm$ 0.38
Disintegration time (second) $\bar{x} \pm SD$	46.33 $\pm$ 1.53	154.33 $\pm$ 1.15	157.33 $\pm$ 2.52	114.33 $\pm$ 2.08	56.00 $\pm$ 1.72
Dispersed time (second) $\bar{x} \pm SD$	28.67 $\pm$ 3.21	58.33 $\pm$ 1.52	106.30 $\pm$ 2.51	71.67 $\pm$ 2.08	55.00 $\pm$ 1.73
Wetting time (second) $\bar{x} \pm SD$	75.2 $\pm$ 3.42	187.2 $\pm$ 3.0	222.6 $\pm$ 1.51	236.0 $\pm$ 1.22	22.4 $\pm$ 3.20
Drug content (mg)	43.7	46.6	48.3	50.0	45.4
Content (%)	87.4	93.2	96.6	100	90.8

The results of the weight uniformity test revealed that Formula I did not satisfy the weight uniformity requirements as stipulated by the Indonesian Pharmacopoeia [10]. However, Formulas II to V met the criteria for weight uniformity according to the same pharmacopeia edition. Calculations of the coefficient of variation (CV) for the five formulations indicated that Formula I yielded the highest CV, thereby failing to meet the weight uniformity CV threshold of 5.42%. In contrast, Formulas II to V exhibited relatively consistent coefficients of variation (CV) in weight uniformity. The relationship between the CV and the formulation factors was modeled using the Simplex Lattice Design (SLD) approach, yielding the following equation:

$Y = 5.42(A) + 1.59(B) - 10.72(A)(B)$, where (A) represents the explotab component and (B) represents the avicel component.

Based on the aforementioned equation, the interaction between explotab and avicel pH-101 emerges as the predominant factor influencing weight uniformity testing. The negative coefficient B12 (A)(B) signifies that at specific proportions, the combination of these two materials reduces the coefficient of variation (CV), thereby minimizing weight variability and ensuring the production of tablets with consistent weight. Figure 1 illustrates the percentage deviation in tablet weight.

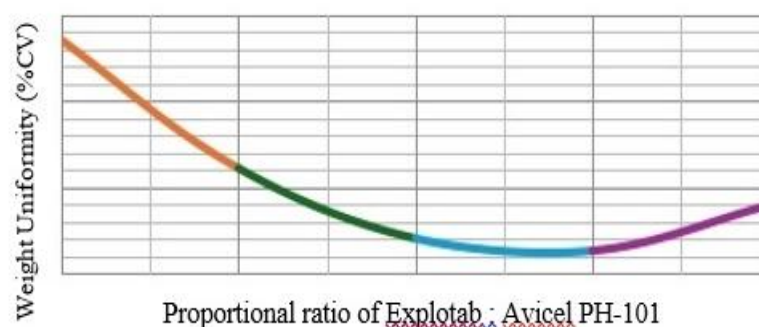


Figure 1. Graph of percentage deviations in tablet weight.

The research findings indicate that the tablet formulations exhibit inconsistencies in thickness; however, all five formulations comply with the physical property tests for uniformity in thickness and diameter as stipulated by the Indonesian Pharmacopoeia, third edition. Notwithstanding the observed variability, the measurements remain within

the permissible range, wherein the diameter must not exceed three times the thickness, which translates to a maximum diameter of 1.1 cm, nor fall below one-third of the tablet thickness, thus ensuring a minimum diameter of 0.48 cm.

The results of the study indicate that Formula I, composed entirely of explotab, exhibits the lowest hardness and fails to meet the specified criteria of 2-5 Kg. This deficiency is attributed to the absence of binding agents in Formula I, which are essential for enhancing tablet compactibility and hardness. Conversely, Formula V consisting entirely of avicel pH-101, demonstrates the highest hardness, measuring at 3.85 Kg. This outcome is due to the strong binding capacity of avicel pH-101 within the mixture, resulting in increased tablet hardness with larger proportions of the compound [19]. The equation for tablet hardness derived from the SLD approach is as follows:

$Y = 1,67(A) + 3,85(B) + 1,02(A)(B)$, where (A) represents explotab component and (B) represents avicel component.

The equation indicates that the combination of explotab and avicel pH-101 exhibits a synergistic interaction contributing to an increase in tablet hardness, albeit modest, as evidenced by the relatively small coefficient B12 (A)(B). The graphical representation of the tablet hardness profile is presented in Figure 2.

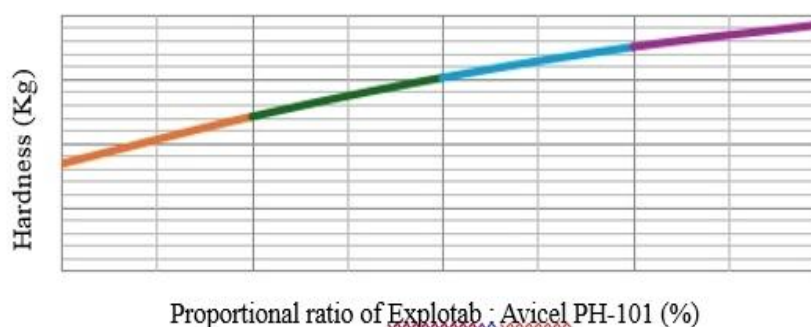


Figure 2. Profile of tablet hardness based on the SLD method.

The friability test results indicated that both Formula I and Formula II did not meet the tablet friability criteria, exhibiting weight losses of 100% and 1.27%, respectively. The physical structure of tablets from Formula I, composed entirely of explotab, predominantly experienced capping, which resulted in compromised hardness and friability. This phenomenon is attributable to the absence of binding agents in the tablet mass, rendering the tablets susceptible to breakage and disintegration upon exposure to mechanical stress or abrasion. The similarity factor (SLD) derived from the friability profile calculations is:

$Y = 100(A) + 0,25(B) - 236,4(A)(B)$, where (A) represents explotab component and (B) represents avicel component.

The equation demonstrates that the combination of explotab and avicel is efficacious in reducing the friability response of tablets, as evidenced by the negative value of the coefficient B12(A)(B). An increased proportion of explotab results in heightened tablet friability, whereas a greater proportion of avicel correlates with diminished tablet friability. This is illustrated by the coefficient B1 (explotab), which reaches 100%, and the coefficient B2 (avicel pH-101), which is 0.25%.

The results of the study indicate that all five tablet formulations conform to the disintegration time requirements for dispersible tablets as stipulated by the British Pharmacopoeia (2009), which mandates disintegration within a period of less than 3 minutes. The formulation composed entirely of explotab (formulation I) and the one consisting solely of avicel (formulation V) exhibit a more rapid disintegration time relative to the formulations containing a combination of these excipients. The equation for the disintegration time, as derived using the SLD approach, is as follows:

$Y = 46,33(A) + 56(B) + 435,99(A)(B)$, where (A) represents explotab component and (B) represents avicel component.

The interaction between the two components emerges as a dominant factor, evidenced by a positive B12(A)(B) coefficient value of 435.99. This indicates that the interaction between explotab and avicel prolongs the disintegration time of the tablets. The disintegration time profile of the dispersible diclofenac potassium tablets, characterized by a downward-opening curved graph, is illustrated in Figure 3.

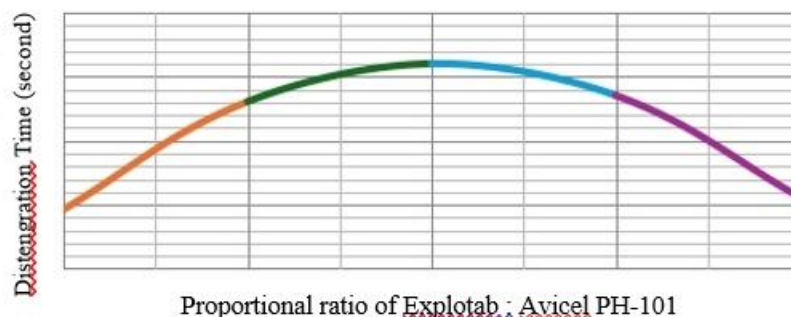


Figure 3. The profile of tablet disintegration time based on SLD method.

The empirical data demonstrate that all five tablet formulations meet the requisite dispersion time for dispersible tablets, successfully dispersing within a period of three minutes [20]. Formula 1 (comprising 100% explotab) and Formula 5 (comprising 100% avicel) demonstrate relatively faster dispersion times compared to formula containing a combination of these excipients, with dispersion times of 28.67 seconds and 55 seconds, respectively. The time-dispersed profile of diclofenac potassium dispersible tablets is illustrated in Figure 4. The equation for dispersion time can be derived using the SLD (Solid-Liquid Dispersion) approach as follows:

$Y = 28,67(A) + 55(B) + 177,32(A)(B)$, where (A) represents explotab component and (B) represents avicel component.

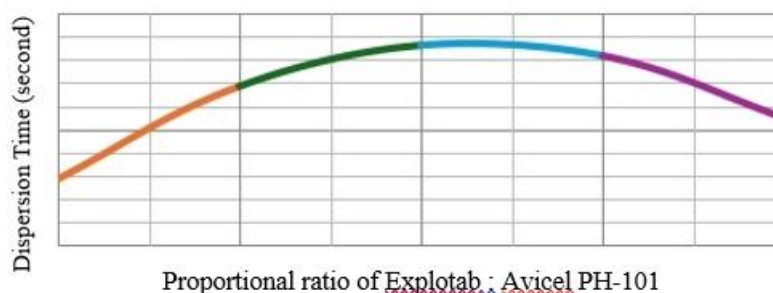


Figure 4. The profile of tablet dispersion time based on SLD method.

Figure 4 illustrates the dispersion time profile of diclofenac potassium dispersible tablets, characterized by a downward-opening curved trajectory. This pattern indicates a positive interaction between explotab and avicel pH-101, leading to an increased dispersion time value. Such an interaction is suboptimal for dispersible tablet formulation, as a higher dispersion time value implies a prolonged duration required for complete tablet dispersion [21].

The experimental results indicate that the fastest wetting time was observed with Formula V, which comprises 100% avicel. This phenomenon is attributed to avicel's extremely small particle size and excellent compressibility, resulting in the formation of hard tablets. Tablets characterized by these properties are capable of rapid wetting and uniform liquid distribution throughout the tablet mass [22] [23]. This mechanism has the potential to expedite the wetting time of the tablet.

In contrast to Formula I, which is composed entirely of explotab, it should be noted that explotab is a modified form of potato starch. Kumar, et al. [24] asserts that disintegrant particles such as starch undergo expansion upon exposure to water, subsequently exerting pressure on their surroundings to facilitate tablet disintegration. This expansion process requires a longer duration compared to the wetting of cellulose particles.

The results of the study indicate that Formula I does not comply with the diclofenac potassium content range specified by the Indonesian Pharmacopeia [10], which stipulates that diclofenac potassium tablets must contain no less than 90.0% and no more than 110.0% of the labeled amount of diclofenac potassium [25]. This discrepancy is attributed to the prevalent occurrence of capping in the tablets of Formula I. Capping results in a significant loss of tablet mass, and assuming homogeneous mixing of ingredients, it is inferred that the diclofenac potassium content is likewise diminished [26].

For formulations II, III, IV, and V, which are presented in tablet form and demonstrate satisfactory weight uniformity, the percentage content obtained conforms to the range established by the Indonesian Pharmacopeia [10]. The respective percentages are 93.2%, 96.6%, 100%, and 90.8%.

Determination of optimum formula

The parameters employed for the determination of the optimal formulation encompass the physical properties of tablets, including weight uniformity, hardness, disintegration time, and dispersion time. Prior to identifying the optimal formulation, it is imperative to standardize the assessment of responses by assigning predetermined weights to each parameter. Each response is assigned a weight, with the cumulative total weight equating to unity. Subsequently, the optimal formulation is discerned based on the maximization of the total response. Hardness and dispersion time, as principal parameters, are assigned a weight of 0.3, whereas disintegration time and weight uniformity are allocated a weight of 0.2. The response value (R) is computed by multiplying the respective parameter (N) by the designated weight, followed by determining the aggregate response value (R total) through summation of all individual response values. The optimal formulation is selected based on the total response value calculated using the equation:

$R_{\text{total}} = (0.2 \times N_{\text{weight uniformity}}) + (0.3 \times N_{\text{hardness}}) + (0.2 \times N_{\text{disintegration time}}) + (0.3 \times N_{\text{dispersion time}})$, where where N represents the normalized value of each response parameter.

The optimal formula was selected based on the highest response value, revealing that a mixture comprising 40% explotab and 60% avicel pH-101 achieved the highest response value of 0.463. Consequently, it can be concluded that the combination of 40% explotab as a disintegrant and 60% avicel pH-101 as a binder constitutes the optimal excipient formulation for the production of dispersible diclofenac potassium tablets. The total response calculations are presented in Table 3.

Table 3. The results of the total response calculations using the SLD method

Explotab	Avicel	R hardness (0.3)	R dispersion (0.3)	R disintegration time (0.2)	R weight uniformity (0.2)	R Total
100	0	- 0.033	0.048	0.052	0.216	0.283
90	10	- 0.0018	0.078	0.096	0.162	0.334
80	20	0.027	0.105	0.13	0.118	0.38
75	25	0.042	0.114	0.144	0.098	0.398
70	30	0.054	0.123	0.156	0.08	0.413
60	40	0.078	0.135	0.172	0.052	0.437
50	50	0.102	0.141	0.178	0.032	0.453
40	60	0.123	0.144	0.174	0.022	0.463
30	70	0.141	0.138	0.16	0.018	0.457
25	75	0.15	0.135	0.15	0.02	0.455
20	80	0.159	0.129	0.138	0.026	0.452
10	90	0.171	0.114	0.104	0.04	0.429
0	100	0.186	0.09	0.062	0.064	0.402

Conclusion

The conclusion of this study, the combination of explotab (disintegrant) and avicel pH-101 (binder) affects increasing the uniformity of weight, hardness, disintegration time and dispersion time of dispersed diclofenac potassium tablets with an optimal formula of explotab 40% and avicel pH-101 10% composition.

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Declarations

- Author contribution : NMA conceptualized and conducted the research, processed and analyzed the data, and drafted the manuscript. VVFRU critically reviewed the manuscript draft. DWK designed and implemented the study, reviewed, and finalized the manuscript.
- Funding statement : The study was conducted utilizing personal funding resources his research.
- Conflict of interest : There are no conflicts of interest among the authors.
- Ethics Declaration : The research did not involve living subjects or objects, thereby obviating the need for ethical clearance his research.
- Additional information : There is no additional information related to the manuscript.

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