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Formulation Study of Acetosal Suppositories Using PEG 400 and PEG 6000: Impact on Physical Properties

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ABSTRACT

Acetosal suppositories are rectal dosage forms that can be used as an alternative route of administration to minimize gastrointestinal irritation associated with oral acetosal therapy. The suppository base plays an important role in determining the physical characteristics of the preparation. The objective of this study was to evaluate how varying concentrations of polyethylene glycol (PEG) 400 and PEG 6000 affect the physical properties of acetosal suppository formulations. Three formulations were prepared using PEG 400:PEG 6000 ratios of F1 (3:7), F2 (1:1), and F3 (7:3). Physical evaluations included organoleptic properties, weight uniformity, melting time, melting point, and hardness. All formulations exhibited similar organoleptic characteristics, namely solid shape, pale white color, and characteristic odor. The average weight uniformity values were 2594.3 ± 61.9 mg (F1), 2526.9 ± 83.1 mg (F2), and 2315.7 ± 45.4 mg (F3), with significant differences among formulations ($p<0.05$). The average melting times were 25.1 ± 0.981 min, 19.5 ± 0.574 min, and 15.9 ± 0.508 min for F1, F2, and F3, respectively ($p<0.05$). The average melting points were 36.3 ± 0.577°C, 35.7 ± 0.577°C, and 34.3 ± 0.577°C for F1, F2, and F3, respectively ($p=0.014$). Hardness values were 1.93 ± 0.115 kg (F1), 1.87 ± 0.115 kg (F2), and 1.53 ± 0.115 kg (F3), with significant differences among formulations ($p<0,05$). In conclusion, variations in PEG 400 and PEG 6000 concentrations significantly affected weight uniformity, melting time, melting point, and hardness, while organoleptic properties remained unchanged. Formulations F1 and F2 fulfilled all physical quality requirements and were considered optimal.

Keywords: Acetosal, suppositories, PEG 400, PEG 6000

Introduction

Analgesic and antipyretic agents are among the most frequently used medications in Indonesia because pain and fever remain common health complaints requiring pharmacological treatment (Supardi et al., 2012). Analgesics function by reducing or eliminating pain without causing loss of consciousness, primarily through modulation of peripheral or central pain pathways. Antipyretics, on the other hand, act by lowering elevated body temperature, mainly through inhibition of prostaglandin synthesis in the hypothalamic thermoregulatory center (Tjay &Rahardja, 2008).

Acetosal a popular analgesic-antipyretic medication, works by irreversibly inhibiting cyclooxygenase enzymes, which lowers the production of prostaglandins that cause pain, inflammation, and fever (Katzung, 2018). Acetosal is an analgesic, antipyretic, and anti-inflammatory medication that is a member of the non-steroidal anti-inflammatory drug class (Rahmadanita and Sumarno, 2020). Acetosal should be taken 300–900 mg every 4-6 hours, up to a daily maximum of 4 g, to produce analgesic and antipyretic effects (Katzung, 2018).

Acetosal is an acidic drug that exhibits slow absorption in the stomach and tends to remain in the gastric environment for an extended period, which may lead to gastric mucosal irritation and adverse gastrointestinal effects. This limitation reduces patient compliance, particularly in long-term therapy (Setiawan, 2006; Katzung, 2018). To overcome these drawbacks, acetosal can be formulated into a suppository dosage form intended to provide systemic therapeutic effects while minimizing direct contact with the gastric mucosa.

Suppositories are solid pharmaceutical dosage forms, generally manufactured in a torpedo shape, intended for rectal, vaginal, or urethral administration. Upon insertion, these preparations melt or dissolve at body temperature, allowing the release of the active pharmaceutical ingredient (Afikoh et al., 2017; Anief, 2000). The rectal route provides several pharmacokinetic benefits, such as partial circumvention of first-pass hepatic metabolism and protection of the drug from the acidic environment of the stomach, which contributes to improved drug stability and increased systemic bioavailability (Allen & Ansel, 2014). Furthermore, the rectum and colon possess sufficient absorptive capacity to allow significant amounts of drug to enter the systemic circulation through passive diffusion across the rectal mucosa (Aulton & Taylor, 2018). Consequently, rectal suppository formulations represent a viable alternative for systemic delivery of acetosal, particularly for patients with gastrointestinal sensitivity or those who experience difficulty with oral administration.

The choice of suppository base significantly affects the release behavior of the active pharmaceutical ingredient, whether the formulation is intended for systemic or local therapeutic effects. The choice of base influences the physical characteristics of suppositories, including melting behavior, mechanical strength, and stability, which are important parameters for product quality(Aulton & Taylor, 2018). Polyethylene glycol (PEG) is one of the most widely used suppositories bases due to its hydrophilic nature and its ability to dissolve readily in rectal fluids, allowing drug release to occur through a dissolution mechanism rather than melting (Anief, 2000; Allen & Ansel, 2014). Polyethylene glycol (PEG) 400, a low molecular weight polymer, is widely utilized to improve the solubility and dissolution of poorly water-soluble drugs by enhancing drug wettability and promoting uniform molecular dispersion within the suppository base matrix (Rowe et al., 2012). In contrast, PEG 6000 has a higher molecular weight and contributes to increased hardness and higher melting point of the suppository, which is important for maintaining physical stability during storage (Aulton & Taylor, 2018). The combination of PEG 400 and PEG 6000 allows

modulation of the melting point, mechanical strength, and drug release profile, as PEG 400 acts as a plasticizer that lowers the melting point and improves flexibility of PEG 6000-based formulations (Norvisari, 2008; Rowe et al., 2012). Therefore, the use of mixed PEG bases is expected to produce suppository formulations with optimal physical properties and controlled drug release behavior.

Based on the description above, the objective of this research is to evaluate the effect of varying concentrations of PEG 400 and PEG 6000 bases on the physical properties of acetosal suppositories

Methodology

Materials

The materials used in this research are acetosal (PT. Inalab), PEG 400 (PT. Brataco), PEG 6000 (PT. Inalab), and paraffin liquidum (PT. Brataco).Statistical analysis was performed using SPSS version 25. Data normality was evaluated using the Shapiro–Wilk test, followed by statistical analysis with one way analysis of variance (ANOVA) and Tukey's Honestly Significant Difference (HSD) post hoc test for multiple comparisons.

Suppositories formulation

Weigh the ingredients according to the calculations, place PEG 6000 into a porcelain crucible, then melt it over at 55-63^{0}Cin water bath. After melting, add PEG 400 and stir until homogeneous. Add the finely ground acetylsalicylic acid, and stir until homogeneous. Pour the suppository mass mixture into the suppository molds, previously coating the mold walls with liquid paraffin. Let it sit at room temperature for about 15 minutes, then place it in the refrigerator for 15 minutes. Next, remove the formed suppositories from the mold. Table 1 shows the formula for making the acetosal suppository.

Table 1. Suppository formula

Material	F1 (%)	F2 (%)	F3 (%)
Acetosal	20	20	20
PEG 400	24	40	56
PEG 6000	56	40	24
Total	100	100	100

Testing the Physical Properties of Suppository Preparations

Organoleptic test

Suppositories are visually examined to observe their shape, color, and odor (Afikoh et al., 2017).

Weight uniformity

A total of 10 suppositories are weighed one by one, then counted and their average weight is determined. The requirement is that no more than 1 suppository may deviate from the average weight by more than the value specified in column A (5%), and no suppository may deviate from the average weight by more than the value specified in column B (10%) (Afikoh et al., 2017).

Melting time test

Suppositories are placed into a glass spiral-shaped cage and inserted into a melting time testing device. The device is supplied with water at a temperature of 37 °C, and the time when the suppositories melt is recorded using a stopwatch (Afikoh et al., 2017).

Melting point test

The melting point test was performed by placing the suppository into a capillary tube, which was subsequently inserted into a melting point apparatus. The melting temperature was then recorded at the point where the suppository completely melted (Ardana et al., 2023).

Hardness test

The hardness test on suppositories is conducted by placing the suppository into the hardness testing device and covering it with a glass plate. A weight of 600 grams is added as the base mass to the suppository, then an additional 200 grams is added at 1-minute intervals until the suppository disintegrates. The hardness value was expressed as the total load required to break the suppository and was reported in kilograms (kg) after conversion from grams (1000 g = 1 kg) (Milala et al., 2013).

Result and Discussion

The organoleptic test was visually observed by 3 different respondents, resulting in an objective value. The organoleptic test aims to observe the shape, color, and smell of the suppositories. The organoleptic suppository of three formulae are determined to be solid, pale white in color, and exhibited a characteristic odor of acetosal. No differences in organoleptic properties were observed among the formulations. Table 2 is present of organoleptic physical property test.

Table2. Organoleptic test results

Parameter	F1	F2	F3
Shape	Solid	Solid	Solid
Color	Pale white	Pale white	Pale white
Odor	Characteristic acetosal odor	Characteristic acetosal odor	Characteristic acetosal odor

Weight Uniformity Testconducted to determine the uniformity of the preparation's weight. This test serves as a production parameter to achieve the desired preparation weight, ensuring it meets the therapeutic safety of the preparation. The weight uniformity test is present in Table 3.

Table 3. Weight Uniformity of Suppositories

No	F1 (mg)	F2 (mg)	F3(mg)
1.	2438	2418	2232
2.	2462	2423	2268
3.	2490	2450	2279

No	F1 (mg)	F2 (mg)	F3(mg)
4.	2544	2486	2304
5.	2548	2507	2318
6.	2565	2530	2336
7.	2571	2583	2336
8.	2580	2616	2347
9.	2601	2627	2355
10.	2633	2629	2382
Average ± SD	2594,3 ± 61,9	2526,9 ± 83,1	2315,7 ± 45,4

The weight uniformity test was conducted by weighing all the acetosal suppository preparations one by one, a total of 10 suppositories, and then calculating the average. The average results obtained for formula 1 = 2594.3 mg, formula 2 = 2526.9 mg, and formula 3 = 2315.7 mg. The weight deviations for formula 1 are column A = 2464.8 mg – 2724 mg and column B = 2334.8 mg – 2853.7 mg, for formula 2 are column A = 2400.5 mg – 2653.2 mg and column B = 2274.2 mg – 2779.5 mg, and for formula 3 are column A = 2199.9 mg – 2431.4 mg and column B = 2084.1 mg – 2547.2 mg.

The weight uniformity test confirmed that all three suppository formulations complied with the accepted physical requirements for suppository preparations. The difference in weight uniformity can be caused by variations in the concentration of the base. An increase in PEG 6000 concentration resulted in a corresponding increase in the weight of the suppository formulation, which can be attributed to the higher molecular weight of PEG 6000 compared with PEG 400. The molecular weight of the base can influence the weight of the suppository preparation, and the effect on the weight of the suppository preparation occurs during the making of the suppository, including incomplete closure of the suppository mold and residual suppository material on the equipment used during the preparation (Rahmawati, 2008).The data are normally distributed, according to an analysis of the statistical results of the physical parameters of weight uniformity, with a significance level of 0.096 ($p>0.05$). A OneWay ANOVA test was used to further evaluate the data, and the results showed a significance of 0.000 ($p<0.05$), suggesting that the physical characteristics of the weight uniformity of asetosal suppositories were impacted by the difference in PEG 400 and PEG 6000 concentrations. Additionally, a Post Hoc ANOVA test was performed to identify the various formulas, and the results showed a significant difference between F1 and F3 with a value of 0.030 ($p<0.05$).

Next, a melting time test was conducted. Subsequently, a melting time test was performed to evaluate the duration required for the suppository to melt in rectal fluid, which is a critical parameter influencing dissolution and subsequent drug release. According to Aryanti (2003), an appropriate melting time ensures that the suppository base can effectively soften and dissolve under physiological conditions, thereby facilitating drug availability. The results demonstrated that formulations F1, F2, and F3 complied with the pharmacopeial requirement for water-soluble suppository bases, namely a melting time not exceeding 60 minutes.

The melting behavior of the suppositories was markedly influenced by the composition of polyethylene glycol (PEG) used as the base. PEG 400, characterized by a relatively low molecular weight (380–420), exhibits a shorter melting time, whereas PEG 6000, with a substantially higher molecular weight (7300–9300), demonstrates a longer melting duration. The combination of PEG 400 and PEG 6000 in appropriate proportions resulted in an optimal melting profile, enabling the formulations to satisfy the required physical characteristics of suppositories. This finding is consistent with the binding and physicochemical behavior of PEG in aqueous systems as reported by Wu et al. (2014).

Statistical analysis of the melting time parameter indicated that the data were normally distributed, with a significance value of 0.244 ($p > 0.05$).The data were further analyzed using a one-way ANOVA, which revealed a statistically significant difference with a significance value of 0.000 ($p < 0.05$). Suggesting that the physical characteristics of the melting time of the acetosal suppository preparation were impacted by the fluctuation in the concentration of PEG 400 and PEG 6000 bases. A Post Hoc Anova test was then used to identify the various formulas, and the results showed a significant difference between F1 and F2 with a significance of 0.000 ($p<0.05$). F1 and F3 differed significantly, with a significance level of 0.000 ($p<0.05$). There was a significant difference between F2 and F3 with a significance of 0.002 ($p<0.05$). The results of physical property test for melting time is presented in Table 4.

Table 4. Melting time of Suppositories

Replicate	Melting time (minutes)		
	F1	F2	F3
R1	24,08	19,05	15,28
R2	25,3	19,39	16,15
R3	26,02	20,17	16,17
Average ± SD	25,1 ± 0,981	19,5 ± 0,574	15,9 ± 0,508

The melting point test was determine when the suppository melts and at what temperature the suppository melts. The requirement for the melting point test is not more than 37^0C (Afikoh et al., 2017). The results of the melting point test is presented in Table 5.

Table 5. Melting point of Suppositories

Replicate	Melting point (^{0}C)		
	F1	F2	F3
R1	36	36	34
R2	36	36	34
R3	37	35	35
Average ± SD	36,3 ± 0,577	35,7 ± 0,577	34,3 ± 0,577

Based on the evaluation of formulations F1, F2, and F3, all formulations complied with the pharmacopeial melting point requirement for suppositories, namely a melting point not exceeding 37 °C. In water-soluble suppository bases, the melting point is strongly influenced by the composition of polyethylene glycol (PEG),

particularly the proportion of PEG 400, which possesses a lower melting point compared to PEG 6000. The PEG matrix is known to dissolve gradually in rectal fluids, a characteristic that may delay drug release. Consequently, increasing the concentration of PEG 400 enhances the hydrophilicity and dissolution rate of the base, thereby increasing the hydrophilicity of the suppository base and influencing its melting and dissolution characteristics. This observation is consistent with findings reported by Nurapni et al. (2023). The normality analysis of the melting point data showed a significance value of 0.208 ($p > 0.05$), indicating that the data were normally distributed. The One Way Anova test, which was used to further evaluate the data, produced a significance of 0.014 ($p<0.05$), suggesting that the physical characteristics of the melting point of acetosal suppositories were impacted by the fluctuation in the concentration of PEG 400 and PEG 6000 bases. A Post Hoc Anova test was then used to identify the various formulas, and the results showed a significant difference between F1 and F3 with a significance of 0.013 ($p<0.05$).

Next, a hardness test was conducted to ensure that the suppositories do not cause difficulties during use, but if their hardness decreases, it will also lead to difficulties in packaging and transportation due to being easily breakable. Therefore, it must meet the hardness test requirement range of 1.8 kg – 2.0 kg (Milala et al., 2013). The physical hardnes result is presented in Table 6.

Table 6. Hardness of Suppositories

Replicate	Hardness (kg)		
	F1	F2	F3
R1	2	1,8	1,6
R2	2	1,8	1,6
R3	1,8	2	1,4
Average ± SD	1,93 ± 0,115	1,87 ± 0,115	1,53 ± 0,115

The hardness test of formulations F1 and F2 complied with the pharmacopeial requirements for suppository hardness, with values not less than 1.8–2.0 kg. In contrast, formulation F3 failed to meet the required hardness criteria, as its measured hardness was below the specified threshold. The insufficient hardness observed in F3 can be attributed to the higher proportion of PEG 400 relative to PEG 6000 in the formulation. PEG 400, characterized by its lower molecular weight and greater plasticizing effect, tends to reduce the structural rigidity of the suppository matrix, resulting in decreased mechanical strength. Conversely, PEG 6000, with its higher molecular weight, contributes to increased mass density, crystallinity, and intermolecular interactions within the PEG matrix, thereby enhancing the mechanical strength and hardness of the suppository base. Several studies have reported that increasing the proportion of high–molecular-weight PEG in suppository formulations improves hardness and overall physical stability, whereas excessive amounts of low–molecular-weight PEG may lead to softer and mechanically weaker preparations (Maderuelo et al., 2012; Rahmanian-Devin et al., 2023; Wibowo, 2019). These findings

confirm that an appropriate balance between PEG 400 and PEG 6000 is essential to achieve suppositories that meet pharmacopeial hardness requirements.

Statistical analysis of the physical hardness data demonstrated that the dataset was normally distributed, as indicated by a significance value of 0.094 ($p > 0.05$). Consequently, parametric analysis was performed using a one-way analysis of variance (ANOVA). The ANOVA results revealed a statistically significant effect of variations in the concentrations of PEG 400 and PEG 6000 on the hardness of acetosal suppositories ($p = 0.011$; $p < 0.05$). To further identify differences among formulations, a post hoc ANOVA test was conducted. The results indicated statistically significant differences in hardness between formulations F1 and F3 ($p = 0.013$; $p < 0.05$) as well as between F2 and F3 ($p = 0.028$; $p < 0.05$). These findings confirm that differences in the ratio of PEG 400 to PEG 6000 significantly influence the mechanical strength of the suppository formulations.

One limitation of this study is that the displacement value of acetosal was not determined during suppository formulation. In suppository preparations, the active pharmaceutical ingredient occupies part of the mold volume and consequently displaces a portion of the suppository base. Therefore, calculation of displacement value is important to ensure accurate adjustment of the base quantity and uniformity of the final dosage form. In the present study, the formulations were prepared using fixed percentages of acetosal and PEG bases without prior determination of the displacement value. Although all formulations met the requirements for weight uniformity, future studies should include displacement value determination to improve formulation accuracy and reproducibility.

Conclusion

The findings of this study indicate that variations in the concentrations of PEG 400 and PEG 6000 significantly affected the physicochemical properties of acetosal suppositories, including weight uniformity, melting time, melting point, and hardness. However, no differences were observed in the organoleptic characteristics of the formulations. Among the tested formulations, F1 and F2 fulfilled all evaluated physical quality requirements and were therefore considered the most suitable formulations for acetosal suppositories. Further studies involving dissolution and drug release testing are required to evaluate the influence of PEG concentration on the release characteristics of acetosal from the suppository base.

Declaration of Competing Interest

The author certifies that the present study was conducted free from any commercial or financial interests that could reasonably be considered a potential conflict of interest. The results also indicate that PEG 400:PEG 6000 ratios between 1:1 and 3:7 may serve as a preliminary formulation guideline for suppositories containing acidic drugs with physicochemical properties comparable to acetosal, as these ratios produced acceptable physical characteristics.

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