

Volume 21 Nomor 1, Januari 2020

eISSN: 2442-5613

Jurnal ILMU DASAR

JID

Terakreditasi SINTA Kemenristekdikti No. 21/E/KPT/2018

Jurnal ILMU DASAR	Vol. 21	No. 1	Hlm. 1 - 72	Jember Januari 2020	eISSN 2442-5613
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Jurnal ILMU DASAR

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Volume 21 Nomor 1 Januari 2020

eISSN 2442 – 5613

Jurnal ILMU DASAR

Terakreditasi SINTA Kemendikbud No. 21/E/KPT/2018 tanggal 9 Juli 2018

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Jurnal ILMU DASAR diterbitkan oleh:
Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Jember.
Terbit sejak Januari 2000 dengan frekuensi penerbitan dua kali setahun (Januari dan Juli).

Alamat Editor/Penerbit:
Jl. Kalimantan 37 Kampus Tegalboto, Jember 68121
Telp. (0331) 334293; Fax. (0331) 330225
E-mail : jjid@unej.ac.id
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Optimization of Povidone K-30 and Sodium Starch Glycolate on Levofloxacin Tablet by Factorial Design

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ABSTRACT

The aim of this study was to determine the effect of binder and disintegrant excipients toward tablet properties of levofloxacin as the latter tends to suffer brittle fracture upon compression. The excipients used were povidone K-30 as the binder and sodium starch glycolate (SSG) as the disintegrant which the tablets were formulated according to factorial design 2² with two factors and two levels on each factor. Four formulas were prepared by wet granulation method using 2 and 4% of each povidone K-30 and sodium starch glycolate in various compositions. Tablet properties were evaluated for its hardness, friability, and disintegration time as well as dissolution profile. The data obtained was statistically analyzed using Minitab® 17 software to optimize the formulation and resulted in different impacts caused by each excipient. Povidone K-30 exhibited an increment in hardness, friability, disintegration time but a decrease indissolution profile of levofloxacin tablet. SSG decreased hardness and disintegration time, but increased friability and dissolution profile of levofloxacin tablet. Overlaid contour plot showed that the optimal formula regarding tablet properties of friability, disintegration time, and dissolution profile is in composition of 2.01% povidone K-30 and 2.01% sodium starch glycolate.

Keywords: levofloxacin tablet, povidone K-30, sodium starch glycolate, factorial design.

INTRODUCTION

Commonly used pharmaceutical dosage form is a tablet and it is available in diverse shapes for oral purpose (Setyawan *et al.*, 2013). Tablet is solid dosage form which contains active pharmaceutical ingredient(s) (APIs) with or without excipient. It is produced by compression with high pressure on powder or granulated mass on a die (Ministry of Health of the Republic of Indonesia, 2014). Tablet properties, such as compressibility, friability, and disintegration time, are influenced by characteristic of excipients and tableting process. Excipients such as binder and disintegration agent can improve tablet manufacturing process to meet required specification (Fatmawati *et al.*, 2017). During compression, both API(s) and excipient(s) can undergo brittle fracture. Brittle fracture is direct consequence of stress released from die wall, tablet powder with low density, and fracture center during decompression. Particles with plastic behavior in tablet powder can absorb stress and improve brittle fracture (Uhumwangho & Okor, 2004).

Levofloxacin is a synthetic, third-generation fluoroquinolone antibiotic agent with broad-spectrum antibacterial activity.

Levofloxacin is used to treat various infections such as community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis, skin and skin structure infection, urinary infection, and acute pyelonephritis (Nazir *et al.*, 2013). Levofloxacin is also known to be slightly soluble in water and tends to suffer brittle fracture that can impact its formulation and dissolution. Levofloxacin is susceptible to break (fragmented) so that it needs binder to improve its physical quality and dissolution rate (Fatmawati *et al.*, 2017).

Polyvinylpyrrolidone, also known as povidone, is normally used as a binder in wet granulation process. It is classified to several types according to its viscosity in aqueous solution that is called as K-value within range of 10-120. Wet granulation using povidone K-30 has characterized to produce harder granules with better flowability dan lower friability (Rowe *et al.*, 2009). A correct amount of binder existed in tablet powder can improve plasticity and increase interparticulate bonding. Therefore, tablet compactibility is increased and tendency for brittle fracture (capping or laminating) can be eliminated (Uhumwangho *et al.*, 2006).

However, increasing binder composition can impact tablet disintegration time significantly as disintegration takes longer time to finish (Chime *et al.*, 2012). To overcome this problem, disintegration agent (abbreviated disintegrant) can be added during process. Disintegrant has major function to reduce the effect of binder and physical treatment during compaction. If high binder composition is present, one should use more effective disintegrant to release API(s) from the tablet form (Mohanachandran *et al.*, 2011).

Superdisintegrant, a new class of disintegrant, is introduced to be more effective and efficient as it possesses greater disintegration effect and mechanical strength (Mohanachandran *et al.*, 2011).

Superdisintegrant acts by absorbing water then swelling to generate pressure outward and cause a tablet to break and disintegrate (Shakar *et al.*, 2012). Sodium starch glycolate (SSG) is one of superdisintegrant which can be used both in direct compression and wet granulation method (Rowe *et al.*, 2009).

Based on aforementioned background, this research was aimed to determine the effect of povidone K-30 as binder and SSG as disintegrant on levofloxacin tablet prepared using wet granulation method. Composition of povidone K-30 and SSG was varied in each formula based on factorial design 2².

Parameters evaluated included hardness, friability, disintegration time, and dissolution profile. All data obtained then were analyzed

with Minitab[®] software to depict tablet's quality profile and predict the optimum formulation.

METHODS

Materials

Materials used in this research were levofloxacin (Shanghai Terpon Chemical Co., LTD., China), povidone K-30 (Sigma Aldrich Co., USA), sodium starch glycolate (Yung ZIP Chemical Co., China), microcrystalline cellulose (Avicel[®] PH-101, FMC Co., USA), and pharmaceutical grade of corn starch, magnesium stearate, and talc.

Formulation

Formulation was designed according to factorial design 2² by two factors on two levels for tablet containing 500 mg of levofloxacin. The factors were povidone K-30 and SSG at two levels of 2 and 4% as low and high concentration, respectively. Hence, four formulas were obtained which the compositions were represented in Table 1. Formula 1 (F1) consisted of povidone K-30 and SSG in lower concentration; F2 consisted of povidone K-30 and SSG in lower and higher concentration, respectively; F3 consisted of povidone K-30 and SSG in higher and lower concentration, respectively. F4 consisted of povidone K-30 and SSG in higher concentration. Tablets were prepared by wet granulation method with aquadest as solvent added. Granule was dried at temperature of 50-60°C and sieved through mesh No. 14-20. Tableting was performed using 13 mm die on tablet hydraulic press by pressure of 9.81 kN. Then, the tablet was evaluated for its properties by parameters of hardness, friability, disintegration time, and also *in vitro* dissolution.

Table 1. Formulations of levofloxacin tablet (mg)

Compounds	Function	F1	F2	F3	F4
Levofloxacin	API	500	500	500	500
Avicel ¹ PH-101	Filler	60	60	60	60
Corn Starch	Filler	40	40	40	40
Povidone K-30	Binder	12.73	13.00	26.02	26.59
SSG	Disintegrant	12.73	26.02	13.00	26.59
Talk	Glidant	6.36	6.50	6.50	6.65
Magnesium stearate	Lubricant	4.77	4.88	4.88	4.98
Aquadest	Solvent	16	16	16	16
Total		636.59	650.40	650.40	664.81

note: F1 (Formula 1); F2 (Formula 2); F3 (Formula 3); F4 (Formula 4).

Evaluation of Tablet Properties

Tablet hardness, friability, and disintegration time were measured in three replications to depict tablet properties. The hardness test was performed using aErweka hardness tester TBH 220 (Germany) upon five tablets from each formula. The tablet hardness was measured in kilogram-force or kilopond (kP).

Value between 4-8 kP is considered to be acceptable (Fatmawati *et al.*, 2017). The friability test was carried out on Erweka friability tester TAP

31914 (Germany). A number of tablets weighed around 6.5 g was rotated at 25 rpm for 4 minutes. The fines were removed first before re-weighing, then weight loss percentage was calculated. The result is acceptable if tablet friability values less than 1% (Türkmen *et al.*, 2018).

The disintegration time was determined with Erweka disintegrator ZT 501 (Germany) which was containing a basket rack assembly with six wire-ended tubes. One tablet was placed in each of six

tubes, followed by a cover disk, then the basket was raised and lowered in medium of 900 mL distilled water at temperature of $37 \pm 2^\circ\text{C}$. Disintegration is considered to be complete when all tablet fragments pass through the mesh and acceptable time is below 15 minutes for uncoated tablet (Schmid & Löbenberg, 2010).

In Vitro Dissolution Test

In vitro dissolution test was conducted using Erweka DT 700 (Erweka, Germany) with basket apparatus in three replicates for each formula. Dissolution medium used 0.1 N HCl in aqueous solution. Each tablet of formula 1-4 was added into 900 mL dissolution medium and stirred at speed of 100 rpm and temperature of $37 \pm 0.5^\circ\text{C}$. About 5.0 mL of dissolution sample was taken at interval of 10, 20, 30, dan 45 minutes then filtered through millipore of 0.45 μm diameter. The filtrate was observed on UV-Vis spectrophotometer (Hitachi UH5300, Japan) at maximum wavelength of levofloxacin ($\lambda = 294.98\text{ nm}$). Obtained absorbance was used to calculate dissolved levofloxacin using a standard calibration curve. Each sample was analyzed in triplicate.

Statistical Analysis

The resulting data were analyzed by one-way analysis of variance (ANOVA) using SPSS 21.0 software (SPSS Inc., USA) with significance limit was set at $\alpha < 0.05$. Minitab[®] 17 (Minitab Inc., Australia) software was used to determine the optimum formula for levofloxacin tablet from hardness, friability, and disintegration time data.

RESULTS AND DISCUSSION

Levofloxacin is known to possess poor tabletability due to its brittleness. It tends to suffer brittle fracture during compaction even with commonly used wet granulation formula (Fatmawati *et al.*, 2017). Adding excipients with plastic properties is believed to be able to overcome brittle fracture issue (Uhumwangho

& Okor, 2004). Therefore, in this study, we suggested alternative formulation for levofloxacin tablet that was prepared using wet granulation method. Factorial design was used to construct our experiment with two factors was analyzed for the effect. The factors were povidone K-30 and SSG as those excipients has been known to affect the properties of levofloxacin tablet. The level was determined at 2 and 4 % because it was within concentration range that allowed in a formulation with specified function of excipient used (Rowe *et al.*, 2009).

Factorial design is the design of choice when experiment is purposed to elucidate the effect of different factors and conditions on the result. Its application on pharmaceutical industry is very useful as the effects of several factors (A, B, C) and their interactions (ab, bc, ac, abc) can be determined simultaneously (Genc & Jalvand, 2008), in this case, with Minitab[®] 17 software. The evaluated properties of levofloxacin tablet are presented in Table 2. Four formulas exhibited tablet hardness in similar value with the lowest one is F3.

However, none these formulas meet the requirement for tablet hardness (within 4-8 kP range). Statistical analysis showed insignificant differences amongst formulas. Those phenomena might be influenced by the type of disintegrant used in this study. Previous study conducted by Prasad & Duraivel (2012) showed that using sodium starch glycolate (Explotab[®]) can increase tablet hardness of glimepiride. Furthermore, Explotab[®] is capable to generate pellets during wet granulation that can bind particle when it is dried. Our result was in agreement with that reference.

Table 2. Result of Tablet Properties Evaluation

Evaluation	F1	F2	F3	F4
Hardness (kP)	17.49 ± 0.03	17.49 ± 0.03	16.56 ± 2.07	17.48 ± 0.00
Friability (%)	1.35 ± 0.16	1.30 ± 0.06	1.27 ± 0.37	0.88 ± 0.01
Disintegration Time (minutes)	8.02 ± 0.23	9.12 ± 0.81	5.91 ± 0.89	4.39 ± 0.10

note: F1 (Formula 1); F2 (Formula 2); F3 (Formula 3); F4 (Formula 4).

The friability test resulted in the similar percentage of weight loss for all formulas. Three out of four formulas showed weight loss greater than 1 % and only F4 that within the criteria requirement. Statistical analysis also indicated that each formula differs

insignificantly ($\alpha > 0.05$). This result might be due to factor of disintegrant type. A study with starch pellets and Explotab[®] produced tablet with higher friability than other disintegrant (Mehta *et al.*, 2011).

In the disintegration test, it was observed

that tablet disintegrated completely less than 10 minutes in four formulas. The result complies to United States Pharmacopeia (USP) criteria that disintegration time is less than 15 minutes (Schmid & Löbenberg, 2010). Every formula demonstrates statistically significant differences ($\alpha < 0.05$).

The dissolution profiles are depicted in Figure 1. Each formula has specific profile, responding to different composition of povidone K-30 and SSG. Percentage of dissolved levofloxacin for F1, F2, F3, and F4 after 45 minutes dissolution test was 93.87 ± 0.67 , 89.69 ± 0.60 , 105.06 ± 1.40 , and $90.68 \pm$

0.58 %, respectively. This result was used for further statistical analysis both with ANOVA and Minitab® software due to compendia requirement for levofloxacin in tablet dosage form. dissolution rate at 45 minutes.

Specification of levofloxacin tablet refers to the United States Pharmacopeia and National Formulary (USP-NF) which is declared that concentration of levofloxacin should be more than 80 % at 45 minutes (The USP Convention, 2011), so that all formulas meet the requirement. Statistical analysis exhibited significant differences ($\alpha < 0.05$).

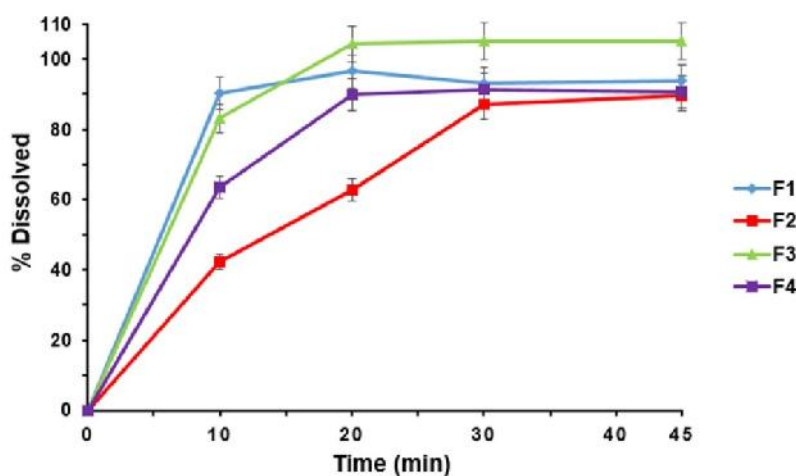


Figure 1. Dissolution profile of levofloxacin tablets in 0.1 N HCl at 37 ± 0.5 °C.

F1 (Formula 1); F2 (Formula 2); F3 (Formula 3); F4 (Formula 4).

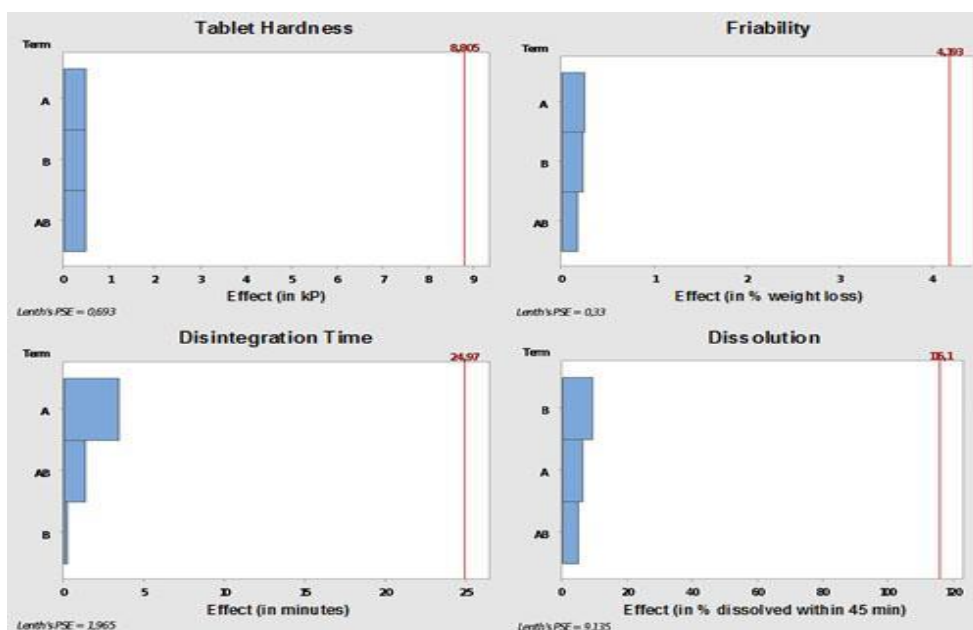


Figure 2. Pareto charts of the effect of povidone K-30 (A) dan SSG (B) as individual factor or in combination (AB) toward levofloxacin tablet properties.

Statistical analysis was further carried out using Minitab® 17 software to determine the effect of the excipients used by graphical presentation. Pareto chart is used to measure statistically the effect of adding povidone K-30 and SSG on tablet hardness, friability, disintegration time, and dissolution and it is given in Figure 2. A chart that crosses the red line is assumed to have significant effect on the parameter calculated. However, as it can be seen in Figure 2, no graphic crosses the red line. Thus, pareto chart analysis indicates that povidone K-30 and SSG do not have major impact on tablet properties and dissolution of

levofloxacin tablet.

Another graphic obtained from Minitab® 17 was main effect plot which shows the impact of different level in concentration of povidone K-30 and SSG. Figure 3 shows that an increase in tablet hardness, friability, and disintegration time occurs as concentration of povidone K-30 increases, however a decrease in percentage dissolved is observed during 45 min dissolution. It also shows that higher level of SSG decreases tablet hardness and disintegration time yet increases friability and dissolution of the tablet.

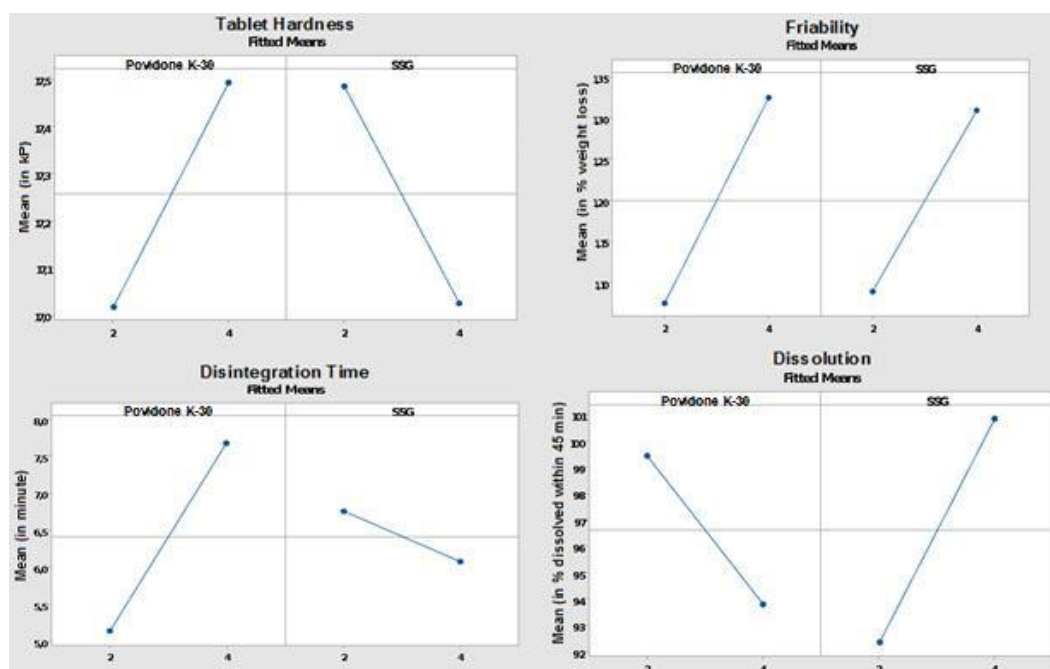


Figure 3. Main effect charts of the effect of povidone K-30 and SSG in two levels toward levofloxacin tablet properties (-1, low level; +1, high level).

Contour plot was also obtained (Figure 4) and it is used to see 3D relationship between povidone K-30 and SSG on levofloxacin tablet properties and dissolution rate. Darker zone represents higher effect on the test conducted. In hardness testing, low concentration of SSG followed by povidone K-30 level increment can increase tablet hardness. Combination of high povidone K-30 concentration with higher concentration of SSG will raise tablet friability. As for disintegration time, it takes longer on increasing level of povidone K-30 in high SSG

concentration. Dissolution is enhanced in low povidone K-30 and higher SSG concentration.

If those contour plots are overlaid together, it will help us to predict the optimum formula to manufacture levofloxacin tablet using povidone K-30 and SSG as it can be seen in Figure 5. The overlay excludes hardness data due to the mismatch of the result to the requirement. White zone on the graphic is the feasible area, thus, the optimum composition of povidone K-30 and SSG for levofloxacin tablet formulation are 2.01 and 2.01 % respectively.

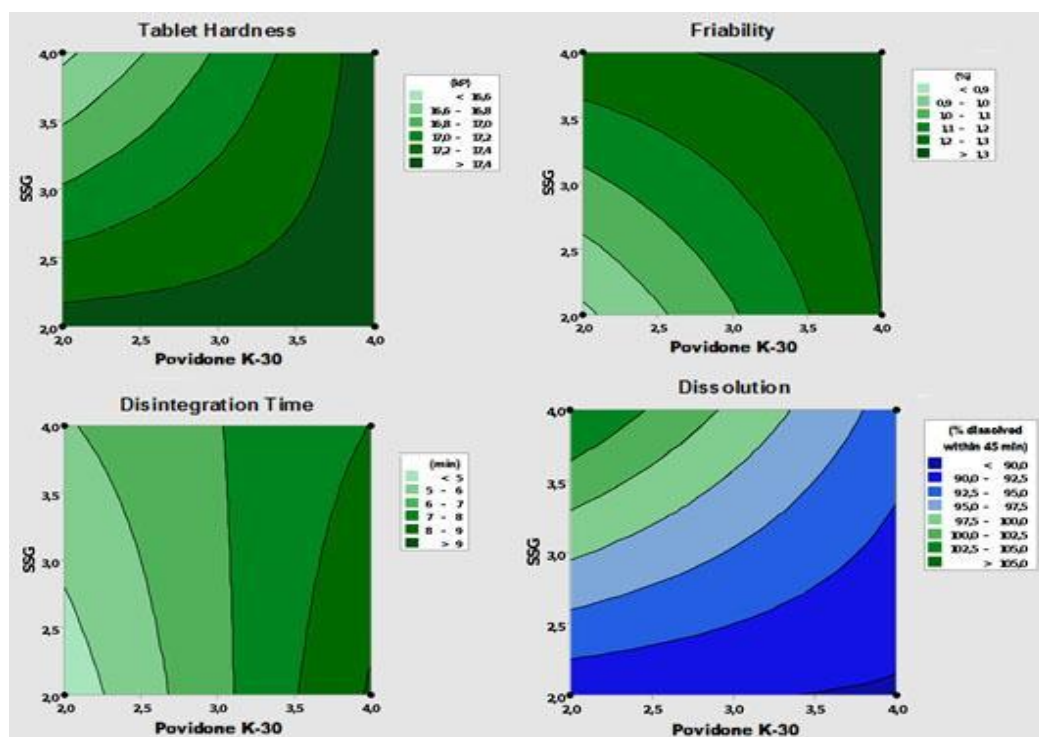


Figure 4. Contour plots of the effect of povidone K-30 and SSG in two level on levofloxacin in tablet properties (2.0, low level; 4.0, high level).

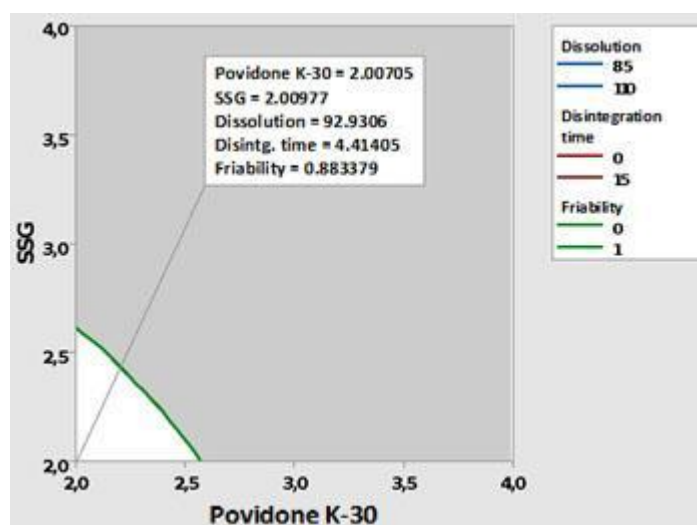


Figure 5. Overlaid contour plot of tablet hardness, friability, and dissolution to determine the optimum formula for levofloxacin tablet.

CONCLUSION

Povidone K-30 and sodium starch glycolate (SSG) were used in this research to improve levofloxacin brittleness and were proved to impact tablet properties and dissolution rate. Povidone K-30 increases tablet hardness and friability, lengthens disintegration time, but reduces dissolution rate. In addition, SSG

reduces tablet hardness, slightly shortens disintegration time, and increases friability and dissolution rate. Prediction of the optimum formulation is allowed from overlaid contour plot that resulted in composition of 2.01 % povidone K-30 and 2.01 % SSG to produce levofloxacin tablet with good tablet properties.

ACKNOWLEDGEMENT

The authors would like to acknowledge Novapharin Pharmaceutical Industries for providing levofloxacin and excipients used in this research.

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