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Research Article

Optimization of Crospovidone and Copovidone in Fast Disintegrating Tablet (FDT) Diphenhydramine HCl Using Factorial Design

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ABSTRACT

Diphenhydramine HCl is a drug used to treat motion sickness. Treatment of motion sickness needs rapid onset for successful therapy. Fast Disintegrating Tablet (FDT) is one dosage form that provides fast onset. The purpose of this study was to identify the dominant factors of crospovidone and copovidone, their interactions, and discover the optimum composition area to produce a FDT dosage form with optimum parameters involving hardness, friability, disintegration time, wetting time, and water absorption ratio. This study was experimental and used a factorial design. The result showed that copovidone significantly influenced friability, disintegration time, wetting time, and water absorption ratio, while their interactions significantly influenced the hardness of FDT diphenhydramine HCl. At the level studied, the optimum composition area was found, which can be predicted as a diphenhydramine HCl FDT dosage form formula.

INTRODUCTION

Diphenhydramine HCl is the first class of antihistamine drugs that can be used for the treatment of nausea and vomiting (Katzung et al., 2012), included in BCS class I with high solubility and permeability (Jyothi et al., 2013). The mechanism of action of diphenhydramine HCl is to compete with histamine to occupy H1 receptors. Diphenhydramine HCl works as an anticholinergic by blocking the passage of impulses through parasympathetic nerves (Whelan and Apfel, 2013).

Tablets are the most widely used dosage form based on their ease and convenience of use. However, the use of conventional oral tablets must be assisted with certain media, for example, water, to help swallow. Water, which is not always available when traveling, limits the use of conventional oral tablets. To overcome this problem, a modification of conventional oral tablet formulations was carried out into the FDT (Fast Disintegrating Tablet) dosage form. One of the advantages of FDT is their fast disintegration time, and their use is more practical compared to conventional oral tablets. The FDT dosage form can disintegrate in the mouth in less than 30 seconds (Food and Drug Administration, 2008). The fast disintegration time will break the tablet into smaller particles in a short time. The small particle shape will increase the solubility of the dosage form, and with high solubility, it will support the rapid onset of the drug so that the resulting effect will be faster. Drugs that have high solubility and permeability have a good prospect of being developed into FDT dosage forms.

In order to obtain an optimal FDT dosage form, it is necessary to select the appropriate manufacturing method and materials. In this study, diphenhydramine HCl was formulated in FDT using crospovidone as a superdisintegrant and copovidone as a binder made by the direct compression method. Crospovidone is widely used as an additive in a formulation to increase the disintegration time of tablets because it has more crosslinks compared to other superdisintegrants. This causes crospovidone to quickly experience swelling without gelling (Mohanachandran et al., 2011). Crospovidone is known to have been used successfully as a

superdisintegrant for ondansetron FDT dosage form and has a faster disintegration time compared to sodium starch glycolate and croscarmellose sodium (Deshmukh et al., 2012; Satpute and Tour, 2013). The presence of a binder has an important role in helping to bind the powder particles that make up the tablet. One of the binders used in FDT formulations is copovidone. This binder has a low moisture content of less than 5%, making copovidone suitable for the hygroscopic active ingredient diphenhydramine HCl (Moroni, 2001). The composition of crospovidone and copovidone affects the physical properties of the FDT produced. The method used in this study was factorial design (FD) to determine the optimum composition area of the FDT dosage form that meets quality requirements including hardness, friability, disintegration time, wetting time, and water absorption ratio, and to know the dominant factors among crospovidone as a superdisintegrant, copovidone as a binder, and the interaction of both excipients in the formulation of diphenhydramine HCl FDT dosage form.

METHODS

Study Design

This study was an experimental method that used factorial design to find the optimum composition area of the FDT diphenhydramine HCl dosage form and the interaction of both excipients.

Variable

The variable in this study was the concentration of crospovidone and copovidone (each 2% and 5%) as independent variables. The dependent variables are the hardness, friability, disintegration time, wetting time, and water absorption ratio of the diphenhydramine HCl tablet.

Instruments and Materials

The instruments used were the OHAUS PA 213 analytical balance, measuring flask, porcelain cup, microtube, cube mixer, glass beaker, mortar, stamper, hardness tester pharma Test GmBH, disintegration tester ATMI Surakarta, friabiliator ATMI Surakarta, mixer Erweka AR 40, tapped density Erweka Sum GmBH, Centrion Scientific C2015, and UV-1800 spectrophotometer.

The materials used were diphenhydramine HCl, working standard diphenhydramine HCl (Supriya, Batch SLL/DPH/0516035), mannitol (Mannogem® EZ Spray Dried, Lot 121506453), crospovidone (Kollidon® CL-SF, Lot 36354116KO, BASF), copovidone (Kollidon® VA 64, Lot 42349924U0, BASF), mint flavor (batch 1002120653), magnesium stearate (batch MGS-T0332), orange flavor (batch 1002361932), aspartame, and ethanol p.a.

Preparation of Powder Mixture

Weighing the ingredients in accordance with the Table 1 formula produced the powder mixture. The first mixing process began with mixing mannitol and crospovidone for 15 minutes using a cube mixer. Then proceed with mixing: orange essence, mint flavor, diphenhydramine HCl, copovidone, and aspartame. This second mixing stage takes 20 minutes for the powder to be homogenized. Then proceed with Mg stearate and mixing for 5 minutes.

Testing Flow Properties of Powder Mixtures

Flow Rate Measurement

A total of ± 100 g of powder mixture was placed into the funnel and dropped into the place provided under the funnel with a height of ± 30 cm. The flow rate is calculated by dividing the weight of the powder by the time required for the powder to flow.

Table 1. Formula FDT *Diphenhydramine HCl*

Ingredients	Formula (mg/tablet)			
	1	a	b	ab
Diphenhydramine HCl	12.5	12.5	12.5	12.5
Crospovidone	3.0	7.5	3.0	7.5
Copovidone	3.0	3.0	7.5	7.5
Mannitol	115.0	115.0	115.0	115.0
Mg Stearate	1.5	1.5	1.5	1.5
Aspartame	12.0	12.0	12.0	12.0
Mint flavour	3.0	3.0	3.0	3.0
Orange flavour	0.5	0.5	0.5	0.5

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Angle of Repose

Angle of Repose Testing is done by measuring the angle of the powder pile. The angle is obtained from the tan arc between the height and radius of the powder.

Hausner Ratio and Carr's Index Testing

A total of ± 100 g of powder was put into a glass with a volume of 250 mL, followed by the height of the powder, which was measured as the unsettled apparent volume ρ . The tap was done 750 times. The height of the powder that has been tapped is measured again as the final tapped ρ. To obtain the Hausner Ratio value, the calculation is done by comparing the final tapped ρ and the unsettled apparent volume ρ, while to obtain the Carr's Index value, the calculation is done by comparing the difference between the final tapped density and the unsettled apparent volume density and the final tapped volume density (British Pharmacopoeia Commission, 2011, Ministry of Health of the Republic of Indonesia, 2014).

Tableting process

The powder, compressed using a tablet machine, used the same punch strength for each formula.

Characteristic Testing of Diphenhydramine HCl FDT Dosage Form

Tablet Hardness Testing

Hardness testing was carried out by measuring the hardness of 10 tablets and replicating each formula three times (Sharma et al., 2015).

Tablet Friability Testing

A total of 20 tablets were cleaned up first before weighing. After weighing, the tablet is inserted in the friabiliator tool and set at 25 rpm for 4 minutes. The tablet was cleaned up again and continued with weighing. The percent loss of tablet weight from the overall weight of the original tablet was calculated.

Disintegration Time Testing

A total of six tablets were inserted into the disintegration time tester. The temperature for the tablet disintegration time testing is 38°C. The longest tablet disintegration time was recorded as the digestion time.

Wetting Time Testing

The wetting time test was carried out by wetting the dry wipes in a Petri dish with a diameter of 6.5 cm using a red solution as an indicator. A tablet is placed on the dry wipes, and then the time required for the water to wet the entire surface of the tablet is recorded (Satpute and Tour, 2013).

Water Absorption Ratio Testing

One tablet was weighed, then placed on the tissue in a Petri dish with a diameter of 6.5 cm that had been wetted by water with red dye. The tablet was left until the red dye wetted all tablet surfaces. Then weigh the weight of the tablets that have been tested (Pabari and Ramtoola, 2012).

Data Analysis

Analysis of response data, including hardness, friability, disintegration time, wetting time, and water absorption ratio ANOVA Factorials are used to determine the significance of factors on the response, while determining the effect of each factor is done by calculating the factor for each factor. For validation, formula testing is carried out using the one-sample T-test by comparing the theoretical value with the value obtained from the research results.

Content Uniformity Testing

Dosage uniformity testing was carried out spectrophotometrically using a UV-1800 spectrophotometer (Mishra et al., 2010). Diphenhydramine HCl has a wavelength of 258 nm. Method validation was carried out before analyzing samples from each formula. The parameters tested were linearity, accuracy, and precision. Sample testing was carried out by weighing 30 mg for each crushed tablet, which was then dissolved in ethanol up to 10 mL. Centrifugation is carried out for 15 minutes at 300 rpm to separate materials that are insoluble in ethanol. Samples were tested with ten replications of 10 tablets for each formula. The tablet content uniformity test refers to the Ministry of Health of the Republic of Indonesia (2020). If it is a solid dosage form, the concentration of each 10 units must be determined using an appropriate analytical method, and the acceptance value is calculated using the equation:

$$|M - \bar{x}| + Ks$$

M is the reference value, $\bar{x}$ is the average of each content, k is the acceptance constant, and s is the sample standard deviation (Ministry of Health, Republic of Indonesia, 2020).

Linearity Testing

Linearity verification was made using five different concentrations of 0.1, 0.2, 0.3, 0.4, and 0.5 mg/mL. The regression line equation was

made from the five concentrations to produce a regression line equation and R-value.

Verification of Accuracy and Precision Method

Verification of accuracy and precision was carried out using the standard addition method. Four different concentrations were made, consisting of one concentration without the addition of a standard with a concentration of 0.25 mg/mL and three concentrations with the addition of different standard concentrations of 0.05, 0.1, and 0.15 mg/mL, so that the total concentration of each was 0.25, 0.3, 0.35, and 0.4 mg/mL. Each concentration was made up of as many as three replicates, so the SD and CV values were obtained accurately and precisely.

RESULTS AND DISCUSSION

FDT diphenhydramine HCl was formulated with different proportions of crospovidone and copovidone for each formula. The tablet manufacturing was done by the direct compression method. The flow properties of the powder are important as a requirement for molding with the direct compression method. Based on Table 2, the results of powder flow rate testing ≥ 74 g/sec, angle of repose testing ≤ 17.3°, Hausner Ratio, and Carr's Index testing ≤ 1.14 and ≤ 17.12. These parameters need to be fulfilled in making FDT by the direct compress method to obtain flow properties of the powder that meet the requirements, so that when compressed, it can produce FDT dosage forms that meet quality requirements. The greater the angle of repose, it is very possible that there are many pores between the powder particles, and when compressed, it will produce tablets with capping. The angle of repose is very good for less than 30° (British Pharmacopoeia Commission, 2011). The Hausner Ratio and Carr's Index tests were carried out to measure the ability of the powder to experience a reduction in volume when pressure is applied to the powder (Qiu et al., 2017). The Hausner ratio is categorized as very good for 1.00–1.11, good for 1.12–1.18, and sufficient for 1.19–1.25 (British Pharmacopoeia Commission, 2011), and the Carr's index is categorized as very good for 1–10%, good for 11–15%, and sufficient for 16–20% (British Pharmacopoeia Commission, 2011).

Testing the Characteristics of Diphenhydramine HCl FDT Dosage Form

Based on the test results in Table 3, the diphenhydramine HCl FDT dosage form meets the desired criteria. Based on content uniformity testing, all formulas are stated to meet the criteria for acceptance values in Indonesian Pharmacopoeia VI. In tablet hardness, all formulas meet good standards for the hardness of the FDT dosage form, namely 1-3 kP (Fatohy and Abdul-Rasool, 2013). For friability, all formulas meet the good standard of friability of the FDT dosage form, which is less than 1% (Gowtham et al., 2011). For a good FDT dosage form, the disintegration time is less than 30 seconds (Food and Drug Administration, 2008). However, in formulas b and ab, the disintegration time of the diphenhydramine HCl FDT dosage form was more than 30 seconds, so the two formulas did not meet the requirements.

Table 2. Result Flow Properties of Powder Mixtures

Flow Properties	Formula 1	Formula a	Formula b	Formula ab
Flow rate (g/s)	81	74	91	77
Angle of Repose (°)	17.3	16	16	15.6
Hausner Ratio	1.14	1.22	1.14	1.21
Carr's Index	12.19	17.73	12.38	17.12

Table 3. Result of Characteristic Testing FDT Diphenhdyramine HCl

Characteristic	Formula 1	Formula a	Formula b	Formula ab
Hardness (kP)	2.130 ± 0.511	1.420 ± 0.372	1.907 ± 0.392	2.390 ± 0.304
Friability (%)	0.390 ± 0.050	0.367 ± 0.044	0.185 ± 0.039	0.171 ± 0.060
Disintegration Time (s)	29.133 ± 2.579	28.333 ± 0.833	32.600 ± 3.934	42.767 ± 6.005
Wetting Time(s)	43.333± 4.735	32.033 ± 1.150	97.100 ± 1.735	33.067 ± 0.723
Water Absortion Ratio(%)	50.602 ± 0.349	54.010 ± 0.263	49.295 ± 0.781	49.506 ± 1.472

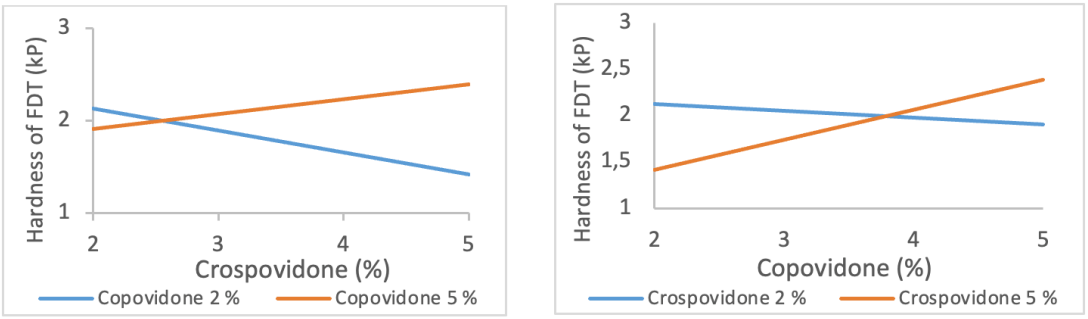
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It is because the addition of binder concentrations in both formulas results in an increase in the disintegration time of the tablet preparation (Chime et al., 2012). A high binder concentration will make the interparticle bonds stronger, so the disintegration time of the tablet will increase. For wetting time, all formulas met the standard for a good FDT dosage form wetting time of 21–159 seconds (Chacko et al., 2010). All formulas for the water absorption ratio met the standard of a good FDT dosage for a water absorption ratio of 44.14%–123.65% (Chacko et al., 2010).

Effect of Crospovidone and Copovidone Composition on Diphenhydramine HCl FDT Dosage Form Characteristics

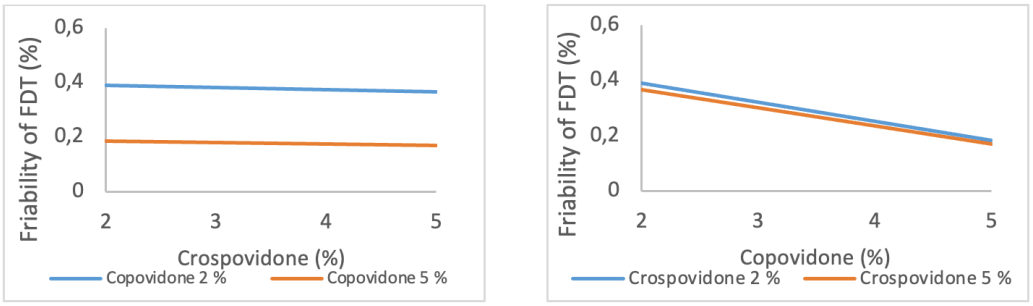
Figure 1 shows the effect of crospovidone and copovidone at the level studied on the hardness of FDT diphenhydramine HCl. Tablet dosage form must fulfill sufficient hardness so that the tablet can overcome the impacts that occur during the packaging and distribution process. On the other hand, the hardness of the tablets produced must also be able to accommodate the disintegration time requirements for the FDT dosage form. The results of the tablet hardness response obtained the following factorial design equation: Y = 3.282 - 0.501 XA - 0.339 XB + 0.1326 XAXB. Based on statistical analysis, the equation can be used to predict the hardness response of the FDT diphenhydramine HCl dosage form. Based on statistical testing, the interaction of crospovidone and copovidone was declared to be the dominant factor affecting the hardness of the FDT diphenhydramine HCl dosage form. Copovidone as a binder had a coefficient value of +0.3735. Crospovidone as a disintegrant had a coefficient value of -0.1135, and the interaction between crospovidone and povidone was the most influential factor because it had the greatest coefficient value of +0.5965. This is presumably due to synergistic interactions between crospovidone and copovidone in increasing tablet hardness. Copovidone is a copolymer consisting of povidone and vinyl acetate, and crospovidone consists of povidone that could interact with vinyl acetate in copovidone, increasing the bond between powder particles and tablet hardness.

Figure 2 shows the effect of crospovidone and copovidone at the level studied on the friability of FDT diphenhydramine HCl. Tablet friability describes the strength of the tablet in maintaining its shape when it receives impacts, for example, during the packaging process. The tablet friability response obtained a factorial design equation: Y = 0.546 - 0.009 XA - 0.070 XB + 0.001 XAXB. Based on statistical analysis, the equation can be used to predict the friability response of the FDT diphenhydramine HCl dosage form. Based on statistical testing, copovidone was declared the dominant factor affecting the friability of the FDT diphenhydramine HCl dosage form. Copovidone as a binder was the most influential factor because it had the greatest coefficient value of -0.05. Crospovidone as a disintegrant had a coefficient value of -0.0185, and the interaction between crospovidone and povidone had a coefficient value of +0.0045.



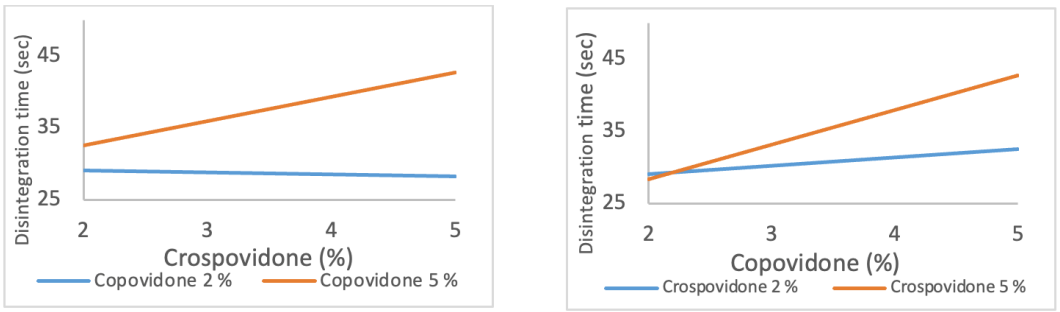
a b

Figure 1. (a) Effect profile of Crospovidone and (b) Effect profile of Crospovidone to hardness of FDT Diphenhydramine HCl



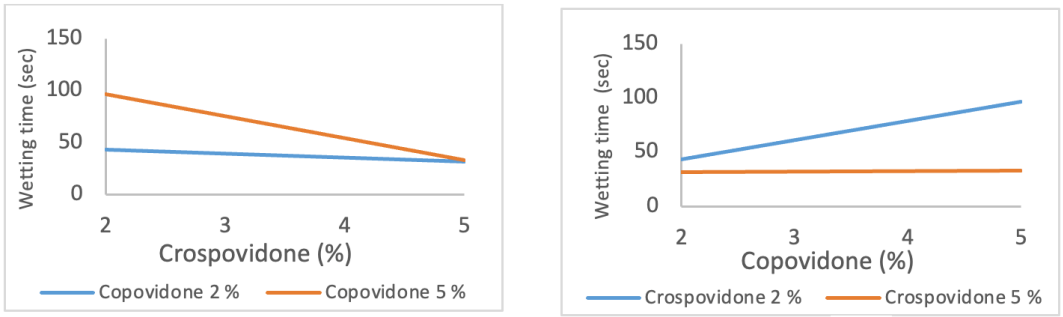
a b

Figure 2. (a) Effect profile of Crospovidone and (b) Effect profile of Crospovidone to friability of FDT Diphenhydramine HCl



a b

Figure 3. (a) Effect profile of Crospovidone and (b) Effect profile of Crospovidone to disintegration time of FDT Diphenhydramine HCl



a b

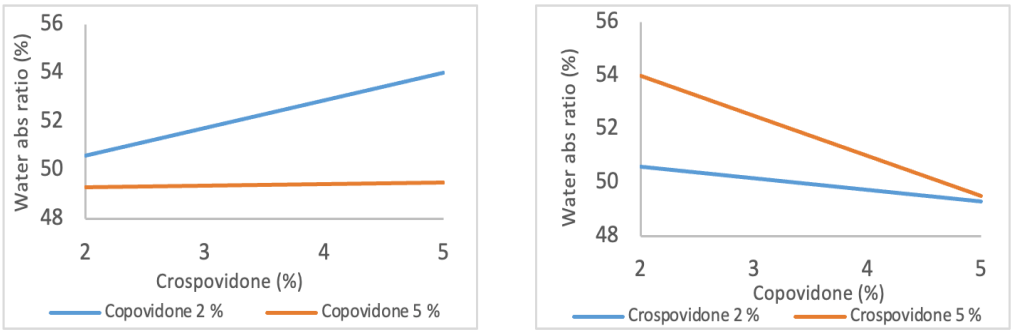
Figure 3. (a) Effect profile of Crospovidone and (b) Effect profile of Crospovidone to wetting time of FDT Diphenhydramine HCl

Figure 3 shows the effect of crospovidone and copovidone at the level studied on the disintegration time of FDT diphenhydramine HCl. The disintegration time is one of the most important physical properties of FDT preparations, because one of the requirements for FDT preparations is to have a fast disintegration time in the oral cavity. The response of tablet disintegration time is obtained from the following factorial design equation: Y = 32.232 - 2.7034 XA - 1.281 XB + 1.218 XAXB. Based on statistical analysis, the equation is stated to be used to predict the disintegration time of the diphenhydramine HCl FDT dosage form. Based on statistical testing, copovidone was declared the dominant and influential factor in the disintegration time of the FDT diphenhydramine HCl dosage form. Copovidone as a binder was the most influential factor because it had the greatest coefficient, +8.950. Crospovidone as a disintegrant had a coefficient value of +4.667, and the interaction between crospovidone and povidone had a coefficient value of +5.483. A higher binder

concentration will make the interparticle bonds stronger, so the disintegration time of the tablet will increase. Copovidone has an irregular structure, so its binding capacity as a binder is getting stronger due to interlocking between particles (Bühler, 2005). In addition, the presence of vinyl acetate makes copovidone more hydrophobic, resulting in an increase in the disintegration time of the tablet (Bühler, 2008).

Figure 4 shows the effect of crospovidone and copovidone at the level studied on the wetting time of FDT diphenhydramine HCl. This test is to determine the time required for the tablet to be wetted by water. The response of tablet wetting time obtained is the following factorial design equation: Y = -8.415 + 7.952 XA + 29.641 XB - 5.859 XAXB. The equation can predict the wetting time response of the diphenhydramine HCl FDT dosage form based on statistical analysis. Based on statistical testing, crospovidone was declared the dominant factor in the wetting time of the FDT diphenhydramine HCl dosage form. Copovidone as a binder had a coefficient value of +27.417. Crospovidone as a disintegrant was the most influential factor because it had a coefficient value of -37.666, and the interaction between crospovidone and povidone had a coefficient value of -26.366. Crospovidone is hydrophilic, so it is easy to attract water and results in a fast tablet wetting time (Bühler, 2005).

Figure 5 shows the effect of crospovidone and copovidone at the level studied on the water absorption ratio of FDT diphenhydramine HCl. This test is to determine the degree of swelling of the tablet when it comes into contact with water. The tablet water absorption ratio response obtained the following factorial design equation: Y = 47.780 - 1.846 XA - 0.274 XB - 0.355 XAXB. Based on statistical analysis, the equation can be used to predict the response of the water absorption ratio of the FDT diphenhydramine HCl dosage form. Based on statistical testing, copovidone was declared the dominant factor affecting the water absorption ratio of the FDT diphenhydramine HCl dosage form. Copovidone as a binder was the most influential factor because it had a coefficient value of -2.9055. Crospovidone as a disintegrant had a coefficient value of +1.8095, and the interaction between crospovidone and povidone had a coefficient value of -1.5985. It is suspected that the vinyl acetate contained in copovidone is hydrophobic, so water will be more difficult to bind and the water absorption ratio of the tablet will be lower (Bühler, 2008).



a b

Figure 5. (a) Effect profile of Crospovidone and (b) Effect profile of Crospovidone to water absorption ratio of FDT Diphenhydramine HCl

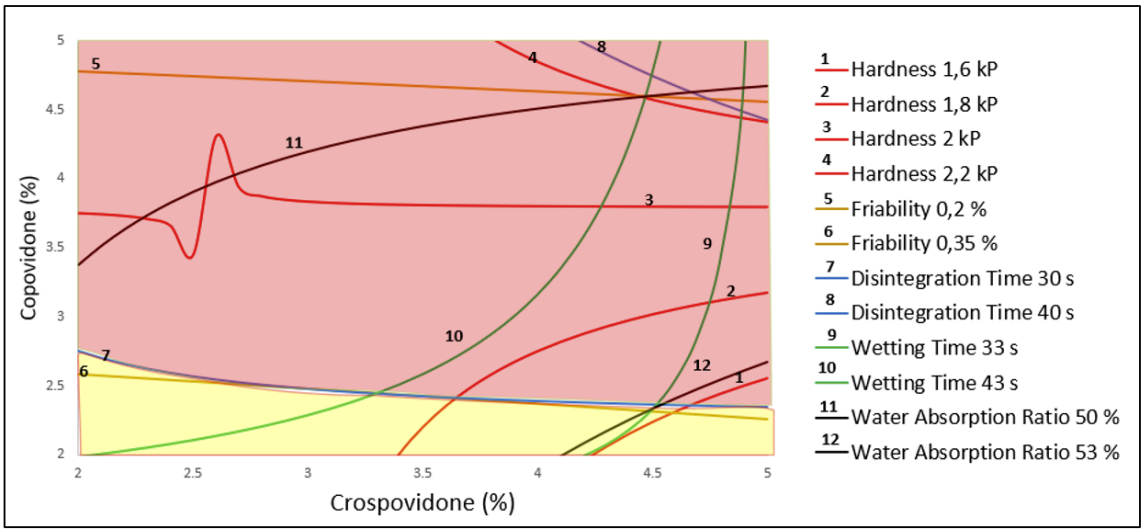


Figure 6. Superimposed contour plot of FDT Diphendyramine HCl

Based on the results of testing the characteristics of the FDT diphenhydramine HCl dosage form, a factorial design equation is obtained for each response. The equation can be made into a contour plot, which is useful for predicting the FDT diphenhydramine HCl dosage form response. A superimposed contour plot is generated from the contour plot so that the composition area of crospovidone and copovidone meets the quality requirements (Figure 6); the yellow area is the optimum area, while the red area is not. At the level studied, the optimum composition area was found, which can be predicted as a diphenhydramine HCl FDT dosage form formula.

Content Uniformity Testing
Method Verification

Method verification consists of linearity, accuracy, and precision. Linearity is done by making a standard curve with five different concentrations. The method is valid if the R-value exceeds 0.995 (Food and Drug Administration, 2014). The R-value obtained is 0.9991, so it can be concluded that the method used has good linearity. To determine accuracy and precision, the standard addition method was carried out. The method used is said to be accurate if the % recovery value is 95–105% with an analyte level of 250 ppm (AOAC International, 2016), while the method is said to be precise if the CV value is less than 3.7% (AOAC International, 2016). Based on the study's results, the accuracy values obtained were 97.405%, 95.086%, and 100.806%, while the precision values were 0.631%, 1.304%, 1.087%, and 0.960%. So from these data, the method is valid in accuracy and precision for concentrations of 0.25 mg/mL–0.40 mg/mL.

Determination of Diphenhydramine HCl FDT Dosage Form Levels

Determination of the dosage form's uniformity can be considered qualified if the acceptance value (NP) is less than 15 as a requirement for content uniformity for active substances with levels ≤ 25 mg or ≤ 25%. This test is done to guarantee the consistency of the dosage units; each formula unit must have an active substance content that approaches the theoretical level. Based on the results obtained, the accepted values of formulas 1, a, b, and ab are 3.24, 7.16, 1.95, and 2.44; it can be concluded that formulas 1, a, b, and ab meet the requirements for dosage uniformity.

CONCLUSIONS

Copovidone is the dominant factor that affects friability, disintegration time, wetting time, and water absorption ratio. At the same time, the interaction between the two is the dominant factor affecting the hardness of the diphenhydramine HCl FDT dosage form. At the level studied, the optimum composition area was found, which can be predicted as a diphenhydramine HCl FDT dosage form formula.

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