DOKUMEN KORESPODENSI

Nama Jurnal : **ACS Omega**
Judul : **Tablet Formulation of 2-((3-(Chloromethyl)benzoyl)oxy)benzoic Acid by Linear and Quadratic Models**
Publisher : ACS Publications
Volume/Issue : 7(38)
Tahun : 2022
DOI : https://doi.org/10.1021/acsomega.2c03147
Index : SJR(2022) 0.694
Penulis Pertama : Wuryanto Hadinugroho
Penulis Korespodensi : Wuryanto Hadinugroho
Tahapan & Lampiran :

No.	Tahapan	Waktu
1.	**Submission to ACS Omega** Email success submitted Manuscript draft	**20-05-2022**
2.	**First revision request** Email first revision request from reviewer Email first revision request from editorial	**16-06-2022**
3.	**Submission of first revision to ACS Omega** Email success submitted first revision Manuscript draft first revision Response to reviewers comments (first revision)	**06-07-2022**
4.	**Second revision request** Email second revision request from reviewer	**02-08-2022**
5.	**Submission of second revision to ACS Omega** Email success submitted second revision Manuscript draft of second revision Response to reviewers comments (second revision)	**03-08-2022**
6.	**Third revision request** Email third revision request from editorial	
7.	**Submission of third revision to ACS Omega** Email success submitted third revision Form Author Charge Manuscript draft of third revision Response to reviewers comments (third revision)	**15-08-2022**
8.	**Accepted for publication** Email accepted for publication	**17-08-2022**
9.	**Journal publishing agreement request** Email Journal publishing agreement request	**17-08-2022**
10.	**Journal publishing agreement received** Email journal publishing agreement received	**18-08-2022**
11.	**Review proof request** Email review proof request	**25-08-2022**
12.	**Corrections proof received** Email corrections proof received Paper proof accepted	**30-08-2022**
13.	**Paper publish** Email paper publish	**13-09-2022**

Hadinugroho, Wuryanto ao-2022-031476 - Manuscript Submission to ACS Omega 20-May-2022

Dari: ACS Omega (onbehalfof@manuscriptcentral.com)

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Tanggal: Jumat, 20 Mei 2022 pukul 22.41 GMT+7

20-May-2022

Journal: ACS Omega
Manuscript ID: ao-2022-031476
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
Authors: Hadinugroho, Wuryanto; Foe, Kuncoro; Tjahjono, Yudy; Caroline, Caroline; Esar, Senny; Jessica, Maria
Manuscript Status: Submitted

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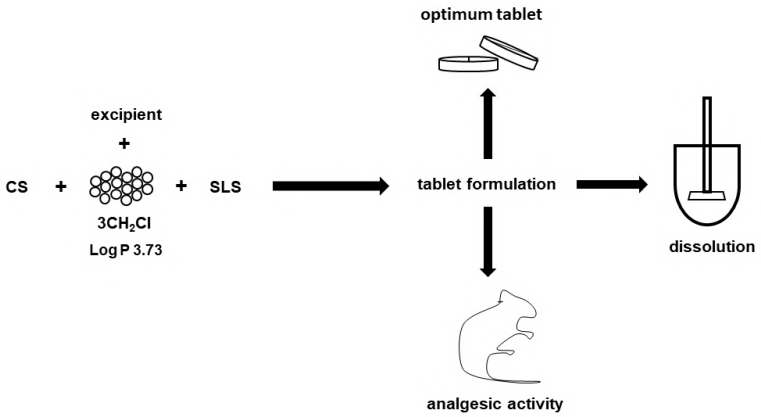
Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Journal:	*ACS Omega*
Manuscript ID	Draft
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Pharmacy Foe, Kuncoro; Widya Mandala Catholic University Surabaya Tjahjono, Yudy; Widya Mandala Catholic University Surabaya, Pharmacy Caroline, Caroline; Widya Mandala Catholic University Surabaya, Pharmacy Esar, Senny; Widya Mandala Catholic University Surabaya, Pharmacy Jessica, Maria ; Widya Mandala Catholic University Surabaya, Pharmacy



338x190mm (96 x 96 DPI)

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

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Abstract

Purpose: This research to determine the effect of sodium lauryl sulfate (SLS) as surfactants, croscarmellose sodium (CS) as a disintegrating agent, and SLS-CS combinations on 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) (log P = 3.73) tablet formulations. In addition, this study aims to determine the optimum of the $3CH_2Cl$ tablet formula.

Methods: The tablets are manufactured through direct compression according to the simplex lattice design. The optimal SLS and CS concentration was determined in-vitro using linear and quadratic models to achieve better tablet disintegration and dissolution.

Results: The same linear and quadratic coefficient profiles of SLS and CS indicate that the combined coefficient of SLS-CS with a quadratic model can be used to predict the effect of the SLS-CS combination. Based on the linear model coefficients, SLS and CS increase the value of flow time (9.35; 7.65), Carr index (26.17; 21.17), hardness (9.84; 7.44), friability (0.38; 0.31), disintegrating time (5.74; 2.62), and drug release (84.28; 58.65). The quadratic model coefficient shows that SLS-CS combinations increase flow time (0.60), Carr index (2.00), hardness (1.00), and disintegrating time (1.04). Meanwhile, SLS-CS combinations decrease friability (-0.02) and drug release (-9.10).

Conclusion: SLS, CS, and SLS-CS combinations affect the quality of tablets mass and tablets. The optimum tablet formula was $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and SDL (ad 800 mg). The $3CH_2Cl$ has analgesic activity despite the presence of tablets excipients and new alternatives to the future analgesic drug.

Introduction

The 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) is a new compound synthesized from acetylsalicylic acid and 3-chloromethyl benzoyl chloride.[1,2] $3CH_2Cl$ is very potential as an analgesic, an anti-platelet aggregation, and an anti-inflammation drug.[1,2] A previous study reported that the active compound of $3CH_2Cl$ could significantly reduce the nociceptive response in mice.[2] The C_{max} value of $3CH_2Cl$ is 0.57 µg/mL. It indicates the ability of $3CH_2Cl$ to distribute and perfuse widely into the very deep interstitial and intracellular parts of the tissue. However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73 [3]. While the optimal log P value of water-soluble compound during tablet formulation is theoretically between 2-3,[4] the reported log P value of $3CH_2Cl$ indicates the difficulties of this active compound for water-solubility.

Tablet form is one of the candidates in $3CH_2Cl$ formulation. Tablets may inhibit the hygroscopic character of $3CH_2Cl$ when stored. Tablet formulation requires the addition of several compounds such as surfactants to overcome the lipophilic character of the $3CH_2Cl$. Tablet formulation also needs a disintegrant to accelerate the dissociation of $3CH_2Cl$. The surfactants and disintegrant agents commonly used in the tablet formulation are sodium lauryl sulfate (SLS) and croscarmellose sodium (CS). The SLS has several characteristics, such as the hollow surface of the particles, easily soluble, and slight oily fatty.[5] The surface of CS has several characteristics such as a thread-root-like form, water-insoluble, and rapidly swells when hydrates.[5] The SLS is expected to accelerate the hydration of the tablet surface and increase the solubility of $3CH_2Cl$ and excipient particles. The CS is expected to accelerate the disintegration of tablets. However, the effect and the optimal amount of SLS and CS for the tablet formulation of $3CH_2Cl$ remain unclear. The novelty of this experiment is the tablet formulation of $3CH_2Cl$ using SLS as a surfactant and CS as a disintegrating agent in tablets. SLS and CS overcome $3CH_2Cl$ lipophilic problems on tablet disintegration and dissolution.

This experiment aimed to determine the effect of SLS, CS, and SLS-CS combinations for the formulation of $3CH_2Cl$-tablet. In addition, this study aims to determine the optimum of the 3CH2Cl tablet formula. The effect of SLS, CS, and SLS-CS combinations was analyzed using linear and quadratic models following the simplex lattice design. It is believed that CS can accelerate the disintegration of tablets, while SLS increases hydrated tablets and the solubility of $3CH_2Cl$. This manuscript demonstrated that the tablet form of $3CH_2Cl$ using CS and SLS exerts an analgesic activity in mice writhing test. $3CH_2Cl$-tablet provides a new form of drug, which is a potential for an analgesic drug.

Material and methods

Raw materials and chemicals

The experiment used the following materials: salicylic acid (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (Sigma-Aldrich, GmbH, USA), pyridine (Merck KgaA, Darmstadt, Germany), ethanol (Merck KgaA, Darmstadt, Germany), neusilin (Gangwal Chemicals, India), croscarmellose sodium (FMC Biopolymer, USA), microcrystalline cellulose (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (Foremost Farm, USA), sodium hydroxide (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (Merck KgaA, Darmstadt, Germany), and distilled water (Brataco Chemical, Indonesia).

Synthesis and characterization of $3CH_2Cl$

Salicylic acid (1.8 mmol), 3-chloromethyl benzoyl chloride (7.2 mmol), pyridine (1.7×10^{-6} mmol), and acetone (14.8×10^{-6} mmol) were mixed homogeneously in Erlenmeyer. The mixture was microwave irradiated for 5 minutes with a Millstone Organic Synthesis Unit (MicroSYNTH). The mixture was then placed in a microwave oven (600 Watt, 1 minute).

Afterwards, the mixture was evaluated with ferric chloride ($FeCl_3$) and thin-layer chromatography (TLC) (silica gel F254 stationary phase and n-hexane: ethanol (1:2) mobile phase). This test is to identify the salicylic acid in the mixture. At the beginning, pasta was prepared and then turned into a solution when irradiated by microwaves, and the final product was solid. The synthesis procedure followed the previous experiment, and the stability of $3CH_2Cl$ was proven.[1,2] Based on these reasons, the compound $3CH_2Cl$ can be used for tablet formulation.

Preparation of tablets

The tablet ingredients were weighted using the formula (Table 1) and the direct compression method. The process began by mixing $3CH_2Cl$ with Ne using a mortar and stamper until homogeneous. The mixture was transferred to a cubic mixer and added with SLS, CS, MCC, and SDL to rotate for 2 minutes at 100 rpm (Erweka). The homogeneous tablet mass was to test flowability and compressibility. The homogeneous tablet mass was compressed to form tablets (800 mg) with a single punch machine (Jenn Chian Machinery, Taiwan). Tablets were evaluated for hardness, friability, disintegration time, and drug dissolution.

Flow time

The mass of the tablet was weighed at 100 g and placed on a flowability tester funnel (Erweka, Germany). The funnel valve opened to drain the tablet mass and determine the flow time parameter. The cone of the tablet mass was scanned by infrared to determine the parameter of the angle of repose.

Compressibility

The glass measuring tube (100 mL) was weighted and recorded. Then, tablet mass was inserted to a glass measuring tube (100 mL) inclined (35^0-40^0). The glass measuring tube filled with the tablet mass was weighed and recorded. The glass measuring tube loaded the tablet mass was placed on a density tap volumeter (Erweka, Germany) and tapped 500 times. The initial and final volumes of tablet mass were recorded to determine the bulk density and tap density. Bulk density is the ratio of the tablet mass to the initial volume, while tap density is the ratio between the tablet mass and volume. Determination of the Carr index value follows Equation 1.[6]

$$Carr\ index\ (\%) = \frac{tap\ density - bulk\ density}{tap\ density}\ x\ 100\% \qquad \text{Equation 1}$$

Hardness

Tablets (6) were randomly selected from all tablets[7,8] and placed in a hardness tester (Schleuniger, Netherlands). The tablet was pressed by a metal rod until the tablet cracked or broke. The hardness of the tablet can be read on the monitor hardness tester.

Friability

Tablets were randomly selected up to a total weight of more than 6500 mg.[7,8] All tablets were dust-free for careful weighing (Wo). The tablets were rotated on a drum friability tester (Erweka, Germany) for 4 minutes at 25 rpm. The tablets were dust-free and carefully reweighed (W1). The value of tablet friability is the difference between the total weight of the initial tablet and the total weight of the final tablet compared to the total weight of the initial tablet. Determination of the friability value follows Equation 2.

$$friability\ (\%) = \frac{Wo - W1}{Wo}\ 100\% \qquad \text{Equation 2}$$

Disintegration time

Tablets (18) were selected, and six of which were randomly selected.[7,8] Tablets were placed in each tube of the disintegration tester (Erweka Z3, Germany). The cylinder moved up and down in the chamber containing distilled water at 37^0C and 900 mL. Disintegration time is the time required by six tablets for no particles/fragments to remain in the mesh in each tube.

Dissolution

Each tablet was placed in a vessel of dissolution tester (Electrolab TDT-08L, India) containing phosphate buffer medium pH 6.8 (37 ± 0.5 C; 50 rpm; 900 mL) using the basket method for 60 minutes.[9,10] A sampling of the release of $3CH_2Cl$ (5 mL) was done at 10, 20, 30, 45, and 60 minutes. The concentration of the dissolved active compound was analyzed using UV-VIS spectrophotometer (Hitachi U-1900, Japan) at the maximum wavelength.

Optimization

The optimization of the tablet formula was generated using the simplex lattice design with a two-factor method. The working concentration of SLS is 0.5%-1%, and CS is 2%-4%. The experiment used three formulas (Table 1) with the proportion of 0.50:4.00 (called TA), TB 0.75:3.00 (called TB), and TC 1.00:2.00 (called TC). Flow time, Carr index, hardness, disintegrating time, and drug release were used as the optimization parameters. The optimization response was analyzed *in-silico* (Design Expert ver.10) to predict the tablet formula of $3CH_2Cl$.

Release kinetics of $3CH_2Cl$ from tablet

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using the following equations 3-6:[11–14]

First order $:\ln Q_t = \ln Q_o + K_o.t$ Equation 3

Qt: the amount of drug dissolved at the time (t), Qo: the initial drug, and Ko: constant drug release.

Higuchi : $Q_t = K_H.\sqrt{t}$ Equation 4

K_H: Higuchi constant and t: time.

Korsmeyer-Peppas : $Q_t/Q_\infty = K_k.\ t^n$ Equation 5

Q_t/Q_∞: fraction of drug released, K_k: Korsmeyer-Peppas constant, and n: diffusion exponential.

Weibull : $\log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve.

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using DDSolver software.

Analgesic activity by writhing test

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g BW) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g BW) or the comparator (2.05 mg/20 g BW) was given in another group. The Writhing behavior was observed within 10 minutes.

Result and discussion

Characterization of $3CH_2Cl$

Infrared spectra show the ester peak C=O at 1732.10 cm^{-1}, while the peak C-O at 1298.22 cm^{-1}, 1279.16 cm^{-1}, and 1262. 18 cm^{-1}. The carboxylate peak C=O appeared at 1694.90 cm^{-1}, while C-O at 1262.18 cm^{-1}. The peak C=C was aromatic at 1606.29 cm^{-1}, and the peak C-Cl at 704.24 cm^{-1}. The Rf value of thin layer chromatography $3CH_2Cl$ compound in the mobile phase of ethyl acetate:ethanol (1:2) is 0.91; n-hexane:ethanol (1:2) is 0.82; and chloroform:ethanol (4:1) was 0.87. The melting point value of $3CH_2Cl$ is at 109-111°C.

Formulation of $3CH_2Cl$ tablets

The $3CH_2Cl$-tablet formula was used excipients Ne, SLS, CS, MCC, SDL. Ne was used to prevent the coagulation of $3CH_2Cl$.[16–18] The SLS-CS combination improved the flowability of $3CH_2Cl$. SLS can accelerate the tablet hydration through disintegration or dissolution media. SLS also lowered the surface tension of $3CH_2Cl$ particles with a hydrating medium, thereby accelerating the solubility of the particles.[19–21] CS can swell when interacting with a hydrating-medium so that the surrounding particles were pushed, resulting in the tablet disintegration.[22–24] The MCC was used as a tablet filler for excellent tablet compatibility, while SDL was used as a high-density filler to adjust the tablet with optimal thickness.[25–27] Both MCC and SDL were ideal excipients for the direct compress method.

Determining the flow time value of $3CH_2Cl$ tablet mass

The flow time values of the three tablet mass formulas are shown in Table 2. All formula has a flow time value of less than 10 seconds. It means the tablet mass can move freely and fill the tablet machine dies.[6] The TA (7.6 seconds) formula has the fastest flow time, followed by TB (8.6 seconds) and TC (9.3 seconds) formula. The coefficient value (Table 3)

from the simplex lattice design method with a linear model shows that SLS (9.35) was dominant in increasing tablet mass flow time, followed by CS (7.65). The linear model coefficient is acceptable based on statistical analysis (see supplementary Table 6). The ANOVA results from the quadratic model show a coefficient profile similar to the linear model, where the coefficients of SLS (9.30) and CS (7.60) increased the tablet mass flow time. Through a quadratic model, the combination coefficient of SLS-CS (0.60) shows that the SLS-CS combinations increased the flow time, but the SLS-CS combinations were not as dominant as SLS and CS.

The hollow form of SLS particles caused the surface of the particles to become rough, which might inhibit the movement and increase the flow time of the tablet mass. The shape of CS particles, such as thread roots, made the particles difficult to move and increases the flow time. In addition, this character can inhibit the movement of other particles of the tablet mass component. The screw root shape of the CS particles can fill the hollow of the SLS particles so that the combination particles have a flatter surface and reduce the resistance to movement of the tablet mass.

Determining the Carr index value of $3CH_2Cl$ tablet mass

The Carr index values of the three tablet mass formulas are shown in Table 2. The TA and TB formulas have a Carr index value of less than 25%, indicating that the tablet mass was good enough to flow and move slightly and to achieve a stable arrangement in the dies chamber of the tablet machine. The TC formula has a Carr index value of more than 25%, indicating that the tablet mass can flow. The particles required more movement to achieve a stable arrangement in the tablet machine dies space. The simplex lattice design-method linear model could generate the coefficient values as presented in Table 3. Meanwhile, SLS (26.17) was the most dominant in increasing the Carr index, followed with CS (21.17). The linear model

coefficient was acceptable based on statistical analysis (see supplementary Table 6). Quadratic model ANOVA had a coefficient profile similar to the linear model. The coefficients of SLS (26.00) and CS (21.00) increased the Carr index of the tablet mass. The quadratic model resulted in the SLS-CS combinations coefficient (2.00), showing that SLS-CS increases the Carr index. The SLS-CS combinations were less dominant than SLS and CS.

The Hollow SLS particles caused brittle particles. Therefore, when particles were subjected to mechanical stress, the particles could break into smaller sizes. The small SLS particles were difficult to flow while producing much porosity in a stable arrangement. The screw root shape of CS particles caused the tablet mass to be difficult to move and have large porosity in a sturdy structure. The CS particles that fill the cavity of SLS particles can improve the surface morphology of the particles. Still, the remaining part of the CS particles outside the hollow can break into fine particles. Smaller CS particle size can inhibit tablet mass flow.

Determining the hardness of $3CH_2Cl$ tablets

The tablet hardness of each formula is shown in Table 2. TC formula tablets were the hardest, followed by TB and TC formula tablets. TC formula tablets had the strongest interlocking between particles among other formula tablets. The simplex lattice design method with a linear model produced the coefficient values (Table 3), while SLS (9.84) was the most dominant in increasing the tablet hardness, followed by CS (7.44). The linear model coefficient was acceptable based on statistical analysis (see supplementary Table 6). The quadratic ANOVA model had a coefficient profile similar to the linear model. SLS (9.76) and CS (7.36) coefficients increased tablet hardness. The quadratic model produced an SLS-CS combination coefficient (1.00), indicating the SLS-CS combinations increased tablet hardness.

The $3CH_2Cl$, Ne, SLS, and CS particles filled random porosity between MCC and SDL particles. When the tablet mass was compressed, a tablet with solid interlocking and little

porosity was formed. The cavity of SLS particles broke when compressed into tablets. Tablets had strong interlocking between particles and little porosity. The screw root shape of the CS particles caused the interlocking between the particles in the tablet to become elastic withstand mechanical stress. The CS particles that filled the SLS particle cavity caused the combination particles to become stronger and more elastic. The resulting tablet had strong interlocking and can withstand mechanical stress.

Determining the friability of $3CH_2Cl$ tablets

The tablet friability of each formula is shown in Table 2. The TC formula tablets were the most brittle, followed by TB and TC formula tablets. Although the tablet formula TC was the hardest, the tablet TC was the most brittle because the interlocking between the particles on the tablet surface cannot withstand mechanical movements. The simplex lattice design method with a linear model produced the coefficient values presented in Table 3, where SLS (0.38) was the most dominant in increasing tablet friability, followed by CS (0.30). The linear model coefficient was acceptable based on statistical analysis (see supplementary Table 6). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (0.38) and CS (0.31) increased tablet friability. The quadratic model resulted in an SLS-CS combinations coefficient (-0.02), indicating that the SLS-CS combinations decreased tablet friability.

The tablet constituent particles on the tablet surface and the interlocking which were not strong can be released when subjected to mechanical movement. SLS particles were at risk of breaking and forming fine particles when compressed because SLS particles are hollow. If the fine particles are on the tablet surface, the fine particles are released when receiving mechanical movement. The screw shape of the CS particles on the tablet surface was difficult for the particles to maintain interlocking when receiving mechanical movements. Particle

combination between SLS and CS particles on the tablet surface can support interlocking with other particles that make up the tablet to withstand mechanical movements.

Determining the disintegration time of $3CH_2Cl$ tablets

The tablet disintegration time for each formula is shown in Table 2. The TA formula tablets were the fastest to disintegrate, followed by TB and TC formula tablets. TA formula tablets contained the highest CS so that the more CS particles hydrate and swollen, caused the tablet to disintegrate quickly. The simplex lattice design method with a linear model produced the coefficient values (Table 3). SLS (5.74) was the most dominant ingredient in increasing tablet friability, followed by CS (2.62). The linear model coefficient was acceptable based on statistical analysis (see supplementary Table 6). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (5.65) and CS (2.53) increased tablet disintegration time. The quadratic model resulted in an SLS-CS combination coefficient (1.04), indicating that the SLS-CS combination increased the tablet disintegration time.

Changes in SLS particle size and the formation of fine particles when the tablet mass was compressed caused the tablet to have a dense porosity. The disintegrating medium was difficult to penetrate the tablet and slow down the disintegration. CS particles can function as disintegrants if particles are hydrated and swell. CS particles needed time to hydrate and swell all the particles so that the tablet disintegrates longer. The SLS-CS combinations particles narrowed the porosity of the tablet so that there was less passage for the disintegrating medium. In addition, tablet hardness increased the disintegration time because the hard tablet had narrow porosity, so the disintegrating medium was difficult to penetrate the tablet.

Determining the drug release of $3CH_2Cl$ tablets

Drug release from each tablet is shown in Table 2 and a detailed profile in Figure 1 (see supplementary Table 5). Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. The TC formula tablets contained the highest SLS, reducing the surface tension between the $3CH_2Cl$ particles and the dissolution medium. The simplex lattice design method with a linear model resulted in the coefficient values as presented in Table 3, where SLS (84.28) was the most dominant in increasing drug release, followed by CS (58.65). The linear model coefficient was acceptable based on statistical analysis (see supplementary Table 6). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (85.04) and CS (59.41) increased the release of $3CH_2Cl$. The quadratic model resulted in an SLS-CS combinations coefficient (-9.10), indicating that the SLS-CS combinations decreased the solubility of $3CH_2Cl$.

Hollow SLS particles can accelerate the solubility of SLS. The dissolved SLS particles reduced the surface tension of the $3CH_2Cl$ particles with the dissolution medium. Swelling CS particles forced the tablet to disintegrate into tiny particles, thereby increasing the surface area of the $3CH_2Cl$ particles in contact with the dissolution medium. SLS-CS combination particles have a narrow porosity, so the medium was difficult to hydrate other particles and inhibits the solubility of $3CH_2Cl$ particles.

Simplex lattice design and ANOVA of $3CH_2Cl$ tablets

This experiment used the simplex lattice design because the optimization factor for the concentration of SLS and CS is an internal factor of the tablet formula, without any external factors. Linear and quadratic models were used to support each other in predicting the effect of SLS, CS, and a combination of SLS-CS (Table 3 and Figure 2). ANOVA from a linear model

can provide R-Squared, Adj R-Squared, Pred R-Squared, and Adeq Precision values to evaluate the model's acceptability. The coefficient of the polynomial equation of the linear model is accepted if the difference between R-Square and Pred R-Square is less than 0.2 and Adeq Precision is more than 4. Thus, the polynomial coefficients can be used to predict the effect of SLS and CS. The weakness of the linear model is that it cannot predict the impact of the combination of SLS with CS. The quadratic model can produce polynomial coefficients for the influence of SLS, CS, and SLS-CS combinations. However, the quadratic model cannot represent ANOVA parameters like a linear model because of the limited experimental formulas. The effort to maximize these two models in predicting the effect of SLS, CS, and SLS-CS combinations by analyzing the similarity of SLS and CS coefficients is critical. The profiles of the SLS and CS coefficients from the two models are similar. In that case, the coefficient values of the SLS-CS combination in the quadratic model can be used to predict the effect of the SLS-CS combination. The profiles of SLS and CS were similar, so that the coefficient values of SLS-CS combined in the quadratic model can be used to predict the effect of the SLS-CS combination on the tablet formulation parameter of the $3CH_2Cl$. Both models are beneficial for experiments using a limited number of formulas due to the availability of $3CH_2Cl$ synthesized by laboratory capacity. Prediction of the optimum formula in this experiment was done numerically according to a linear model, and predicted optimum formula and quality are presented in Table 2.

Release kinetics of $3CH_2Cl$ tablets

The release kinetics models of $3CH_2Cl$ from tablets were analyzed using DDSolver. Rsqr_adj shows the correlation between dissolution time and release of $3CH_2Cl$. MSE_root determinated the correlation analysis correction, while AIC demonstrated the suitability of the

equation for determining the release kinetics model.[28–31] The results of the DDSolver analysis are shown in Table 4 and Figure 3 (detail see supplementary Figure 5-7).

The TA and TC formulas following the Weibull release kinetics model show that $3CH_2Cl$ was released from the tablet without any delay. The presence of SLS lowered the surface tension of $3CH_2Cl$ with the dissolution medium so that the particles dissolved quickly. This was also supported by the presence of CS, which accelerates the disintegration of tablets into granules or particles thereby expanding the surface of the particles to dissolve.

The Higuchi release kinetics model of TB formula shows that the release was influenced by the diffusion mechanism of $3CH_2Cl$ out of the tablet. SLS on the tablet surface accelerated hydrating and was followed by the formation of a hydration layer so that the particles dissolve and leave the tablet. CS served as a disintegrating agent after hydrating and swelling. This condition took time, so that $3CH_2Cl$ was allowed to dissolve and diffuse before the CS can function.

The $3CH_2Cl$-tablet showed analgesic activity in mice writhing test

This experiment was conducted to determine the effect of the presence of excipients on the analgesic activity of $3CH_2Cl$. The results of the analgesic activity test of $3CH_2Cl$ are presented in Figure 4. The control group produced a very high amount of writhing-response (78.83 ± 4.17), indicating the success of pain induction using 0.6% acetic acid (dose of 0.01 mL/g BW). The number of writhes of the active compound group (18.17 ± 3.19) was less than the control group, showing that the active compound can suppress pain. The analgesic activity of the active compound was more effective than that of the comparison compound because the active compound had less amount of writhe than the comparison compound (52.83 ± 3.87). The significant difference in the amount of writhe of the three groups ($P < 0.05$) shows that the $3CH_2Cl$ had analgesic activity despite presence tablets excipients.

Conclusion

The polynomial coefficient values of the two models show that the SLS, CS, and SLS-CS combinations increased the parameter values of flow time, Carr index, hardness, and disintegration time. The SLS-CS combination decreased the friability value and the drug release parameters. The optimum tablet formulas of $3CH_2Cl$ tablet were $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and adjusted with SDL until 800 mg total weight. Quality predictions of tablet mass were flow time (9.07 seconds); Carr index (25.33%). Quality tablets predictions are hardness (9.44 kp), friability (0.37%), disintegration time (5.22 minutes), and drug released 60 minutes (80%). The SLS was to increase the solubility particles of $3CH_2Cl$ and excipient. The CS had accelerated the disintegration of tablets into particles. The tablet dosage form of $3CH_2Cl$ provided a new alternative of the analgesic drug future.

Acknowledgment

The authors thank the Research and Community Service Institute of Widya Mandala Catholic University, Surabaya, Indonesia was supporting grants (5230/WM01/N/2021). The authors also would like to thank Khaterine Irene Phuk, Sherlilyta Stiara Dewi, Angela Tiffany, and Meidelin Ribka Abiati for their assistance during the experiment.

Declarations

Competing interest statement

The authors declare no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: Designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Kuncoro Foe, Yudy Tjahjono, Caroline, Senny

Yesery Esar, Maria Annabela Jessica: performed the experiments, analyzed, and interpreted the data.

Statement of Human and Animal Rights

Experiments using experimental animals (mice) have been declared to meet the ethical requirements from the Research Ethics Commission of the Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta, Indonesia with No. 001/EC-FKH/Ex./2022 dated January 14, 2022.

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Table 1. Detailed of experimental formula and prediction of optimum formula

Component	Unit	Formula			
		TA	TB	TC	T Opt.
$3CH_2Cl$	[mg]	300.00	300.00	300.00	300.00
Ne	[%]	9.38	9.38	9.38	9.38
	[mg]	75.00	75.00	75.00	75.00
SLS	[%]	0.50	0.75	1.00	0.92
	[mg]	4.00	6.00	8.00	7.36
CS	[%]	4.00	3.00	2.00	2.33
	[mg]	32.00	24.00	16.00	18.64
MCC	[%]	5.00	5.00	5.00	5.00
	[mg]	20.00	20.00	20.00	20.00
SDL ad	[mg]	800.00	800.00	800.00	800.00

Table 2. Evaluate of tablets mass, tablets, and dissolution on formulations of $3CH_2Cl$

Tablet code	SLS [mg]	CS [mg]	Flow time [s]	SD	Carr index [%]	Hardness [kp]	SD	Friability [%]	Disintegrating time [min.]	Drug release [%]
TA	4.00	32.00	7.63	0.06	21.00	7.36	0.77	0.31	2.53	59.41
TB	6.00	24.00	8.60	0.10	24.00	8.81	0.97	0.34	4.35	69.95
TC	8.00	16.00	9.33	0.06	26.00	9.76	0.59	0.38	5.65	85.04
T Opt.	7.36	18.64	9.07	-	25.33	9.44	-	0.37	5.22	80.00

The quality evaluation of tablets mass, tablets, and dissolution of each formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00) and T Opt. (0.92:2.33).

Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

Polynomial coefficients according to the simplex lattice design with the linear and quadratic system. The tablet formula used contains SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

Table 4. Evaluation of the release kinetics of $3CH_2Cl$

Formula code	Parameter	First order		Higuchi		Korsmeyer-Peppas		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	
TA	Rsqr_adj	0.8545	0.02	0.9721	0.01	0.9779	0.01	0.9907	0.01	Weibull
	MSE_root	8.4740	0.47	3.6791	0.57	3.2431	0.75	2.0408	0.80	
	AIC	37.2882	0.67	27.1910	1.89	26.2323	2.67	20.5635	4.56	
TB	Rsqr_adj	0.9475	0.01	0.9966	0.00	0.9961	0.00	0.9917	0.00	Higuchi
	MSE_root	5.7427	0.56	1.4227	0.47	1.5214	0.53	2.2621	0.46	
	AIC	32.5953	1.14	15.3644	4.53	16.8557	4.27	22.229	2.35	
TC	Rsqr_adj	0.9578	0.01	0.9885	0.00	0.9949	0.00	0.9963	0.00	Weibull
	MSE_root	6.3475	0.45	3.3264	0.47	2.221	0.13	1.8553	0.28	
	AIC	33.8125	0.87	26.0793	1.49	21.8932	0.65	19.9178	1.81	

The release kinetics of $3CH_2Cl$ from each tablet formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

The model selection was high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC).

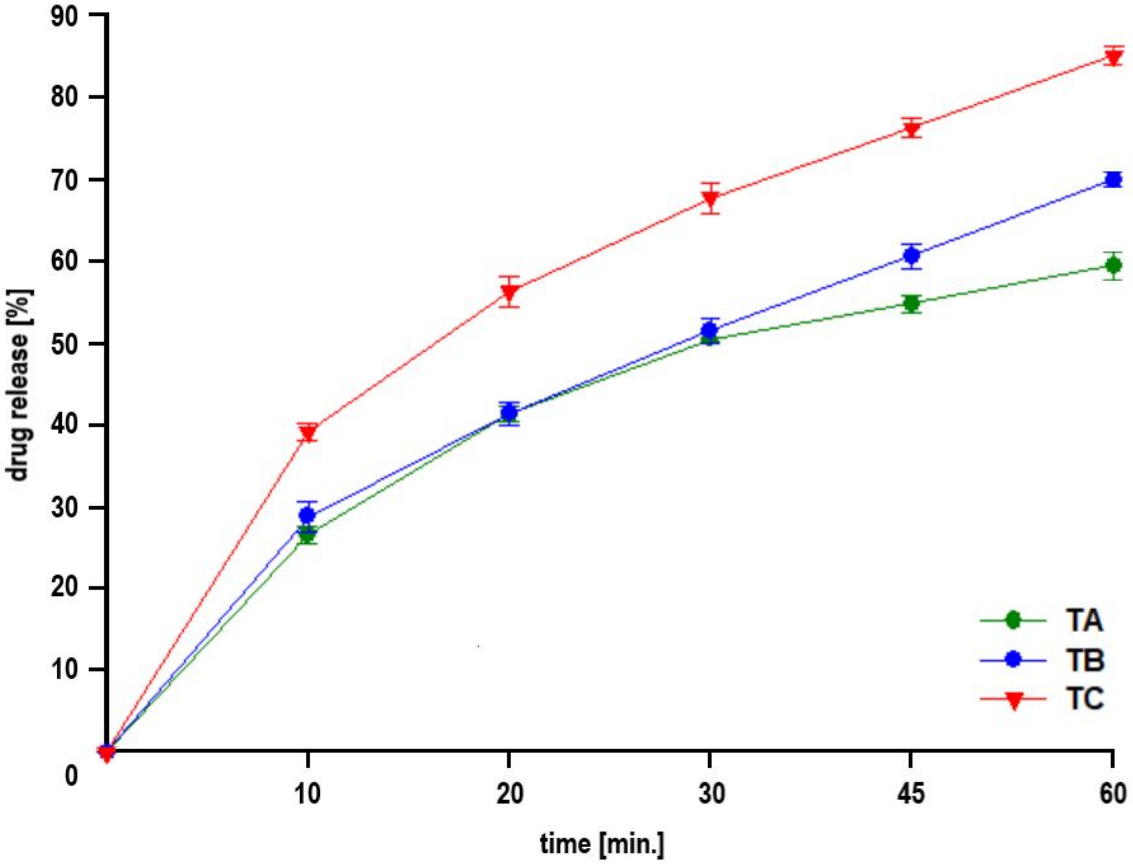

Figure 1. Dissolution profile of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

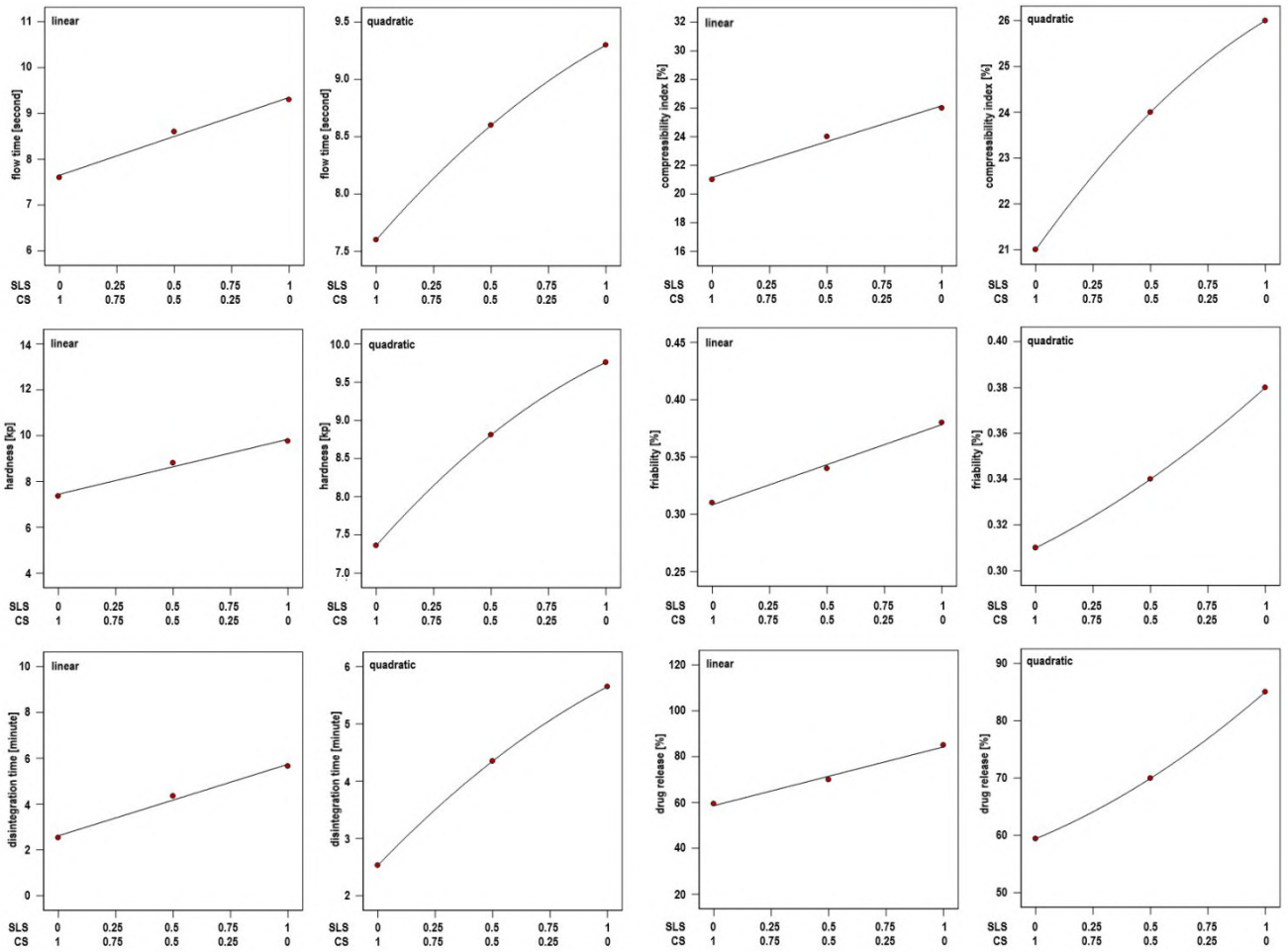

Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

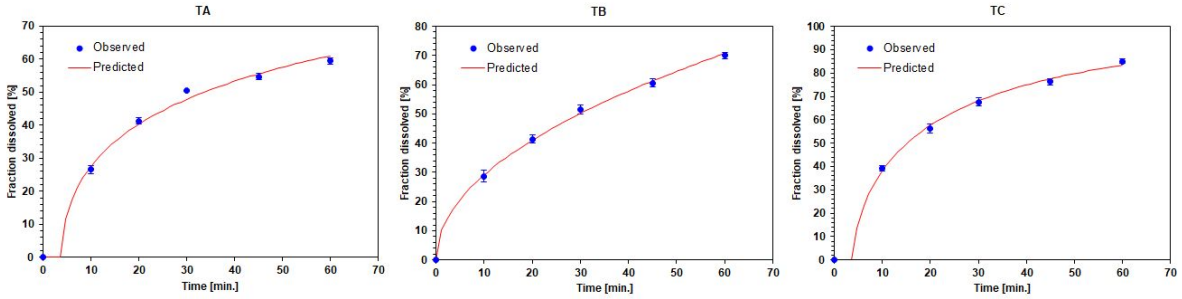

Figure 3. The kinetics profile of the release of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00) (Weibull), TB (0.75:3.00) (Higuchi), and TC (1.00:2.00) (Weibull).

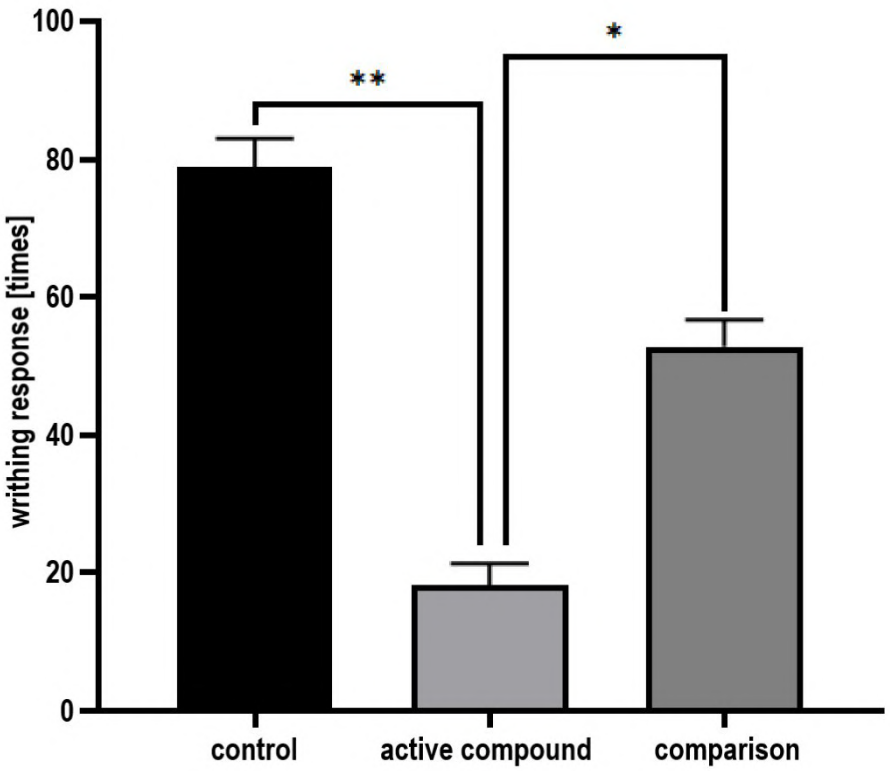

Figure 4. Analgesic activity of $3CH_2Cl$. The control group is mice given excipient tablets. The active compound group in mice was assigned $3CH_2Cl$ tablets. The comparison group was mice given acetylsalicylic acid tablets. The three groups induced pain using 0.01 mL/g BW of 0.6% acetic acid. The significant difference in the amount of writhe of the three groups ($P < 0.05$) indicated that $3CH_2Cl$ still has analgesic activity despite the presence of tablet excipients.

Hadinugroho, Wuryanto ao-2022-031476 - Manuscript Revision Request 15-Jun-2022

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Journal: ACS Omega
Manuscript ID: ao-2022-031476
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation: Do not publish.

Comments:
Although the research is well-performed and the manuscript is well-presented the subject under research is clearly intended for a pharmaceutical journal, in particular about pharmaceutics. It is important to note that the chemical part of this manuscript is just associated to drug preparation and the physical kinetics of release from tablets but no discussion about these processes is observed.
In this way I could suggest "Drug Development and Industrial Pharmacy", "Journal of Drug Delivery Science and Technology" or "MDPI Pharmaceutics", among others.

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes

Please evaluate the degree of novelty and originality of the research reported: Good

Are the conclusions adequately supported by the data presented?: Yes

Are the literature references appropriate and up to date?: Yes

Reviewer: 2

Recommendation: Publish after minor revisions.

Comments:
This manuscript analyzed the effect of sodium lauryl sulfate and croscarmellose sodium, and SLC-CS combinations on 3CH2Cl tablet formulation. Determined the optimized composition of 3CH2Cl tablet formulation using simplex lattice design with a two factor method. and researched the release kinetics of 3CH2Cl.
Questions:

1. the writing of this manuscript should be further improved, and unexpected errors should be check carefully. such as in Page 15 Line 328-329, the tablets with the release of 3CH2Cl were the highest, followed by tablets with TB and TA formulas. Then another same sentense was rewritten again.
2. The workload of this paper is sufficient, but innovation needs to be more prominent.

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes

Please evaluate the degree of novelty and originality of the research reported: Fair

Are the conclusions adequately supported by the data presented?: Yes

Are the literature references appropriate and up to date?: Yes

Reviewer: 3

Recommendation: Publish after major revisions.

Comments:
The study by Wuryanto et. al. nicely describes the optimization for tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid along with its functionality as an analgesic drug. The authors offer a new approach for delivering this lipophilic drug and provided information related to the characteristics and drug release profile of each formulation, which can be useful for the generation of a new analgesic drug.
Thus, I recommend for the publication after the major comments are addressed.
1. Here, the author has provided the composition of the drug, Ne, SLS, CS, MCC, and SDL to generate the optimum tablet formulation (as labeled T Opt.). Thus, the author should include the drug release profile of this T Opt. formulation.
2. The author must include the information of which tablet formulation was used for the drug writhing test. Instead of labeling the data as “active compound”, the author should investigate the analgesic activity of all tablet formulations (TA, TB, TC, T.Opt). Especially since the TA, TB, and TC showed different release profiles, pain-induced mice are expected to react differently to oral administration of these formulations.

Minor comments:
1. Raw material and chemicals: Provide the purity of each material used in this work.
2. L58 : “…lipophilic value of 3CH2Cl (log P) is 3.73.3”
3. L182: What is parameter “a” in equation 6?
4. Add the units for all parameters in equation 3-6.
5. L192: Expand BW when this abbreviation is used for the first time.
6. L197: “The writhing behavior was observed…”
7. Table 3: use “linear” instead of “linier”

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes

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Manuscript Type: Article
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
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Hadinugroho, Wuryanto ao-2022-031476.R1 - Revised Manuscript Submission to ACS Omega 05-Jul-2022

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Tanggal: Rabu, 6 Juli 2022 pukul 06.59 GMT+7

05-Jul-2022

Journal: ACS Omega
Manuscript ID: ao-2022-031476.R1
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
Authors: Hadinugroho, Wuryanto; Foe, Kuncoro; Tjahjono, Yudy; Caroline, Caroline; Esar, Senny; Jessica, Maria
Manuscript Status: Submitted

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Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Journal:	*ACS Omega*
Manuscript ID	ao-2022-031476.R1
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Pharmacy Foe, Kuncoro; Widya Mandala Catholic University Surabaya Tjahjono, Yudy; Widya Mandala Catholic University Surabaya, Pharmacy Caroline, Caroline; Widya Mandala Catholic University Surabaya, Pharmacy Esar, Senny; Widya Mandala Catholic University Surabaya, Pharmacy Jessica, Maria ; Widya Mandala Catholic University Surabaya, Pharmacy

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Abstract

Purpose: This research to determine the effect of sodium lauryl sulfate (SLS) as surfactants, croscarmellose sodium (CS) as a disintegrating agent, and SLS-CS combinations on 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) (log P = 3.73) tablet formulations. In addition, this study aims to determine the optimum of the $3CH_2Cl$ tablet formula.

Methods: The tablets are manufactured through direct compression according to the simplex lattice design. The optimal SLS and CS concentration was determined in-vitro using linear and quadratic models to achieve better tablet disintegration and dissolution.

Results: The same linear and quadratic coefficient profiles of SLS and CS indicate that the combined coefficient of SLS-CS with a quadratic model can be used to predict the effect of the SLS-CS combination. Based on the linear model coefficients, SLS and CS increase the value of flow time (9.35; 7.65), Carr index (26.17; 21.17), hardness (9.84; 7.44), friability (0.38; 0.31), disintegrating time (5.74; 2.62), and drug release (84.28; 58.65). The quadratic model coefficient shows that SLS-CS combinations increase flow time (0.60), Carr index (2.00), hardness (1.00), and disintegrating time (1.04). Meanwhile, SLS-CS combinations decrease friability (-0.02) and drug release (-9.10).

Conclusion: SLS, CS, and SLS-CS combinations affect the quality of tablets mass and tablets. The optimum tablet formula was $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and SDL (ad 800 mg). The $3CH_2Cl$ has analgesic activity despite the presence of tablet excipients. The $3CH_2Cl$ tablet is an innovative formulation and new alternative to the future analgesic drug.

Introduction

The 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) is a new compound synthesized from acetylsalicylic acid and 3-chloromethyl benzoyl chloride.[1,2] $3CH_2Cl$ is very potential as an analgesic, an anti-platelet aggregation, and an anti-inflammation drug.[1,2] A previous study reported that the active compound of $3CH_2Cl$ could significantly reduce the nociceptive response in mice.[2] The C_{max} value of $3CH_2Cl$ is 0.57 µg/mL. It indicates the ability of $3CH_2Cl$ to distribute and perfuse widely into the very deep interstitial and intracellular parts of the tissue. However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73.[3] While the optimal log P value of water-soluble compound during tablet formulation is theoretically between 2-3,[4] the reported log P value of $3CH_2Cl$ indicates the difficulties of this active compound for water-solubility.

Tablet form is one of the candidates in $3CH_2Cl$ formulation. Tablets may inhibit the hygroscopic character of $3CH_2Cl$ when stored. Tablet formulation requires the addition of several compounds such as surfactants to overcome the lipophilic character of the $3CH_2Cl$. Tablet formulation also needs a disintegrant to accelerate the dissociation of $3CH_2Cl$. The surfactants and disintegrant agents commonly used in the tablet formulation are sodium lauryl sulfate (SLS) and croscarmellose sodium (CS). The SLS has several characteristics, such as the hollow surface of the particles, easily soluble, and slight oily fatty.[5] The surface of CS has several characteristics such as a thread-root-like form, water-insoluble, and rapidly swells when hydrates.[5] The SLS is expected to accelerate the hydration of the tablet surface and increase the solubility of $3CH_2Cl$ and excipient particles. The CS is expected to accelerate the disintegration of tablets. However, the effect and the optimal amount of SLS and CS for the tablet formulation of $3CH_2Cl$ remain unclear. The novelty of this experiment is the tablet formulation of $3CH_2Cl$ using SLS as a surfactant and CS as a disintegrating agent in tablets. SLS and CS overcome $3CH_2Cl$ lipophilic problems on tablet disintegration and dissolution.

This formulation is an innovation of $3CH_2Cl$ made in tablets and new alternatives to the future analgesic drug.

This experiment aimed to determine the effect of SLS, CS, and SLS-CS combinations for the formulation of $3CH_2Cl$-tablet. In addition, this study aims to determine the optimum of the 3CH2Cl tablet formula. The effect of SLS, CS, and SLS-CS combinations was analyzed using linear and quadratic models following the simplex lattice design. It is believed that CS can accelerate the disintegration of tablets, while SLS increases hydrated tablets and the solubility of $3CH_2Cl$. This manuscript demonstrated that the tablet form of $3CH_2Cl$ using CS and SLS exerts an analgesic activity in mice writhing test. $3CH_2Cl$-tablet provides a new form of drug, which is a potential for an analgesic drug.

Material and methods

Raw materials and chemicals

Experiments using quality materials such as pro-analytical (p.a.), pharmaceutical grade (p.g.), and food grade (f.g.): salicylic acid (p.g.) (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (p.a.) (Sigma-Aldrich, GmbH, USA), pyridine (p.a.) (Merck KgaA, Darmstadt, Germany), ethanol (p.a.) (Merck KgaA, Darmstadt, Germany), neusilin (p.g.) (Gangwal Chemicals, India), croscarmellose sodium (p.g.) (FMC Biopolymer, USA), microcrystalline cellulose (p.g.) (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (p.g.) (Foremost Farm, USA), sodium hydroxide (p.a.) (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (p.a.) (Merck KgaA, Darmstadt, Germany), and distilled water (f.g.) (Brataco Chemical, Indonesia).

Synthesis and characterization of $3CH_2Cl$

Salicylic acid (1.8 mmol), 3-chloromethyl benzoyl chloride (7.2 mmol), pyridine (1.7 x 10^{-6} mmol), and acetone (14.8 x 10^{-6} mmol) were mixed homogeneously in Erlenmeyer. The mixture was microwave irradiated for 5 minutes with a Millstone Organic Synthesis Unit (MicroSYNTH). The mixture was then placed in a microwave oven (600 Watt, 1 minute). Afterwards, the mixture was evaluated with ferric chloride ($FeCl_3$) and thin-layer chromatography (TLC) (silica gel F254 stationary phase and n-hexane: ethanol (1:2) mobile phase). This test is to identify the salicylic acid in the mixture. At the beginning, pasta was prepared and then turned into a solution when irradiated by microwaves, and the final product was solid. The synthesis procedure followed the previous experiment, and the stability of $3CH_2Cl$ was proven.[1,2] Based on these reasons, the compound $3CH_2Cl$ can be used for tablet formulation.

Preparation of tablets

The tablet ingredients were weighted using the formula (Table 1) and the direct compression method. The process began by mixing $3CH_2Cl$ with Ne using a mortar and stamper until homogeneous. The mixture was transferred to a cubic mixer and added with SLS, CS, MCC, and SDL to rotate for 2 minutes at 100 rpm (Erweka). The homogeneous tablet mass was to test flowability and compressibility. The homogeneous tablet mass was compressed to form tablets (800 mg) with a single punch machine (Jenn Chian Machinery, Taiwan). Tablets were evaluated for hardness, friability, disintegration time, and drug dissolution.

Table 1. Detailed of experimental formula and prediction of optimum formula

Component	Unit	Formula			
		TA	TB	TC	T Opt.
$3CH_2Cl$	[mg]	300.00	300.00	300.00	300.00
Ne	[%]	9.38	9.38	9.38	9.38
	[mg]	75.00	75.00	75.00	75.00
SLS	[%]	0.50	0.75	1.00	0.92
	[mg]	4.00	6.00	8.00	7.36
CS	[%]	4.00	3.00	2.00	2.33
	[mg]	32.00	24.00	16.00	18.64
MCC	[%]	5.00	5.00	5.00	5.00
	[mg]	20.00	20.00	20.00	20.00
SDL ad	[mg]	800.00	800.00	800.00	800.00

Flow time

The mass of the tablet was weighed at 100 g and placed on a flowability tester funnel (Erweka, Germany). The funnel valve opened to drain the tablet mass and determine the flow time parameter. The cone of the tablet mass was scanned by infrared to determine the parameter of the angle of repose.

Compressibility

The glass measuring tube (100 mL) was weighted and recorded. Then, tablet mass was inserted to a glass measuring tube (100 mL) inclined (35^0-40^0). The glass measuring tube filled with the tablet mass was weighed and recorded. The glass measuring tube loaded the tablet mass was placed on a density tap volumeter (Erweka, Germany) and tapped 500 times. The initial and final volumes of tablet mass were recorded to determine the bulk density and tap density. Bulk density is the ratio of the tablet mass to the initial volume, while tap density is the ratio between the tablet mass and volume. Determination of the Carr index value follows Equation 1.[6]

$$Carr\ index\ (\%) = \frac{tap\ density - bulk\ density}{tap\ density}\ x\ 100\% \qquad \text{Equation 1}$$

Table 2. Evaluate of tablets mass, tablets, and dissolution on formulations of $3CH_2Cl$

Tablet code	SLS [mg]	CS [mg]	Flow time [s]	SD	Carr index [%]	Hardness [kp]	SD	Friability [%]	Disintegrating time [min.]	Drug release [%]	SD
TA	4.00	32.00	7.63	0.06	21.00	7.36	0.77	0.31	2.53	59.41	0.95
TB	6.00	24.00	8.60	0.10	24.00	8.81	0.97	0.34	4.35	69.95	1.00
TC	8.00	16.00	9.33	0.06	26.00	9.76	0.59	0.38	5.65	85.04	1.05
T Opt.	7.36	18.64	9.10	0.10	25.00	9.48	0.52	0.36	5.25	81.53	0.86
P Opt.	7.36	18.64	9.07	-	25.33	9.44	-	0.37	5.22	80.00	

The quality evaluation of tablets mass, tablets, and dissolution of each formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Hardness

Tablets (6) were randomly selected from all tablets[7,8] and placed in a hardness tester (Schleuniger, Netherlands). The tablet was pressed by a metal rod until the tablet cracked or broke. The hardness of the tablet can be read on the monitor hardness tester.

Friability

Tablets were randomly selected up to a total weight of more than 6500 mg.[7,8] All tablets were dust-free for careful weighing (Wo). The tablets were rotated on a drum friability tester (Erweka, Germany) for 4 minutes at 25 rpm. The tablets were dust-free and carefully reweighed (W1). The value of tablet friability is the difference between the total weight of the initial tablet and the total weight of the final tablet compared to the total weight of the initial tablet. Determination of the friability value follows Equation 2.

$$friability\ (\%) = \frac{Wo - W1}{Wo}\,100\% \qquad \text{Equation 2}$$

Disintegration time

Tablets (18) were selected, and six of which were randomly selected.[7,8] Tablets were placed in each tube of the disintegration tester (Erweka Z3, Germany). The cylinder moved up and down in the chamber containing distilled water at 37^0C and 900 mL. Disintegration time is the time required by six tablets for no particles/fragments to remain in the mesh in each tube.

Dissolution

Each tablet was placed in a vessel of dissolution tester (Electrolab TDT-08L, India) containing phosphate buffer medium pH 6.8 (37 ± 0.5 C; 50 rpm; 900 mL) using the basket method for 60 minutes.[9,10] A sampling of the release of $3CH_2Cl$ (5 mL) was done at 10, 20, 30,

45, and 60 minutes. The concentration of the dissolved active compound was analyzed using UV-VIS spectrophotometer (Hitachi U-1900, Japan) at the maximum wavelength.

Optimization

The optimization of the tablet formula was generated using the simplex lattice design with a two-factor method. The working concentration of SLS is 0.5%-1%, and CS is 2%-4%. The experiment used three formulas (Table 1) with the proportion of 0.50:4.00 (called TA), TB 0.75:3.00 (called TB), TC 1.00:2.00 (called TC), 0.92:2.33 (T Opt.), Flow time, Carr index, hardness, disintegrating time, and drug release were used as the optimization parameters. The optimization response was analyzed *in-silico* (Design Expert ver.10) to predict the tablet formula of $3CH_2Cl$.

Release kinetics of $3CH_2Cl$ from tablet

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using the following equations 3-6:[11–14]

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 3

Qt: the amount of drug dissolved at the time (t) [mg], Qo: the initial drug [mg], and Ko: constant drug release [mg/minute^{-1}].

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 4

Qt: the amount of drug [mg], K_H: Higuchi constant [mg/minute$^{1/2}$], and t: time [minute].

Korsmeyer-Peppas $: Q_t/Q_\infty = K_k.\ t^n$ Equation 5

Q_t/Q_∞: fraction of drug released [mg], K_k: Korsmeyer-Peppas constant [mg/minute^{-1}], and n: diffusion exponential.

Weibull $: \log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug [mg], Ti: the lag time before dissolution, a: initial fraction of drug [mg], b: shape parameter obtained from the slope of the obtained curve.

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using DDSolver software.

Analgesic activity by writhing test

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g body weight) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g body weight) or the comparator (2.05 mg/20 g body weight) was given in another group. The writhing behavior was observed within 10 minutes.

Result and discussion

Characterization of $3CH_2Cl$

Infrared spectra show the ester peak C=O at 1732.10 cm^{-1}, while the peak C-O at 1298.22 cm^{-1}, 1279.16 cm^{-1}, and 1262. 18 cm^{-1}. The carboxylate peak C=O appeared at 1694.90 cm^{-1}, while C-O at 1262.18 cm^{-1}. The peak C=C was aromatic at 1606.29 cm^{-1}, and the peak C-Cl at 704.24 cm^{-1}. The Rf value of thin layer chromatography $3CH_2Cl$ compound in the mobile phase of ethyl acetate:ethanol (1:2) is 0.91; n-hexane:ethanol (1:2) is 0.82; and chloroform:ethanol (4:1) was 0.87. The melting point value of $3CH_2Cl$ is at 109-111°C.

Formulation of $3CH_2Cl$ tablets

The $3CH_2Cl$-tablet formula was used excipients Ne, SLS, CS, MCC, SDL. Ne was used to prevent the coagulation of $3CH_2Cl$.[16–18] The SLS-CS combination improved the flowability of $3CH_2Cl$. SLS can accelerate the tablet hydration through disintegration or dissolution media. SLS also lowered the surface tension of $3CH_2Cl$ particles with a hydrating medium, thereby accelerating the solubility of the particles.[19–21] CS can swell when interacting with a hydrating-medium so that the surrounding particles were pushed, resulting in the tablet disintegration.[22–24] The MCC was used as a tablet filler for excellent tablet compatibility, while SDL was used as a high-density filler to adjust the tablet with optimal thickness.[25–27] Both MCC and SDL were ideal excipients for the direct compress method.

Determining the flow time value of $3CH_2Cl$ tablet mass

The flow time values of the three tablet mass formulas are shown in Table 2. All formula has a flow time value of less than 10 seconds. It means the tablet mass can move freely and fill the tablet machine dies.[6] The TA (7.6 seconds) formula has the fastest flow time, followed by TB (8.6 seconds) and TC (9.3 seconds) formula. The coefficient value (Table 3) from the simplex lattice design method with a linear model shows that SLS (9.35) was dominant in increasing tablet mass flow time, followed by CS (7.65). The linear model coefficient is acceptable based on statistical analysis (see supporting information Table S2). The ANOVA results from the quadratic model show a coefficient profile similar to the linear model, where the coefficients of SLS (9.30) and CS (7.60) increased the tablet mass flow time. Through a quadratic model, the combination coefficient of SLS-CS (0.60) shows that the SLS-CS combinations increased the flow time, but the SLS-CS combinations were not as dominant as SLS and CS.

Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

Polynomial coefficients according to the simplex lattice design with the linear and quadratic system. The tablet formula used contains SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

The hollow form of SLS particles caused the surface of the particles to become rough, which might inhibit the movement and increase the flow time of the tablet mass. The shape of CS particles, such as thread roots, made the particles difficult to move and increases the flow time. In addition, this character can inhibit the movement of other particles of the tablet mass component. The screw root shape of the CS particles can fill the hollow of the SLS particles so that the combination particles have a flatter surface and reduce the resistance to movement of the tablet mass.

Determining the Carr index value of $3CH_2Cl$ tablet mass

The Carr index values of the three tablet mass formulas are shown in Table 2. The TA and TB formulas have a Carr index value of less than 25%, indicating that the tablet mass was good enough to flow and move slightly and to achieve a stable arrangement in the dies chamber of the tablet machine. The TC formula has a Carr index value of more than 25%, indicating that the tablet mass can flow. The particles required more movement to achieve a stable arrangement in the tablet machine dies space. The simplex lattice design-method linear model could generate the coefficient values as presented in Table 3. Meanwhile, SLS (26.17) was the most dominant in increasing the Carr index, followed with CS (21.17). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). Quadratic model ANOVA had a coefficient profile similar to the linear model. The coefficients of SLS (26.00) and CS (21.00) increased the Carr index of the tablet mass. The quadratic model resulted in the SLS-CS combinations coefficient (2.00), showing that SLS-CS increases the Carr index. The SLS-CS combinations were less dominant than SLS and CS.

The Hollow SLS particles caused brittle particles. Therefore, when particles were subjected to mechanical stress, the particles could break into smaller sizes. The small SLS particles were difficult to flow while producing much porosity in a stable arrangement. The

screw root shape of CS particles caused the tablet mass to be difficult to move and have large porosity in a sturdy structure. The CS particles that fill the cavity of SLS particles can improve the surface morphology of the particles. Still, the remaining part of the CS particles outside the hollow can break into fine particles. Smaller CS particle size can inhibit tablet mass flow.

Determining the hardness of $3CH_2Cl$ tablets

The tablet hardness of each formula is shown in Table 2. The TC tablets were the hardest than TA and TB tablets. TC formula tablets had the strongest interlocking between particles among other formula tablets. The simplex lattice design method with a linear model produced the coefficient values (Table 3), while SLS (9.84) was the most dominant in increasing the tablet hardness, followed by CS (7.44). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. SLS (9.76) and CS (7.36) coefficients increased tablet hardness. The quadratic model produced an SLS-CS combination coefficient (1.00), indicating the SLS-CS combinations increased tablet hardness.

The $3CH_2Cl$, Ne, SLS, and CS particles filled random porosity between MCC and SDL particles. When the tablet mass was compressed, a tablet with solid interlocking and little porosity was formed. The cavity of SLS particles broke when compressed into tablets. Tablets had strong interlocking between particles and little porosity. The screw root shape of the CS particles caused the interlocking between the particles in the tablet to become elastic withstand mechanical stress. The CS particles that filled the SLS particle cavity caused the combination particles to become stronger and more elastic. The resulting tablet had strong interlocking and can withstand mechanical stress.

Determining the friability of $3CH_2Cl$ tablets

The tablet friability of each formula is shown in Table 2. The tablet orders of the most friable were TC, TB, and TA tablets. Although the tablet formula TC was the hardest, the tablet TC was the most brittle because the interlocking between the particles on the tablet surface cannot withstand mechanical movements. The simplex lattice design method with a linear model produced the coefficient values presented in Table 3, where SLS (0.38) was the most dominant in increasing tablet friability, followed by CS (0.30). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (0.38) and CS (0.31) increased tablet friability. The quadratic model resulted in an SLS-CS combinations coefficient (-0.02), indicating that the SLS-CS combinations decreased tablet friability.

The tablet constituent particles on the tablet surface and the interlocking which were not strong can be released when subjected to mechanical movement. SLS particles were at risk of breaking and forming fine particles when compressed because SLS particles are hollow. If the fine particles are on the tablet surface, the fine particles are released when receiving mechanical movement. The screw shape of the CS particles on the tablet surface was difficult for the particles to maintain interlocking when receiving mechanical movements. Particle combination between SLS and CS particles on the tablet surface can support interlocking with other particles that make up the tablet to withstand mechanical movements.

Determining the disintegration time of $3CH_2Cl$ tablets

The tablet disintegration time for each formula is shown in Table 2. The TA tablets were the fastest to disintegrate than TB and TC tablets. TA formula tablets contained the highest CS so that the more CS particles hydrate and swollen, caused the tablet to disintegrate quickly. The simplex lattice design method with a linear model produced the coefficient values

(Table 3). SLS (5.74) was the most dominant ingredient in increasing tablet friability, followed by CS (2.62). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (5.65) and CS (2.53) increased tablet disintegration time. The quadratic model resulted in an SLS-CS combination coefficient (1.04), indicating that the SLS-CS combination increased the tablet disintegration time.

Changes in SLS particle size and the formation of fine particles when the tablet mass was compressed caused the tablet to have a dense porosity. The disintegrating medium was difficult to penetrate the tablet and slow down the disintegration. CS particles can function as disintegrants if particles are hydrated and swell. CS particles needed time to hydrate and swell all the particles so that the tablet disintegrates longer. The SLS-CS combinations particles narrowed the porosity of the tablet so that there was less passage for the disintegrating medium. In addition, tablet hardness increased the disintegration time because the hard tablet had narrow porosity, so the disintegrating medium was difficult to penetrate the tablet.

Determining the drug release of $3CH_2Cl$ tablets

Drug release from each tablet is shown in Table 2 and a detailed profile in Figure 1 (detail see supporting information Table S1). Tablets TC with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. ~~Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas.~~ The TC formula tablets contained the highest SLS, reducing the surface tension between the $3CH_2Cl$ particles and the dissolution medium. The simplex lattice design method with a linear model resulted in the coefficient values as presented in Table 3, where SLS (84.28) was the most dominant in increasing drug release, followed by CS (58.65). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a

coefficient profile similar to the linear model. The coefficients of SLS (85.04) and CS (59.41) increased the release of $3CH_2Cl$. The quadratic model resulted in an SLS-CS combinations coefficient (-9.10), indicating that the SLS-CS combinations decreased the solubility of $3CH_2Cl$.

Hollow SLS particles can accelerate the solubility of SLS. The dissolved SLS particles reduced the surface tension of the $3CH_2Cl$ particles with the dissolution medium. Swelling CS particles forced the tablet to disintegrate into tiny particles, thereby increasing the surface area of the $3CH_2Cl$ particles in contact with the dissolution medium. SLS-CS combination particles have a narrow porosity, so the medium was difficult to hydrate other particles and inhibits the solubility of $3CH_2Cl$ particles.

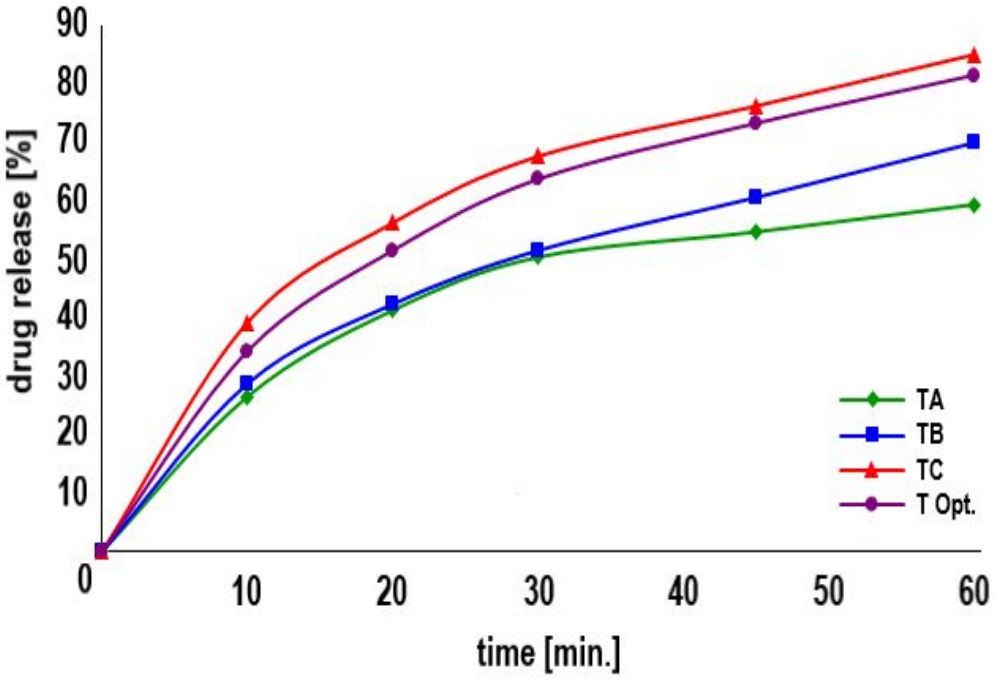

Figure 1. Dissolution profile of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Simplex lattice design and ANOVA of $3CH_2Cl$ tablets

This experiment used the simplex lattice design because the optimization factor for the concentration of SLS and CS is an internal factor of the tablet formula, without any external factors. Linear and quadratic models were used to support each other in predicting the effect of SLS, CS, and a combination of SLS-CS (Table 3 and Figure 2). ANOVA from a linear model can provide R-Squared, Adj R-Squared, Pred R-Squared, and Adeq Precision values to evaluate the model's acceptability. The coefficient of the polynomial equation of the linear model is accepted if the difference between R-Square and Pred R-Square is less than 0.2 and Adeq Precision is more than 4. Thus, the polynomial coefficients can be used to predict the effect of SLS and CS. The weakness of the linear model is that it cannot predict the impact of the combination of SLS with CS. The quadratic model can produce polynomial coefficients for the influence of SLS, CS, and SLS-CS combinations. However, the quadratic model cannot represent ANOVA parameters like a linear model because of the limited experimental formulas. The effort to maximize these two models in predicting the effect of SLS, CS, and SLS-CS combinations by analyzing the similarity of SLS and CS coefficients is critical. The profiles of the SLS and CS coefficients from the two models are similar. In that case, the coefficient values of the SLS-CS combination in the quadratic model can be used to predict the effect of the SLS-CS combination. The profiles of SLS and CS were similar, so that the coefficient values of SLS-CS combined in the quadratic model can be used to predict the effect of the SLS-CS combination on the tablet formulation parameter of the $3CH_2Cl$. Both models are beneficial for experiments using a limited number of formulas due to the availability of $3CH_2Cl$ synthesized by laboratory capacity. Prediction of the optimum formula in this experiment was done numerically according to a linear model. Predicted (P Opt.) and verified (T Opt.) optimum tablet formulas are presented in Table 2.

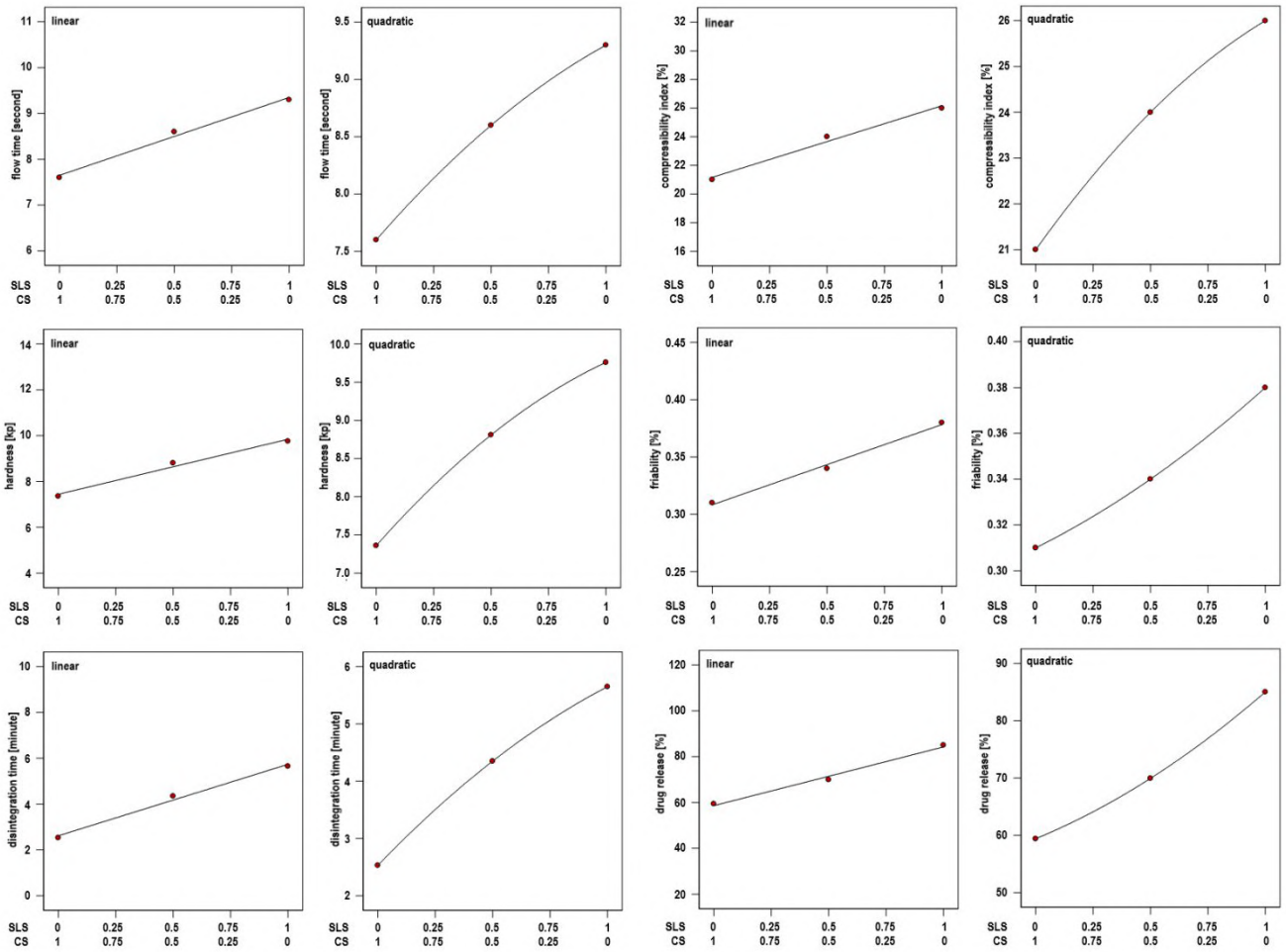

Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

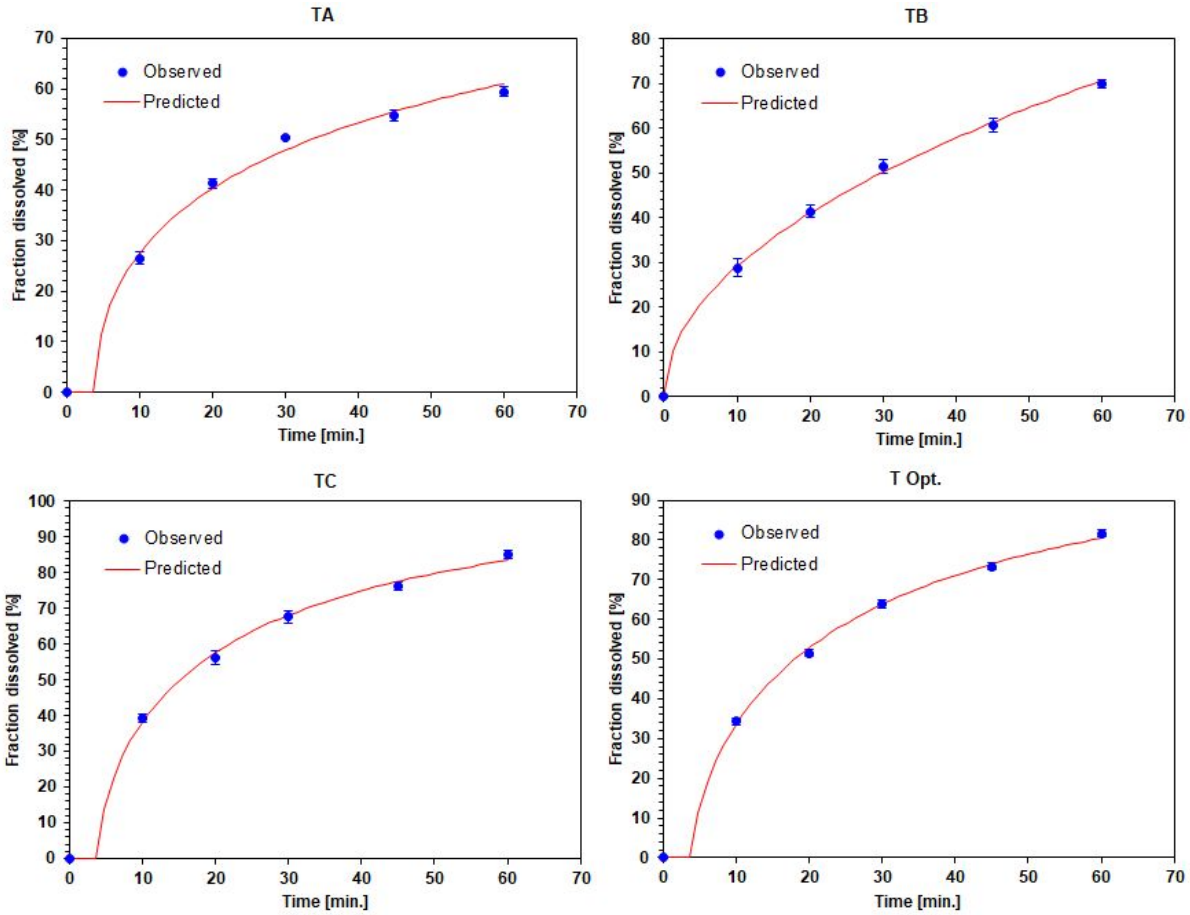

Figure 3. The kinetics profile of the release of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00) (Weibull), TB (0.75:3.00) (Higuchi), TC (1.00:2.00) (Weibull), and T Opt. (0.92:2.33) (Weibull).

Release kinetics of $3CH_2Cl$ tablets

The release kinetics models of $3CH_2Cl$ from tablets were analyzed using DDSolver. Rsqr_adj shows the correlation between dissolution time and release of $3CH_2Cl$. MSE_root determinated the correlation analysis correction, while AIC demonstrated the suitability of the equation for determining the release kinetics model.[28–31] The results of the DDSolver analysis are shown in Table 4 and Figure 3 (detail see supporting information Figure S1-S4).

The TA and TC formulas following the Weibull release kinetics model show that $3CH_2Cl$ was released from the tablet without any delay. The presence of SLS lowered the

surface tension of $3CH_2Cl$ with the dissolution medium so that the particles dissolved quickly. This was also supported by the presence of CS, which accelerates the disintegration of tablets into granules or particles thereby expanding the surface of the particles to dissolve.

The Higuchi release kinetics model of TB formula shows that the release was influenced by the diffusion mechanism of $3CH_2Cl$ out of the tablet. SLS on the tablet surface accelerated hydrating and was followed by the formation of a hydration layer so that the particles dissolve and leave the tablet. CS served as a disintegrating agent after hydrating and swelling. This condition took time, so that $3CH_2Cl$ was allowed to dissolve and diffuse before the CS can function.

Table 4. Evaluation of the release kinetics of $3CH_2Cl$

Formula code	Parameter	First order		Higuchi		Korsmeyer-Peppas		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	
TA	Rsqr_adj	0.8545	0.02	0.9721	0.01	0.9779	0.01	0.9907	0.01	Weibull
	MSE_root	8.4740	0.47	3.6791	0.57	3.2431	0.75	2.0408	0.80	
	AIC	37.2882	0.67	27.1910	1.89	26.2323	2.67	20.5635	4.56	
TB	Rsqr_adj	0.9475	0.01	0.9966	0.00	0.9961	0.00	0.9917	0.00	Higuchi
	MSE_root	5.7427	0.56	1.4227	0.47	1.5214	0.53	2.2621	0.46	
	AIC	32.5953	1.14	15.3644	4.53	16.8557	4.27	22.229	2.35	
TC	Rsqr_adj	0.9578	0.01	0.9885	0.00	0.9949	0.00	0.9963	0.00	Weibull
	MSE_root	6.3475	0.45	3.3264	0.47	2.221	0.13	1.8553	0.28	
	AIC	33.8125	0.87	26.0793	1.49	21.8932	0.65	19.9178	1.81	
T Opt.	Rsqr_adj	0.9686	0.01	0.9926	0.00	0.9925	0.01	0.9979	0.00	Weibull
	MSE_root	5.2892	0.42	2.5394	0.52	2.5334	0.39	1.2986	0.53	
	AIC	31.6188	0.97	22.6583	2.61	23.2554	0.57	14.8858	5.82	

The release kinetics of $3CH_2Cl$ from each tablet formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33). The model selection was high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC).

The $3CH_2Cl$-tablet showed analgesic activity in mice writhing test

This experiment was conducted using a T Opt. tablet to determine the effect of excipients on the analgesic activity of $3CH_2Cl$. The results of the analgesic activity test of $3CH_2Cl$ are presented in Figure 4. The control group produced a very high amount of writhing-

response (78.83 ± 4.17), indicating the success of pain induction using 0.6% acetic acid (dose of 0.01 mL/g body weight). The number of writhes of the T Opt. group (18.17 ± 3.19) was less than the control group, showing that the $3CH_2Cl$ can suppress pain. The analgesic activity of the $3CH_2Cl$ was more effective than that of the comparison compound because the $3CH_2Cl$ had less amount of writhe than the comparison compound (52.83 ± 3.87). The significant difference in the amount of writhe of the three groups ($P < 0.05$) shows that the $3CH_2Cl$ had analgesic activity despite presence tablets excipients.

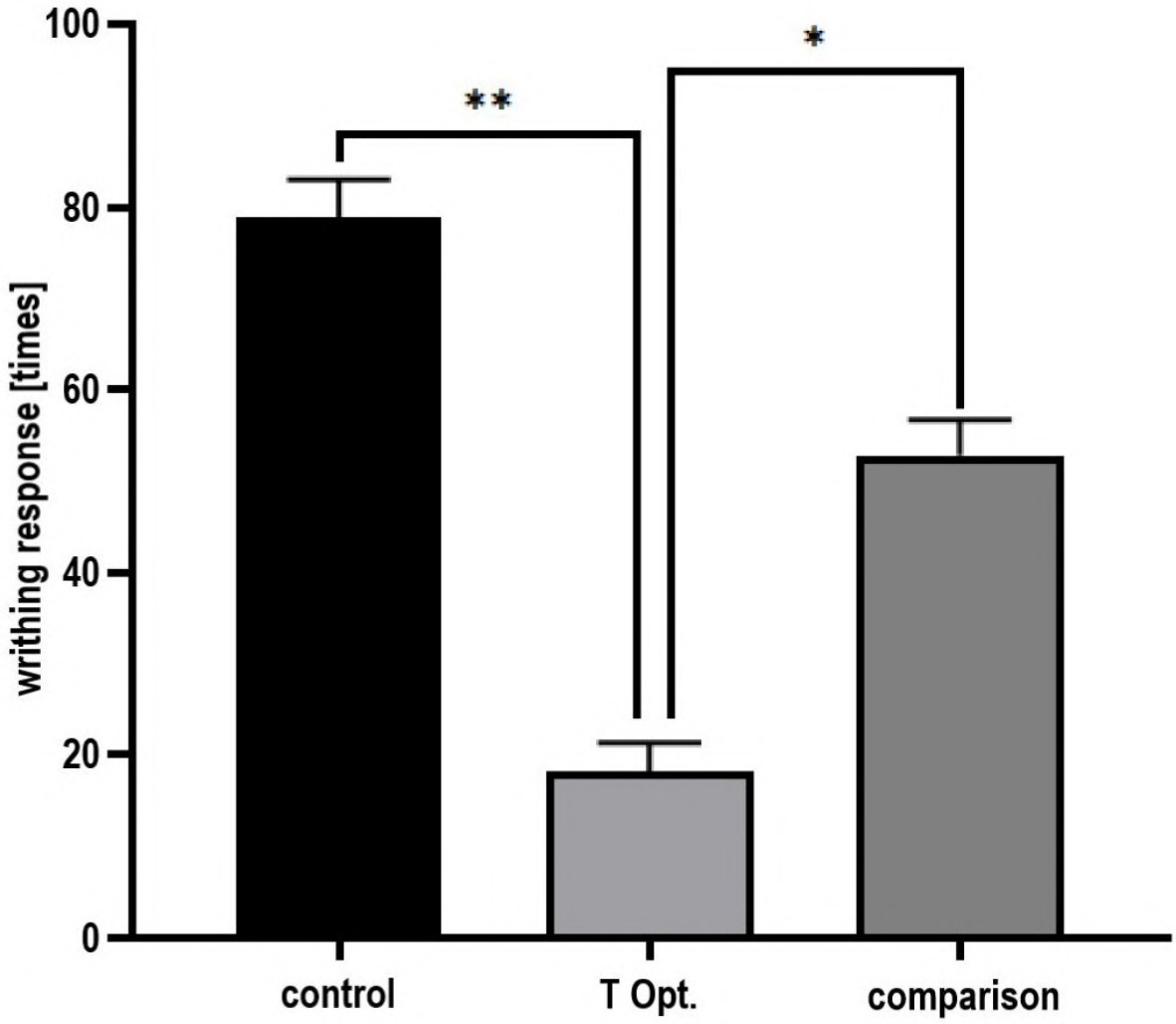

Figure 4. Analgesic activity of $3CH_2Cl$.

The control group is mice given excipient tablets. The active compound group in mice was assigned $3CH_2Cl$ tablets. The comparison group was mice given acetylsalicylic acid tablets. The three groups induced pain using 0.01 mL/g body weight of 0.6% acetic acid. The significant difference in the amount of writhe of the three groups ($P < 0.05$) indicated that $3CH_2Cl$ still has analgesic activity despite the presence of tablet excipients.

Conclusion

The polynomial coefficient values of the two models show that the SLS, CS, and SLS-CS combinations increased the parameter values of flow time, Carr index, hardness, and disintegration time. The SLS-CS combination decreased the friability value and the drug release parameters. The optimum tablet formulas of $3CH_2Cl$ tablet were $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and adjusted with SDL until 800 mg total weight. Quality predictions of tablet mass were flow time (9.07 seconds); Carr index (25.33%). Quality tablets predictions are hardness (9.44 kp), friability (0.37%), disintegration time (5.22 minutes), and drug released 60 minutes (80%). The SLS was to increase the solubility particles of $3CH_2Cl$ and excipient. The CS had accelerated the disintegration of tablets into particles. The tablet dosage form of $3CH_2Cl$ is an innovative formulation and a new alternative to the future analgesic drug.

Associated Content

Supporting Information

Tablet dosage calculation; the release of $3CH_2Cl$ from the tablets; statistical analysis of $3CH_2Cl$ tablets; the kinetics profile of the release of $3CH_2Cl$ from TA, TB, TC, and T Opt. tablets.

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Acknowledgment

The authors thank the Research and Community Service Institute of Widya Mandala Catholic University, Surabaya, Indonesia was supporting grants (5230/WM01/N/2021). The authors also would like to thank Khaterine Irene Phuk, Sherlilyta Stiara Dewi, Angela Tiffany, and Meidelin Ribka Abiati for their assistance during the experiment.

Declarations

Competing interest statement

The authors declare no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: Designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Kuncoro Foe, Yudy Tjahjono, Caroline, Senny Yesery Esar, Maria Annabela Jessica: performed the experiments, analyzed, and interpreted the data.

Statement of Human and Animal Rights

Experiments using experimental animals (mice) have been declared to meet the ethical requirements from the Research Ethics Commission of the Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta, Indonesia with No. 001/EC-FKH/Ex./2022 dated January 14, 2022.

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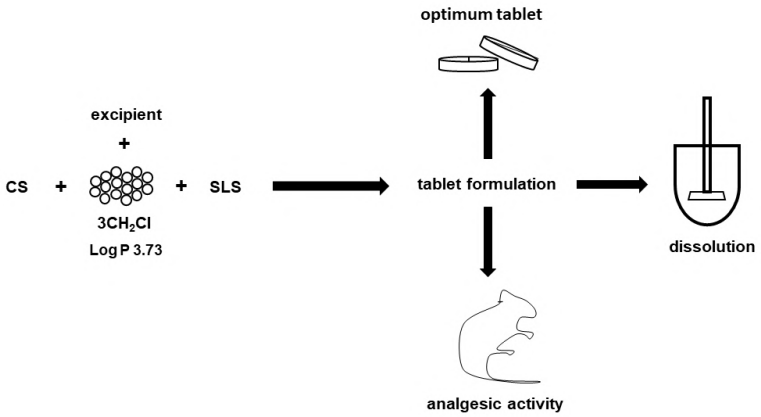


338x190mm (96 x 96 DPI)

Response to Reviewer comments

Comment of Reviewer 1

Although the research is well-performed and the manuscript is well-presented the subject under research is clearly intended for a pharmaceutical journal, in particular about pharmaceutics. It is important to note that the chemical part of this manuscript is just associated to drug preparation and the physical kinetics of release from tablets but no discussion about these processes is observed.
In this way I could suggest "Drug Development and Industrial Pharmacy", "Journal of Drug Delivery Science and Technology" or "MDPI Pharmaceutics", among others.
Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes
Please evaluate the degree of novelty and originality of the research reported: Good
Are the conclusions adequately supported by the data presented?: Yes
Are the literature references appropriate and up to date?: Yes

Response:

Thank you for the comment and the suggestions.

Comment of Reviewer 2

This manuscript analyzed the effect of sodium lauryl sulfate and croscarmellose sodium, and SLC-CS combinations on 3CH2Cl tablet formulation. Determined the optimized composition of 3CH2Cl tablet formulation using simplex lattice design with a two factor method. and researched the release kinetics of 3CH2Cl.
Questions:
1. the writing of this manuscript should be further improved, and unexpected errors should be check carefully. such as in Page 15 Line 328-329, the tablets with the release of 3CH2Cl were the highest, followed by tablets with TB and TA formulas. Then another same sentense was rewritten again.
2. The workload of this paper is sufficient, but innovation needs to be more prominent.

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes
Please evaluate the degree of novelty and originality of the research reported: Fair
Are the conclusions adequately supported by the data presented?: Yes
Are the literature references appropriate and up to date?: Yes

Questions of attached document:

1. **The writing of this manuscript should be further improved, and unexpected errors should be check carefully. such as in Page 15 Line 328-329, the tablets with the release of 3CH2Cl were the highest, followed by tablets with TB and TA formulas. Then another same sentense was rewritten again.**

   Response:

   Thank you for the suggestions. We have tried to improve sentences and delete sentences that have similar meanings. In addition, we try to paraphrase so that the sentences do not seem monotonous.

   Original manuscript

   TC formula tablets were the hardest, followed by TB and TC formula tablets.

Revised manuscript
The TC tablets were the hardest than TA and TB tablets.

Original manuscript
The TC formula tablets were the most brittle, followed by TB and TC formula tablets.
Revised manuscript
The tablet orders of the most friable were TC, TB, and TA tablets.

Original manuscript
The TA formula tablets were the fastest to disintegrate, followed by TB and TC formula tablets.
Revised manuscript
The TA tablets were the fastest to disintegrate than TB and TC tablets.

Original manuscript
Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas.
Revised manuscript
Tablets TC with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. ~~Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas.~~

2. The workload of this paper is sufficient, but innovation needs to be more prominent.
Response:
Thank you for the suggestions. We have tried adding sentences highlighting innovation in this research in the abstract, introduction, and conclusion.

Abstract
Original manuscript
The $3CH_2Cl$ has analgesic activity despite the presence of tablet excipients and new alternatives to the future analgesic drug.
Revised manuscript
The $3CH_2Cl$ has analgesic activity despite the presence of tablet excipients. The $3CH_2Cl$ tablet is an innovative formulation and new alternative to the future analgesic drug.

Introduction
Revised manuscript
This formulation is an innovation of $3CH_2Cl$ made in tablets and new alternatives to the future analgesic drug.

Conclusion
Original manuscript
The tablet dosage form of $3CH_2Cl$ provided a new alternative of the analgesic drug future.
Revised manuscript
The tablet dosage form of $3CH_2Cl$ is an innovative formulation and a new alternative to the future analgesic drug.

Comment of Reviewer 3

The study by Wuryanto et. al. nicely describes the optimization for tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid along with its functionality as an analgesic drug. The authors offer a new approach for delivering this lipophilic drug and provided information related to the characteristics and drug release profile of each formulation, which can be useful for the generation of a new analgesic drug.

Thus, I recommend for the publication after the major comments are addressed.

1. Here, the author has provided the composition of the drug, Ne, SLS, CS, MCC, and SDL to generate the optimum tablet formulation (as labeled T Opt.). Thus, the author should include the drug release profile of this T Opt. formulation.
2. The author must include the information of which tablet formulation was used for the drug writhing test. Instead of labeling the data as "active compound", the author should investigate the analgesic activity of all tablet formulations (TA, TB, TC, T.Opt). Especially since the TA, TB, and TC showed different release profiles, pain-induced mice are expected to react differently to oral administration of these formulations.

Minor comments:

1. Raw material and chemicals: Provide the purity of each material used in this work.
2. L58 : "…lipophilic value of 3CH2Cl (log P) is 3.73.3"
3. L182: What is parameter "a" in equation 6?
4. Add the units for all parameters in equation 3-6.
5. L192: Expand BW when this abbreviation is used for the first time.
6. L197: "The writhing behavior was observed…"
7. Table 3: use "linear" instead of "linier"

Additional Questions:

Is the technical quality of the research reported within valid and appropriate?: Yes
Please evaluate the degree of novelty and originality of the research reported: Good
Are the conclusions adequately supported by the data presented?: Yes
Are the literature references appropriate and up to date?: Yes

I have already included the necessary changes that needs to be done in the document file. Please follow and complete the requirements and correct the paper accordingly. Thank you for your efforts!

Questions of attached document:

1. Here, the author has provided the composition of the drug, Ne, SLS, CS, MCC, and SDL to generate the optimum tablet formulation (as labeled T Opt.). Thus, the author should include the drug release profile of this T Opt. formulation.

Response:

Thank you for the suggestions. The value of each parameter for evaluating the mass quality of tablets and tablets in Table 2 for P Opt is a prediction from optimization software (Design Expert). We have been to verify by the formula T Opt. have evaluation parameters value approach P Opt parameters value. T Opt. have good quality and drug release more 80%.

2. **The author must include the information of which tablet formulation was used for the drug writhing test. Instead of labeling the data as "active compound", the author should investigate the analgesic activity of all tablet formulations (TA, TB, TC, T Opt). Especially since the TA, TB, and TC showed different release profiles, pain-induced mice are expected to react differently to oral administration of these formulations.**

Response:

Thank you for the suggestions. The purpose of the writhing test in this study was to determine the effect of tablet excipients on analgesic activity. In this experiment, we used T Opt. tablets for the writhing test because they have good tablet quality and release $3CH_2Cl$ more than 80% in 60 minutes. This information is expected to support further research, primarily pharmacological and clinical trials. We have tried to correct the sentence in the section "The 3CH2Cl-tablet showed analgesic activity in mice writhing test." In addition, we have replaced the term active compound with T Opt. in Figure 4.

Original manuscript

This experiment was conducted to determine the effect of excipients on the analgesic activity of $3CH_2Cl$.

Revised manuscript

This experiment was conducted using a T Opt. to determine the effect of excipients on the analgesic activity of $3CH_2Cl$.

Minor comments:

1. Raw material and chemicals: Provide the purity of each material used in this work.

Response:

Thank you for the suggestions. We have added a description of the quality of materials in the raw materials and chemicals section. In addition, we attach some sample labels or certificates of analysis of the material.

Original manuscript

The experiment used the following materials: salicylic acid (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (Sigma-Aldrich, GmbH, USA), pyridine (Merck KgaA, Darmstadt, Germany), ethanol (Merck KgaA, Darmstadt, Germany), neusilin (Gangwal Chemicals, India), croscarmellose sodium (FMC Biopolymer, USA), microcrystalline cellulose (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (Foremost Farm, USA), sodium hydroxide (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (Merck KgaA, Darmstadt, Germany), and distilled water (Brataco Chemical, Indonesia).

Revised manuscript

Experiments using quality materials such as pro-analytical (p.a.), pharmaceutical grade (p.g.), and food grade (f.g.): salicylic acid (p.g.) (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (p.a.) (Sigma-Aldrich, GmbH, USA), pyridine (p.a.) (Merck KgaA, Darmstadt, Germany), ethanol (p.a.) (Merck KgaA, Darmstadt, Germany), neusilin (p.g.) (Gangwal Chemicals, India), croscarmellose sodium (p.g.) (FMC Biopolymer, USA), microcrystalline cellulose (p.g.) (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (p.g.) (Foremost Farm, USA), sodium hydroxide (p.a.) (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (p.a.) (Merck KgaA, Darmstadt, Germany), and distilled water (f.g.) (Brataco Chemical, Indonesia).

2. L58: "…lipophilic value of 3CH2Cl (log P) is 3.73.3"

Response:

Thank you for the suggestions. We have fixed writing by separating the log P-value by the reference citation number.

Original manuscript

However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73 [3].

Revised manuscript

However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73.[3]

3. L182: What is parameter "a" in equation 6?

Response:

Thank you for the suggestions. We have added a symbol definition to the equation.

Original manuscript

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve.

Revised manuscript

(1-m): fraction of insoluble drug [mg], Ti: the lag time before dissolution, a: initial fraction of drug [mg], b: shape parameter obtained from the slope of the obtained curve.

4. Add the units for all parameters in equation 3-6.

Response:

Thank you for the suggestions. We have added the units of each symbol to the equation.

Original manuscript

First order $: \ln Q_t = \ln Q_o + K_o . t$ Equation 3

Qt: the amount of drug dissolved at the time (t), Qo: the initial drug, and Ko: constant drug release.

Higuchi $: Q_t = K_H . \sqrt{t}$ Equation 4

K_H: Higuchi constant and t: time.

Korsmeyer-Peppas $: Q_t/Q_\infty = K_k . t^n$ Equation 5

Q_t/Q_∞: fraction of drug released, K_k: Korsmeyer-Peppas constant, and n: diffusion exponential.

Weibull $: \log[\ln - (1 - m)] = b \log(t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve.

Revised manuscript

First order $: \ln Q_t = \ln Q_o + K_o . t$ Equation 3

Qt: the amount of drug dissolved at the time (t) [mg], Qo: the initial drug [mg], and Ko: constant drug release [$mg/minute^{-1}$].

Higuchi $: Q_t = K_H . \sqrt{t}$ Equation 4

Qt: the amount of drug [mg], K_H: Higuchi constant [$mg/minute^{1/2}$], and t: time [minute].

Korsmeyer-Peppas $: Q_t/Q_\infty = K_k . t^n$ Equation 5

Q_t/Q_∞: fraction of drug released [mg], K_k: Korsmeyer-Peppas constant [mg/minute^{-1}], and n: diffusion exponential.

Weibull : $\log[\ln - (1 - m)] = b \log(t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug [mg], Ti: the lag time before dissolution, a: initial fraction of drug [mg], b: shape parameter obtained from the slope of the obtained curve.

5. L192: Expand BW when this abbreviation is used for the first time.

Response:

Thank you for the suggestions. We have replaced BW with body weight.

Original manuscript

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g BW) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g BW) or the comparator (2.05 mg/20 g BW) was given in another group.

Revised manuscript

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g body weight) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g body weight) or the comparator (2.05 mg/20 g body weight) was given in another group.

6. L197: “The writhing behavior was observed…”

Response:

Thank you for the suggestions. We have fixed it as per suggestions.

Original manuscript

The Writhing behavior was observed within 10 minutes.

Revised manuscript

The writhing behavior was observed within 10 minutes.

7. Table 3: use “linear” instead of “linier”

Response:

Thank you for the suggestions. We have replaced "linier" with "linear" in table 3.

Original manuscript

Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

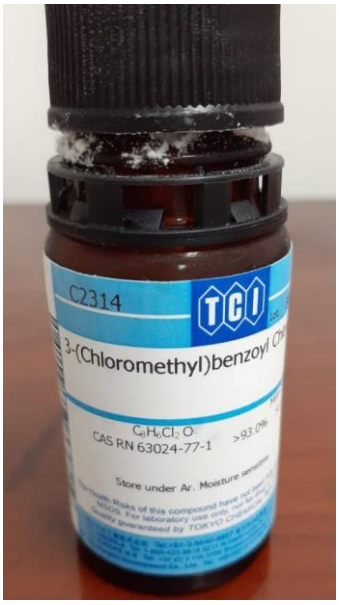
Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic	linier	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

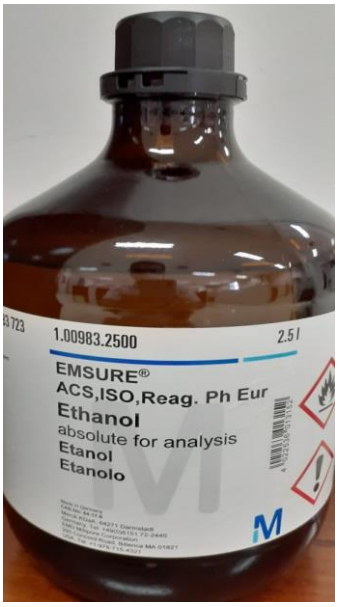
Revised manuscript

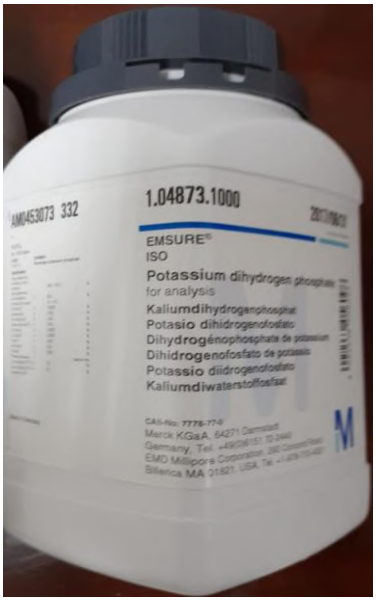
Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

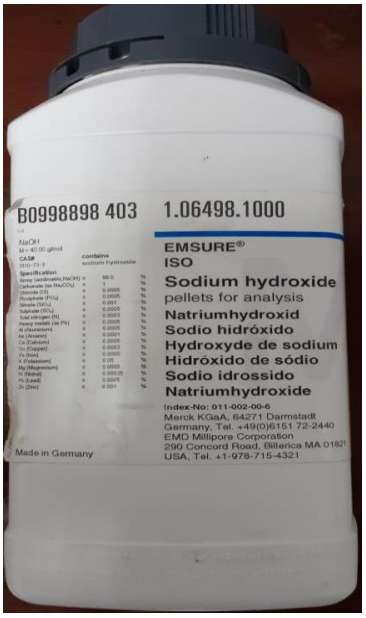
Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

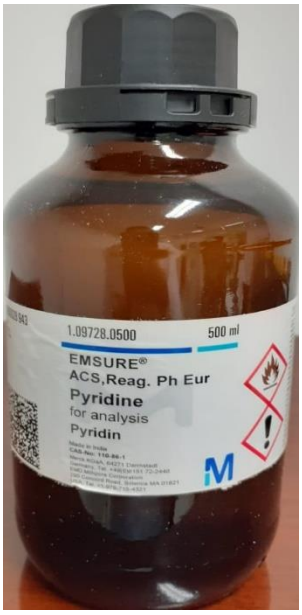
Label and Certificate of Raw Material

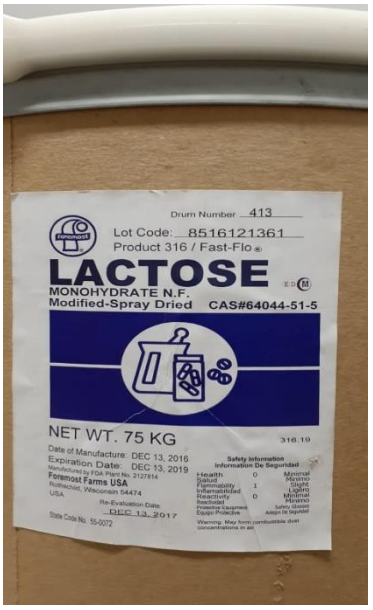












Label and Certificate of Raw Material

accent

QUALITY CONTROL
CERTIFICATE OF ANALYSIS

Product	CROSCARMELLOSE SODIUM
Grade	AcDiSOL L.R
MDA	USP/NF/JP, Ph. Eur./BP
Description	White or almost white. Practically insoluble in water, dilute acid and most of organic solvents. Slightly soluble or dilute NaOH solution
Batch No.	
Mfg. Date	May'2018
Re-evaluation Date	April'2023
Batch Qty.	1000 Kgs

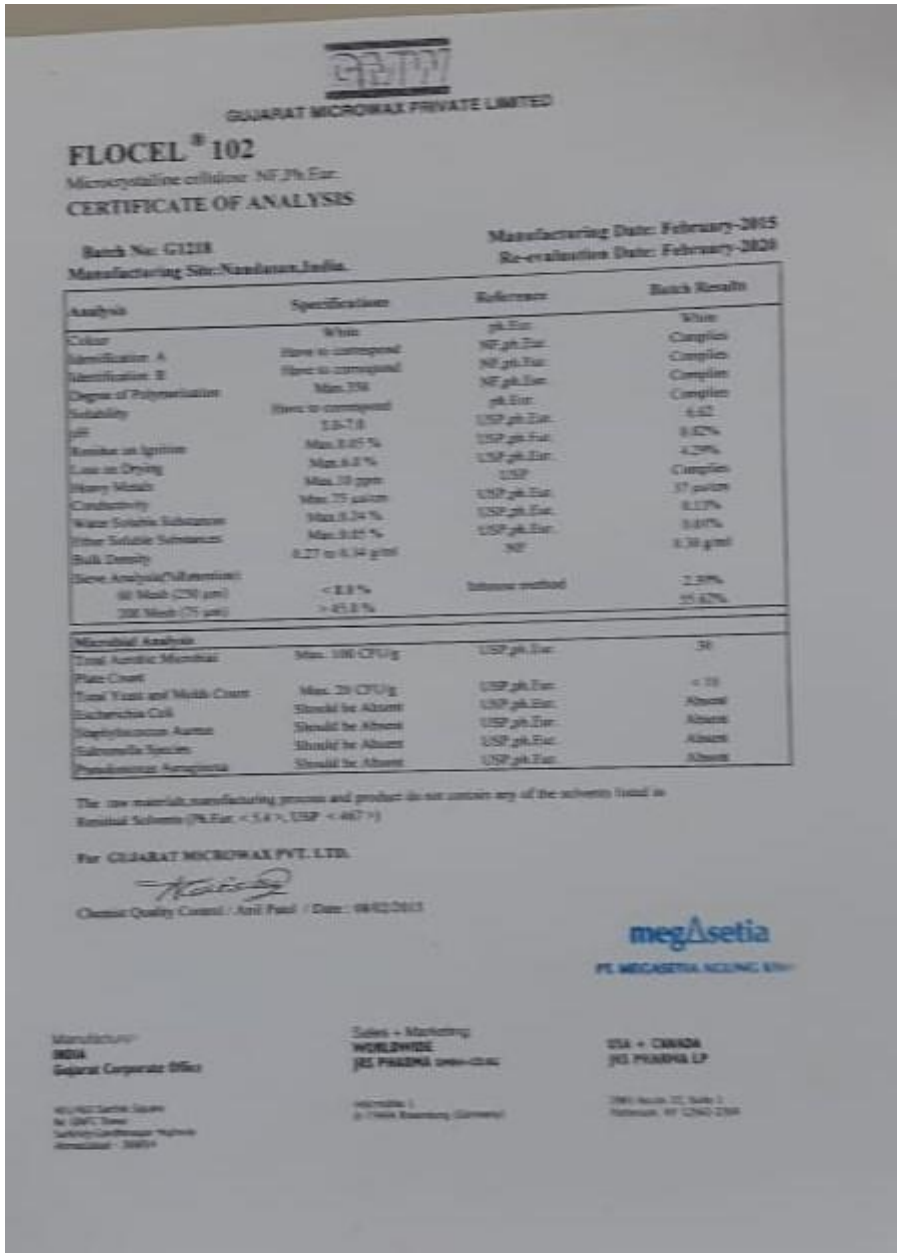
Pharmacopoeial test items	Batch Results	Specification
Identification (A,B,C) (1,2,3)	Passes	Have to correspond to USP/NF,JP,Ph.Eur.,BP
Degree of substitution	Complies	0.60 to 0.85 on USP/NF,JP,Ph.Eur.,BP
Loss on Drying	4.43 %	NMT 10.0% on USP/NF,JP,Ph.Eur.,BP
pH	5.92	5.0-7.0 on USP/NF,JP,Ph.Eur.,BP
Contents of Water - Soluble Substances	7.60 %	NMT 10.0% on USP/NF,JP,Ph.Eur.,BP
Residue on Ignition / Sulphated Ash	20.33 %	14.0% to 28.0% on USP/NF,JP,Ph.Eur.,BP
Settling Volume	18.0 ml	10 to 30 ml on USP/NF, Ph. Eur.,BP
Sodium chloride & sodium glycolate	0.57 %	NMT 0.5% on USP/NF, Ph. Eur.,BP
Heavy Metals	Complies	NMT 10 PPM on USP/NF, Ph. Eur.,BP
Iron	Complies	NMT 10 PPM on USP/NF, Ph. Eur.,BP
Particle size (% Passes through)		
100 Mesh	99.78%	NLT 98.0%

MICROBIAL LIMITS

Total Viable Aerobic Count	Complies	N.M.T. 1000 cfu/g on USP/NF, Ph. Eur.,BP
Total yeast & Mould Count	Complies	N.M.T. 100 cfu/g on USP/NF, Ph. Eur.,BP
Staphylococcus aureus	Complies	Absent on USP/NF, Ph. Eur.,BP
Escherichia Coli	Complies	Absent on USP/NF, Ph. Eur.,BP
Pseudomonas aeruginosa	Complies	Absent on USP/NF, Ph. Eur.,BP
Salmonella species	Complies	Absent on USP/NF, Ph. Eur.,BP

The raw materials, manufacturing process, and product do not contain any of solvents listed in Organic Volatile Impurities (USP<467>) & residual solvents (Ph. Eur<5.4>).
Storage recommendation: Preserve in tight containers.

Authorised Signatory
Quality Control
Ansuri Microwax Pvt Ltd.



GUJARAT MICROWAX PRIVATE LIMITED

FLOCEL ® 102
Microcrystalline cellulose NF,Ph.Eur.
CERTIFICATE OF ANALYSIS

Batch No: G1218
Manufacturing Site:Nandesari,India.
Manufacturing Date: February-2015
Re-evaluation Date: February-2020

Analysis	Specifications	Reference	Batch Results
Colour	White	ph.Eur.	White
Identification: A	Have to correspond	NF,ph.Eur.	Complies
Identification: B	Have to correspond	NF,ph.Eur.	Complies
Degree of Polymerization	Max.350	NF,ph.Eur.	Complies
Solubility	Have to correspond	ph.Eur.	Complies
pH	5.0-7.0	USP,ph.Eur.	6.62
Residue on Ignition	Max.0.05 %	USP,ph.Eur.	0.02%
Loss on Drying	Max.6.0 %	USP,ph.Eur.	4.29%
Heavy Metals	Max.10 ppm	USP	Complies
Conductivity	Max.75 µs/cm	USP,ph.Eur.	57 µs/cm
Water Soluble Substances	Max.0.24 %	USP,ph.Eur.	0.13%
Other Soluble Substances	Max.0.05 %	USP,ph.Eur.	0.05%
Bulk Density	0.27 to 0.34 g/ml	NF	0.30 g/ml
Sieve Analysis(Fulfamation):			
60 Mesh (250 µm)	< 8.0 %	Intouse method	2.39%
200 Mesh (75 µm)	> 45.0 %		55.62%

Microbial Analysis			
Total Aerobic Microbial Plate Count	Max. 100 CFU/g	USP,ph.Eur.	50
Total Yeast and Molds Count	Max. 20 CFU/g	USP,ph.Eur.	< 10
Escherichia Coli	Should be Absent	USP,ph.Eur.	Absent
Staphylococcus Aureus	Should be Absent	USP,ph.Eur.	Absent
Salmonella Species	Should be Absent	USP,ph.Eur.	Absent
Pseudomonas Aeruginosa	Should be Absent	USP,ph.Eur.	Absent

The raw materials,manufacturing process and product do not contain any of the solvents listed in Residual Solvents (Ph.Eur. < 5.4 >, USP < 467 >)

For GUJARAT MICROWAX PVT. LTD.

Chemist Quality Control / Anil Patel / Date : 04/02/2015

megAsetia

Manufacturer
INDIA
Gujarat Corporate Office

Sales + Marketing
WORLDWIDE

USA + CANADA

Hadinugroho, Wuryanto ao-2022-031476.R1 - Manuscript Revision Request - Formatting Changes 02-Aug-2022

Dari: ACS Omega (onbehalfof@manuscriptcentral.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Selasa, 2 Agustus 2022 pukul 21.03 GMT+7

02-Aug-2022

Journal: ACS Omega
Manuscript ID: ao-2022-031476.R1
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
Author(s): Hadinugroho, Wuryanto; Foe, Kuncoro; Tjahjono, Yudy; Caroline, Caroline; Esar, Senny; Jessica, Maria

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We are flexible in these unprecedented times affecting the global research community. If you need more time to complete authoring or reviewing tasks, please contact the editorial office and request an extension.

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- Include the authors' affiliations on the top of the manuscript file (below the title and author list).
- Kindly mark all the authors with an affiliation mark, which should also appear before the affiliation information. (except when the affiliation is the same for all AU)
- Only the corresponding author(s)' contact information and email addresses for all authors should be placed in the 'Author Information' section before the references
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We look forward to seeing your paper in ACS Omega.

Sincerely,

Dr. Krishna Ganesh
Coeditor
ACS Omega
Phone: (202) 657-6323
Email: Ganesh-office@omega.acs.org

Thank you.

Hadinugroho, Wuryanto ao-2022-031476.R2 - Revised Manuscript Submission to ACS Omega 03-Aug-2022

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Cc: wuryanto.hadinugroho@ymail.com; kuncoro@ukwms.ac.id; kuncorofoe@yahoo.com; yudy.tjahjono@ukwms.ac.id; caroline@ukwms.ac.id; senny_93@ukwms.ac.id; hendy_wijaya@ukwms.ac.id; marbel@ukwms.ac.id

Tanggal: Kamis, 4 Agustus 2022 pukul 04.38 GMT+7

03-Aug-2022

Journal: ACS Omega
Manuscript ID: ao-2022-031476.R2
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
Authors: Hadinugroho, Wuryanto; Foe, Kuncoro; Tjahjono, Yudy; Caroline, Caroline; Esar, Senny; Wijaya, Hendy; Jessica, Maria
Manuscript Status: Submitted

Dear Dr. Hadinugroho:

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Sincerely,

Dr. Krishna Ganesh and Dr. Deqing Zhang
ACS Omega

Thank you.

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Journal:	*ACS Omega*
Manuscript ID	ao-2022-031476.R2
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Pharmacy Foe, Kuncoro; Widya Mandala Catholic University Surabaya Tjahjono, Yudy; Widya Mandala Catholic University Surabaya, Pharmacy Caroline, Caroline; Widya Mandala Catholic University Surabaya, Pharmacy Esar, Senny; Widya Mandala Catholic University Surabaya, Pharmacy Wijaya, Hendy; Widya Mandala Catholic University Surabaya, Pharmacy Jessica, Maria ; Widya Mandala Catholic University Surabaya, Pharmacy

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica

Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, Indonesia

Abstract

Purpose: This research to determine the effect of sodium lauryl sulfate (SLS) as surfactants, croscarmellose sodium (CS) as a disintegrating agent, and SLS-CS combinations on 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) (log P = 3.73) tablet formulations. In addition, this study aims to determine the optimum of the $3CH_2Cl$ tablet formula.

Methods: The tablets are manufactured through direct compression according to the simplex lattice design. The optimal SLS and CS concentration was determined in-vitro using linear and quadratic models to achieve better tablet disintegration and dissolution.

Results: The same linear and quadratic coefficient profiles of SLS and CS indicate that the combined coefficient of SLS-CS with a quadratic model can be used to predict the effect of the SLS-CS combination. Based on the linear model coefficients, SLS and CS increase the value of flow time (9.35; 7.65), Carr index (26.17; 21.17), hardness (9.84; 7.44), friability (0.38; 0.31), disintegrating time (5.74; 2.62), and drug release (84.28; 58.65). The quadratic model coefficient shows that SLS-CS combinations increase flow time (0.60), Carr index (2.00), hardness (1.00), and disintegrating time (1.04). Meanwhile, SLS-CS combinations decrease friability (-0.02) and drug release (-9.10).

Conclusion: SLS, CS, and SLS-CS combinations affect the quality of tablets mass and tablets. The optimum tablet formula was $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and SDL (ad 800 mg). The $3CH_2Cl$ has analgesic activity despite the presence of tablet excipients. The $3CH_2Cl$ tablet is an innovative formulation and new alternative to the future analgesic drug.

Introduction

The 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) is a new compound synthesized from acetylsalicylic acid and 3-chloromethyl benzoyl chloride.[1,2] $3CH_2Cl$ is very potential as an analgesic, an anti-platelet aggregation, and an anti-inflammation drug.[1,2] A previous study reported that the active compound of $3CH_2Cl$ could significantly reduce the nociceptive response in mice.[2] The C_{max} value of $3CH_2Cl$ is 0.57 µg/mL. It indicates the ability of $3CH_2Cl$ to distribute and perfuse widely into the very deep interstitial and intracellular parts of the tissue. However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73.[3] While the optimal log P value of water-soluble compound during tablet formulation is theoretically between 2-3,[4] the reported log P value of $3CH_2Cl$ indicates the difficulties of this active compound for water-solubility.

Tablet form is one of the candidates in $3CH_2Cl$ formulation. Tablets may inhibit the hygroscopic character of $3CH_2Cl$ when stored. Tablet formulation requires the addition of several compounds such as surfactants to overcome the lipophilic character of the $3CH_2Cl$. Tablet formulation also needs a disintegrant to accelerate the dissociation of $3CH_2Cl$. The surfactants and disintegrant agents commonly used in the tablet formulation are sodium lauryl sulfate (SLS) and croscarmellose sodium (CS). The SLS has several characteristics, such as the hollow surface of the particles, easily soluble, and slight oily fatty.[5] The surface of CS has several characteristics such as a thread-root-like form, water-insoluble, and rapidly swells when hydrates.[5] The SLS is expected to accelerate the hydration of the tablet surface and increase the solubility of $3CH_2Cl$ and excipient particles. The CS is expected to accelerate the disintegration of tablets. However, the effect and the optimal amount of SLS and CS for the tablet formulation of $3CH_2Cl$ remain unclear. The novelty of this experiment is the tablet formulation of $3CH_2Cl$ using SLS as a surfactant and CS as a disintegrating agent in tablets. SLS and CS overcome $3CH_2Cl$ lipophilic problems on tablet disintegration and dissolution.

This formulation is an innovation of $3CH_2Cl$ made in tablets and new alternatives to the future analgesic drug.

This experiment aimed to determine the effect of SLS, CS, and SLS-CS combinations for the formulation of $3CH_2Cl$-tablet. In addition, this study aims to determine the optimum of the 3CH2Cl tablet formula. The effect of SLS, CS, and SLS-CS combinations was analyzed using linear and quadratic models following the simplex lattice design. It is believed that CS can accelerate the disintegration of tablets, while SLS increases hydrated tablets and the solubility of $3CH_2Cl$. This manuscript demonstrated that the tablet form of $3CH_2Cl$ using CS and SLS exerts an analgesic activity in mice writhing test. $3CH_2Cl$-tablet provides a new form of drug, which is a potential for an analgesic drug.

Material and methods

Raw materials and chemicals

Experiments using quality materials such as pro-analytical (p.a.), pharmaceutical grade (p.g.), and food grade (f.g.): salicylic acid (p.g.) (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (p.a.) (Sigma-Aldrich, GmbH, USA), pyridine (p.a.) (Merck KgaA, Darmstadt, Germany), ethanol (p.a.) (Merck KgaA, Darmstadt, Germany), neusilin (p.g.) (Gangwal Chemicals, India), croscarmellose sodium (p.g.) (FMC Biopolymer, USA), microcrystalline cellulose (p.g.) (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (p.g.) (Foremost Farm, USA), sodium hydroxide (p.a.) (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (p.a.) (Merck KgaA, Darmstadt, Germany), and distilled water (f.g.) (Brataco Chemical, Indonesia).

Synthesis and characterization of $3CH_2Cl$

Salicylic acid (1.8 mmol), 3-chloromethyl benzoyl chloride (7.2 mmol), pyridine (1.7 x 10^{-6} mmol), and acetone (14.8 x 10^{-6} mmol) were mixed homogeneously in Erlenmeyer. The mixture was microwave irradiated for 5 minutes with a Millstone Organic Synthesis Unit (MicroSYNTH). The mixture was then placed in a microwave oven (600 Watt, 1 minute). Afterwards, the mixture was evaluated with ferric chloride ($FeCl_3$) and thin-layer chromatography (TLC) (silica gel F254 stationary phase and n-hexane: ethanol (1:2) mobile phase). This test is to identify the salicylic acid in the mixture. At the beginning, pasta was prepared and then turned into a solution when irradiated by microwaves, and the final product was solid. The synthesis procedure followed the previous experiment, and the stability of $3CH_2Cl$ was proven.[1,2] Based on these reasons, the compound $3CH_2Cl$ can be used for tablet formulation.

Preparation of tablets

The tablet ingredients were weighted using the formula (Table 1) and the direct compression method. The process began by mixing $3CH_2Cl$ with Ne using a mortar and stamper until homogeneous. The mixture was transferred to a cubic mixer and added with SLS, CS, MCC, and SDL to rotate for 2 minutes at 100 rpm (Erweka). The homogeneous tablet mass was to test flowability and compressibility. The homogeneous tablet mass was compressed to form tablets (800 mg) with a single punch machine (Jenn Chian Machinery, Taiwan). Tablets were evaluated for hardness, friability, disintegration time, and drug dissolution.

Table 1. Detailed of experimental formula and prediction of optimum formula

Component	Unit	Formula			
		TA	TB	TC	T Opt.
$3CH_2Cl$	[mg]	300.00	300.00	300.00	300.00
Ne	[%]	9.38	9.38	9.38	9.38
	[mg]	75.00	75.00	75.00	75.00
SLS	[%]	0.50	0.75	1.00	0.92
	[mg]	4.00	6.00	8.00	7.36
CS	[%]	4.00	3.00	2.00	2.33
	[mg]	32.00	24.00	16.00	18.64
MCC	[%]	5.00	5.00	5.00	5.00
	[mg]	20.00	20.00	20.00	20.00
SDL ad	[mg]	800.00	800.00	800.00	800.00

Flow time

The mass of the tablet was weighed at 100 g and placed on a flowability tester funnel (Erweka, Germany). The funnel valve opened to drain the tablet mass and determine the flow time parameter. The cone of the tablet mass was scanned by infrared to determine the parameter of the angle of repose.

Compressibility

The glass measuring tube (100 mL) was weighted and recorded. Then, tablet mass was inserted to a glass measuring tube (100 mL) inclined (35^0-40^0). The glass measuring tube filled with the tablet mass was weighed and recorded. The glass measuring tube loaded the tablet mass was placed on a density tap volumeter (Erweka, Germany) and tapped 500 times. The initial and final volumes of tablet mass were recorded to determine the bulk density and tap density. Bulk density is the ratio of the tablet mass to the initial volume, while tap density is the ratio between the tablet mass and volume. Determination of the Carr index value follows Equation 1.[6]

$$Carr\ index\ (\%) = \frac{tap\ density - bulk\ density}{tap\ density}\ x\ 100\% \qquad \text{Equation 1}$$

Table 2. Evaluate of tablets mass, tablets, and dissolution on formulations of $3CH_2Cl$

Tablet code	SLS [mg]	CS [mg]	Flow time [s]	SD	Carr index [%]	Hardness [kp]	SD	Friability [%]	Disintegrating time [min.]	Drug release [%]	SD
TA	4.00	32.00	7.63	0.06	21.00	7.36	0.77	0.31	2.53	59.41	0.95
TB	6.00	24.00	8.60	0.10	24.00	8.81	0.97	0.34	4.35	69.95	1.00
TC	8.00	16.00	9.33	0.06	26.00	9.76	0.59	0.38	5.65	85.04	1.05
T Opt.	7.36	18.64	9.10	0.10	25.00	9.48	0.52	0.36	5.25	81.53	0.86
P Opt.	7.36	18.64	9.07	-	25.33	9.44	-	0.37	5.22	80.00	

The quality evaluation of tablets mass, tablets, and dissolution of each formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Hardness

Tablets (6) were randomly selected from all tablets[7,8] and placed in a hardness tester (Schleuniger, Netherlands). The tablet was pressed by a metal rod until the tablet cracked or broke. The hardness of the tablet can be read on the monitor hardness tester.

Friability

Tablets were randomly selected up to a total weight of more than 6500 mg.[7,8] All tablets were dust-free for careful weighing (Wo). The tablets were rotated on a drum friability tester (Erweka, Germany) for 4 minutes at 25 rpm. The tablets were dust-free and carefully reweighed (W1). The value of tablet friability is the difference between the total weight of the initial tablet and the total weight of the final tablet compared to the total weight of the initial tablet. Determination of the friability value follows Equation 2.

$$friability\ (\%) = \frac{Wo - W1}{Wo}\,100\% \qquad \text{Equation 2}$$

Disintegration time

Tablets (18) were selected, and six of which were randomly selected.[7,8] Tablets were placed in each tube of the disintegration tester (Erweka Z3, Germany). The cylinder moved up and down in the chamber containing distilled water at 37^0C and 900 mL. Disintegration time is the time required by six tablets for no particles/fragments to remain in the mesh in each tube.

Dissolution

Each tablet was placed in a vessel of dissolution tester (Electrolab TDT-08L, India) containing phosphate buffer medium pH 6.8 (37 ± 0.5 C; 50 rpm; 900 mL) using the basket method for 60 minutes.[9,10] A sampling of the release of $3CH_2Cl$ (5 mL) was done at 10, 20, 30,

45, and 60 minutes. The concentration of the dissolved active compound was analyzed using UV-VIS spectrophotometer (Hitachi U-1900, Japan) at the maximum wavelength.

Optimization

The optimization of the tablet formula was generated using the simplex lattice design with a two-factor method. The working concentration of SLS is 0.5%-1%, and CS is 2%-4%. The experiment used three formulas (Table 1) with the proportion of 0.50:4.00 (called TA), TB 0.75:3.00 (called TB), TC 1.00:2.00 (called TC), 0.92:2.33 (T Opt.), Flow time, Carr index, hardness, disintegrating time, and drug release were used as the optimization parameters. The optimization response was analyzed *in-silico* (Design Expert ver.10) to predict the tablet formula of $3CH_2Cl$.

Release kinetics of $3CH_2Cl$ from tablet

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using the following equations 3-6:[11–14]

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 3

Qt: the amount of drug dissolved at the time (t) [mg], Qo: the initial drug [mg], and Ko: constant drug release [mg/minute^{-1}].

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 4

Qt: the amount of drug [mg], K_H: Higuchi constant [mg/minute$^{1/2}$], and t: time [minute].

Korsmeyer-Peppas $: Q_t/Q_\infty = K_k.\ t^n$ Equation 5

Q_t/Q_∞: fraction of drug released [mg], K_k: Korsmeyer-Peppas constant [mg/minute^{-1}], and n: diffusion exponential.

Weibull $: \log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug [mg], Ti: the lag time before dissolution, a: initial fraction of drug [mg], b: shape parameter obtained from the slope of the obtained curve.

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using DDSolver software.

Analgesic activity by writhing test

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g body weight) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g body weight) or the comparator (2.05 mg/20 g body weight) was given in another group. The writhing behavior was observed within 10 minutes.

Result and discussion

Characterization of $3CH_2Cl$

Infrared spectra show the ester peak C=O at 1732.10 cm^{-1}, while the peak C-O at 1298.22 cm^{-1}, 1279.16 cm^{-1}, and 1262. 18 cm^{-1}. The carboxylate peak C=O appeared at 1694.90 cm^{-1}, while C-O at 1262.18 cm^{-1}. The peak C=C was aromatic at 1606.29 cm^{-1}, and the peak C-Cl at 704.24 cm^{-1}. The Rf value of thin layer chromatography $3CH_2Cl$ compound in the mobile phase of ethyl acetate:ethanol (1:2) is 0.91; n-hexane:ethanol (1:2) is 0.82; and chloroform:ethanol (4:1) was 0.87. The melting point value of $3CH_2Cl$ is at 109-111°C.

Formulation of $3CH_2Cl$ tablets

The $3CH_2Cl$-tablet formula was used excipients Ne, SLS, CS, MCC, SDL. Ne was used to prevent the coagulation of $3CH_2Cl$.[16–18] The SLS-CS combination improved the flowability of $3CH_2Cl$. SLS can accelerate the tablet hydration through disintegration or dissolution media. SLS also lowered the surface tension of $3CH_2Cl$ particles with a hydrating medium, thereby accelerating the solubility of the particles.[19–21] CS can swell when interacting with a hydrating-medium so that the surrounding particles were pushed, resulting in the tablet disintegration.[22–24] The MCC was used as a tablet filler for excellent tablet compatibility, while SDL was used as a high-density filler to adjust the tablet with optimal thickness.[25–27] Both MCC and SDL were ideal excipients for the direct compress method.

Determining the flow time value of $3CH_2Cl$ tablet mass

The flow time values of the three tablet mass formulas are shown in Table 2. All formula has a flow time value of less than 10 seconds. It means the tablet mass can move freely and fill the tablet machine dies.[6] The TA (7.6 seconds) formula has the fastest flow time, followed by TB (8.6 seconds) and TC (9.3 seconds) formula. The coefficient value (Table 3) from the simplex lattice design method with a linear model shows that SLS (9.35) was dominant in increasing tablet mass flow time, followed by CS (7.65). The linear model coefficient is acceptable based on statistical analysis (see supporting information Table S2). The ANOVA results from the quadratic model show a coefficient profile similar to the linear model, where the coefficients of SLS (9.30) and CS (7.60) increased the tablet mass flow time. Through a quadratic model, the combination coefficient of SLS-CS (0.60) shows that the SLS-CS combinations increased the flow time, but the SLS-CS combinations were not as dominant as SLS and CS.

Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

Polynomial coefficients according to the simplex lattice design with the linear and quadratic system. The tablet formula used contains SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

The hollow form of SLS particles caused the surface of the particles to become rough, which might inhibit the movement and increase the flow time of the tablet mass. The shape of CS particles, such as thread roots, made the particles difficult to move and increases the flow time. In addition, this character can inhibit the movement of other particles of the tablet mass component. The screw root shape of the CS particles can fill the hollow of the SLS particles so that the combination particles have a flatter surface and reduce the resistance to movement of the tablet mass.

Determining the Carr index value of $3CH_2Cl$ tablet mass

The Carr index values of the three tablet mass formulas are shown in Table 2. The TA and TB formulas have a Carr index value of less than 25%, indicating that the tablet mass was good enough to flow and move slightly and to achieve a stable arrangement in the dies chamber of the tablet machine. The TC formula has a Carr index value of more than 25%, indicating that the tablet mass can flow. The particles required more movement to achieve a stable arrangement in the tablet machine dies space. The simplex lattice design-method linear model could generate the coefficient values as presented in Table 3. Meanwhile, SLS (26.17) was the most dominant in increasing the Carr index, followed with CS (21.17). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). Quadratic model ANOVA had a coefficient profile similar to the linear model. The coefficients of SLS (26.00) and CS (21.00) increased the Carr index of the tablet mass. The quadratic model resulted in the SLS-CS combinations coefficient (2.00), showing that SLS-CS increases the Carr index. The SLS-CS combinations were less dominant than SLS and CS.

The Hollow SLS particles caused brittle particles. Therefore, when particles were subjected to mechanical stress, the particles could break into smaller sizes. The small SLS particles were difficult to flow while producing much porosity in a stable arrangement. The

screw root shape of CS particles caused the tablet mass to be difficult to move and have large porosity in a sturdy structure. The CS particles that fill the cavity of SLS particles can improve the surface morphology of the particles. Still, the remaining part of the CS particles outside the hollow can break into fine particles. Smaller CS particle size can inhibit tablet mass flow.

Determining the hardness of $3CH_2Cl$ tablets

The tablet hardness of each formula is shown in Table 2. The TC tablets were the hardest than TA and TB tablets. TC formula tablets had the strongest interlocking between particles among other formula tablets. The simplex lattice design method with a linear model produced the coefficient values (Table 3), while SLS (9.84) was the most dominant in increasing the tablet hardness, followed by CS (7.44). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. SLS (9.76) and CS (7.36) coefficients increased tablet hardness. The quadratic model produced an SLS-CS combination coefficient (1.00), indicating the SLS-CS combinations increased tablet hardness.

The $3CH_2Cl$, Ne, SLS, and CS particles filled random porosity between MCC and SDL particles. When the tablet mass was compressed, a tablet with solid interlocking and little porosity was formed. The cavity of SLS particles broke when compressed into tablets. Tablets had strong interlocking between particles and little porosity. The screw root shape of the CS particles caused the interlocking between the particles in the tablet to become elastic withstand mechanical stress. The CS particles that filled the SLS particle cavity caused the combination particles to become stronger and more elastic. The resulting tablet had strong interlocking and can withstand mechanical stress.

Determining the friability of $3CH_2Cl$ tablets

The tablet friability of each formula is shown in Table 2. The tablet orders of the most friable were TC, TB, and TA tablets. Although the tablet formula TC was the hardest, the tablet TC was the most brittle because the interlocking between the particles on the tablet surface cannot withstand mechanical movements. The simplex lattice design method with a linear model produced the coefficient values presented in Table 3, where SLS (0.38) was the most dominant in increasing tablet friability, followed by CS (0.30). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (0.38) and CS (0.31) increased tablet friability. The quadratic model resulted in an SLS-CS combinations coefficient (-0.02), indicating that the SLS-CS combinations decreased tablet friability.

The tablet constituent particles on the tablet surface and the interlocking which were not strong can be released when subjected to mechanical movement. SLS particles were at risk of breaking and forming fine particles when compressed because SLS particles are hollow. If the fine particles are on the tablet surface, the fine particles are released when receiving mechanical movement. The screw shape of the CS particles on the tablet surface was difficult for the particles to maintain interlocking when receiving mechanical movements. Particle combination between SLS and CS particles on the tablet surface can support interlocking with other particles that make up the tablet to withstand mechanical movements.

Determining the disintegration time of $3CH_2Cl$ tablets

The tablet disintegration time for each formula is shown in Table 2. The TA tablets were the fastest to disintegrate than TB and TC tablets. TA formula tablets contained the highest CS so that the more CS particles hydrate and swollen, caused the tablet to disintegrate quickly. The simplex lattice design method with a linear model produced the coefficient values

(Table 3). SLS (5.74) was the most dominant ingredient in increasing tablet friability, followed by CS (2.62). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (5.65) and CS (2.53) increased tablet disintegration time. The quadratic model resulted in an SLS-CS combination coefficient (1.04), indicating that the SLS-CS combination increased the tablet disintegration time.

Changes in SLS particle size and the formation of fine particles when the tablet mass was compressed caused the tablet to have a dense porosity. The disintegrating medium was difficult to penetrate the tablet and slow down the disintegration. CS particles can function as disintegrants if particles are hydrated and swell. CS particles needed time to hydrate and swell all the particles so that the tablet disintegrates longer. The SLS-CS combinations particles narrowed the porosity of the tablet so that there was less passage for the disintegrating medium. In addition, tablet hardness increased the disintegration time because the hard tablet had narrow porosity, so the disintegrating medium was difficult to penetrate the tablet.

Determining the drug release of $3CH_2Cl$ tablets

Drug release from each tablet is shown in Table 2 and a detailed profile in Figure 1 (detail see supporting information Table S1). Tablets TC with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. The TC formula tablets contained the highest SLS, reducing the surface tension between the $3CH_2Cl$ particles and the dissolution medium. The simplex lattice design method with a linear model resulted in the coefficient values as presented in Table 3, where SLS (84.28) was the most dominant in increasing drug release, followed by CS (58.65). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (85.04) and CS (59.41)

increased the release of $3CH_2Cl$. The quadratic model resulted in an SLS-CS combinations coefficient (-9.10), indicating that the SLS-CS combinations decreased the solubility of $3CH_2Cl$.

Hollow SLS particles can accelerate the solubility of SLS. The dissolved SLS particles reduced the surface tension of the $3CH_2Cl$ particles with the dissolution medium. Swelling CS particles forced the tablet to disintegrate into tiny particles, thereby increasing the surface area of the $3CH_2Cl$ particles in contact with the dissolution medium. SLS-CS combination particles have a narrow porosity, so the medium was difficult to hydrate other particles and inhibits the solubility of $3CH_2Cl$ particles.

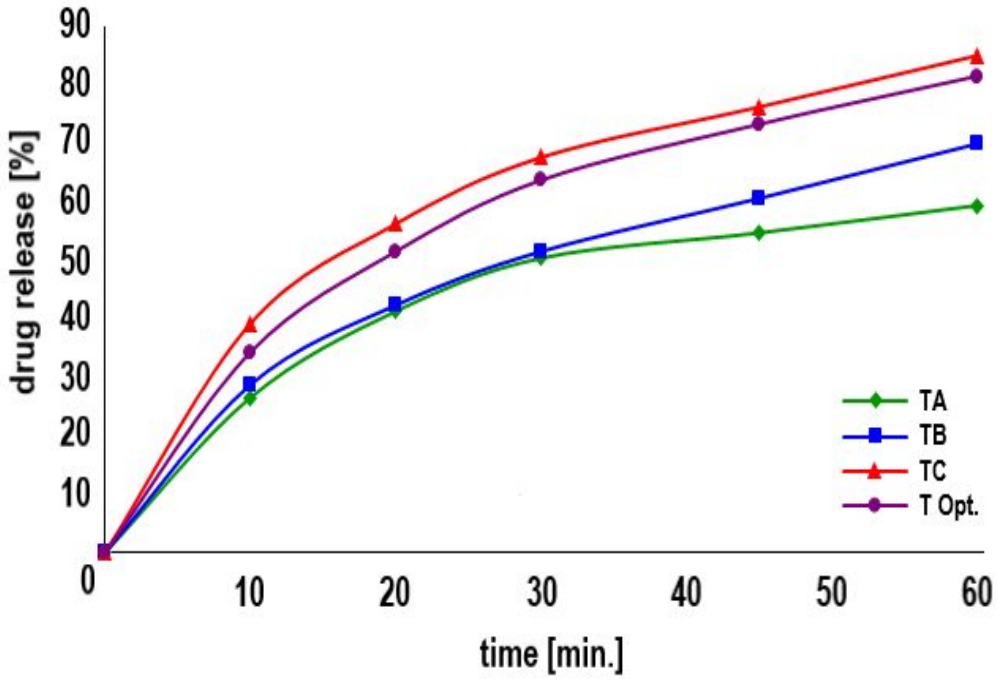

Figure 1. Dissolution profile of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Simplex lattice design and ANOVA of $3CH_2Cl$ tablets

This experiment used the simplex lattice design because the optimization factor for the concentration of SLS and CS is an internal factor of the tablet formula, without any external factors. Linear and quadratic models were used to support each other in predicting the effect of SLS, CS, and a combination of SLS-CS (Table 3 and Figure 2). ANOVA from a linear model can provide R-Squared, Adj R-Squared, Pred R-Squared, and Adeq Precision values to evaluate the model's acceptability. The coefficient of the polynomial equation of the linear model is accepted if the difference between R-Square and Pred R-Square is less than 0.2 and Adeq Precision is more than 4. Thus, the polynomial coefficients can be used to predict the effect of SLS and CS. The weakness of the linear model is that it cannot predict the impact of the combination of SLS with CS. The quadratic model can produce polynomial coefficients for the influence of SLS, CS, and SLS-CS combinations. However, the quadratic model cannot represent ANOVA parameters like a linear model because of the limited experimental formulas. The effort to maximize these two models in predicting the effect of SLS, CS, and SLS-CS combinations by analyzing the similarity of SLS and CS coefficients is critical. The profiles of the SLS and CS coefficients from the two models are similar. In that case, the coefficient values of the SLS-CS combination in the quadratic model can be used to predict the effect of the SLS-CS combination. The profiles of SLS and CS were similar, so that the coefficient values of SLS-CS combined in the quadratic model can be used to predict the effect of the SLS-CS combination on the tablet formulation parameter of the $3CH_2Cl$. Both models are beneficial for experiments using a limited number of formulas due to the availability of $3CH_2Cl$ synthesized by laboratory capacity. Prediction of the optimum formula in this experiment was done numerically according to a linear model. Predicted (P Opt.) and verified (T Opt.) optimum tablet formulas are presented in Table 2.

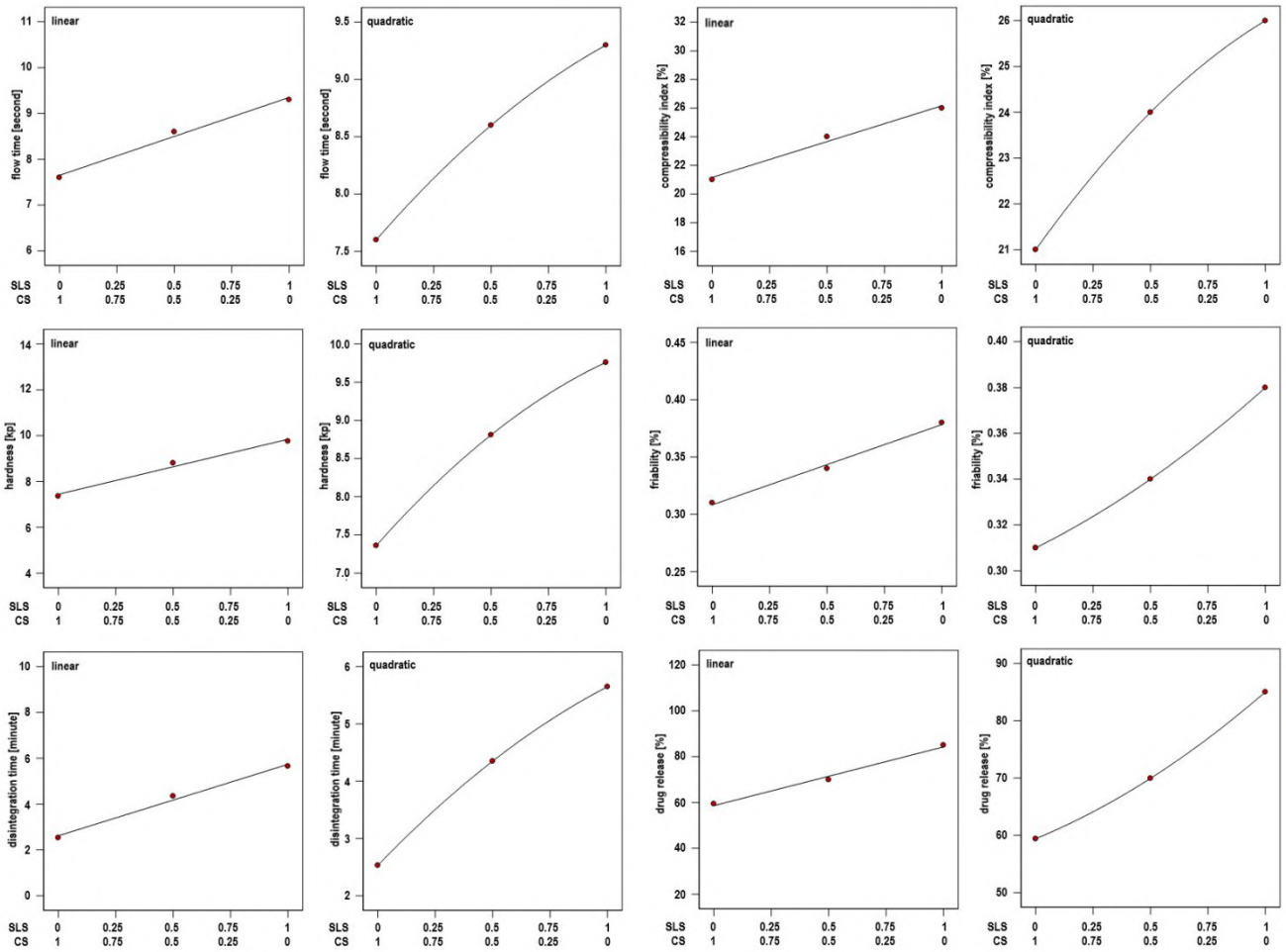

Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

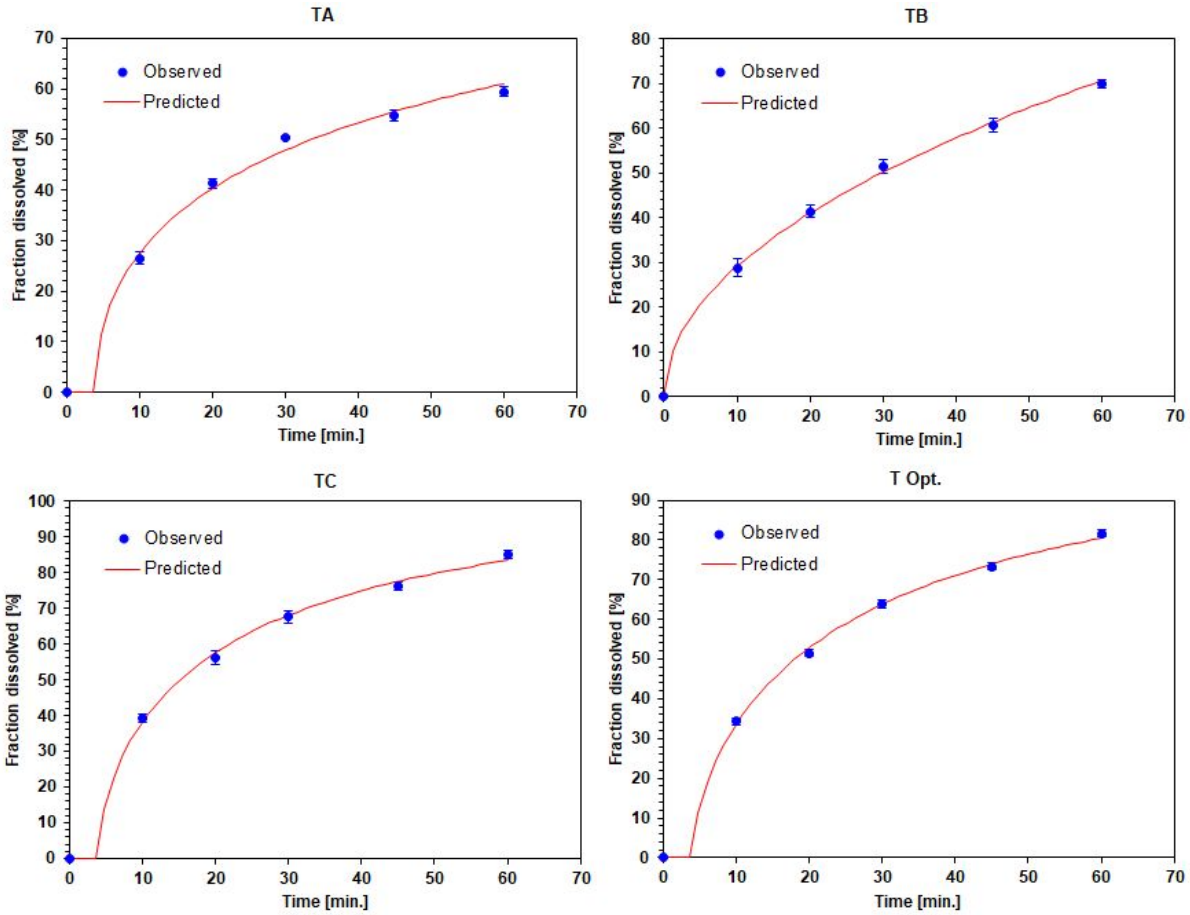

Figure 3. The kinetics profile of the release of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00) (Weibull), TB (0.75:3.00) (Higuchi), TC (1.00:2.00) (Weibull), and T Opt. (0.92:2.33) (Weibull).

Release kinetics of $3CH_2Cl$ tablets

The release kinetics models of $3CH_2Cl$ from tablets were analyzed using DDSolver. Rsqr_adj shows the correlation between dissolution time and release of $3CH_2Cl$. MSE_root determinated the correlation analysis correction, while AIC demonstrated the suitability of the equation for determining the release kinetics model.[28–31] The results of the DDSolver analysis are shown in Table 4 and Figure 3 (detail see supporting information Figure S1-S4).

The TA and TC formulas following the Weibull release kinetics model show that $3CH_2Cl$ was released from the tablet without any delay. The presence of SLS lowered the

surface tension of $3CH_2Cl$ with the dissolution medium so that the particles dissolved quickly. This was also supported by the presence of CS, which accelerates the disintegration of tablets into granules or particles thereby expanding the surface of the particles to dissolve.

The Higuchi release kinetics model of TB formula shows that the release was influenced by the diffusion mechanism of $3CH_2Cl$ out of the tablet. SLS on the tablet surface accelerated hydrating and was followed by the formation of a hydration layer so that the particles dissolve and leave the tablet. CS served as a disintegrating agent after hydrating and swelling. This condition took time, so that $3CH_2Cl$ was allowed to dissolve and diffuse before the CS can function.

Table 4. Evaluation of the release kinetics of $3CH_2Cl$

Formula code	Parameter	First order		Higuchi		Korsmeyer-Peppas		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	
TA	Rsqr_adj	0.8545	0.02	0.9721	0.01	0.9779	0.01	0.9907	0.01	Weibull
	MSE_root	8.4740	0.47	3.6791	0.57	3.2431	0.75	2.0408	0.80	
	AIC	37.2882	0.67	27.1910	1.89	26.2323	2.67	20.5635	4.56	
TB	Rsqr_adj	0.9475	0.01	0.9966	0.00	0.9961	0.00	0.9917	0.00	Higuchi
	MSE_root	5.7427	0.56	1.4227	0.47	1.5214	0.53	2.2621	0.46	
	AIC	32.5953	1.14	15.3644	4.53	16.8557	4.27	22.229	2.35	
TC	Rsqr_adj	0.9578	0.01	0.9885	0.00	0.9949	0.00	0.9963	0.00	Weibull
	MSE_root	6.3475	0.45	3.3264	0.47	2.221	0.13	1.8553	0.28	
	AIC	33.8125	0.87	26.0793	1.49	21.8932	0.65	19.9178	1.81	
T Opt.	Rsqr_adj	0.9686	0.01	0.9926	0.00	0.9925	0.01	0.9979	0.00	Weibull
	MSE_root	5.2892	0.42	2.5394	0.52	2.5334	0.39	1.2986	0.53	
	AIC	31.6188	0.97	22.6583	2.61	23.2554	0.57	14.8858	5.82	

The release kinetics of $3CH_2Cl$ from each tablet formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33). The model selection was high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC).

The $3CH_2Cl$-tablet showed analgesic activity in mice writhing test

This experiment was conducted using a T Opt. tablet to determine the effect of excipients on the analgesic activity of $3CH_2Cl$. The results of the analgesic activity test of $3CH_2Cl$ are presented in Figure 4. The control group produced a very high amount of writhing-

response (78.83 ± 4.17), indicating the success of pain induction using 0.6% acetic acid (dose of 0.01 mL/g body weight). The number of writhes of the T Opt. group (18.17 ± 3.19) was less than the control group, showing that the $3CH_2Cl$ can suppress pain. The analgesic activity of the $3CH_2Cl$ was more effective than that of the comparison compound because the $3CH_2Cl$ had less amount of writhe than the comparison compound (52.83 ± 3.87). The significant difference in the amount of writhe of the three groups ($P < 0.05$) shows that the $3CH_2Cl$ had analgesic activity despite presence tablets excipients.

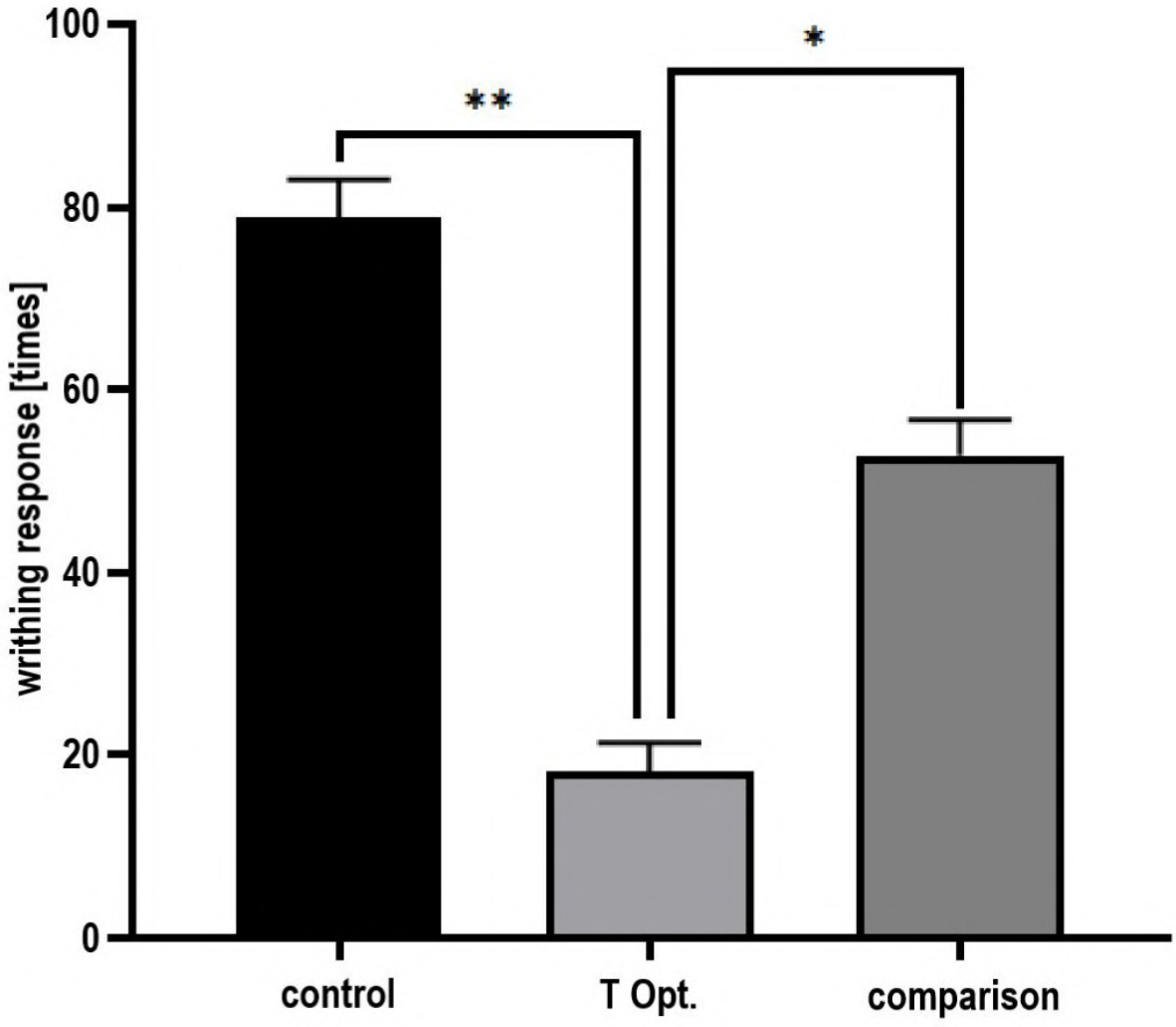

Figure 4. Analgesic activity of $3CH_2Cl$.

The control group is mice given excipient tablets. The active compound group in mice was assigned $3CH_2Cl$ tablets. The comparison group was mice given acetylsalicylic acid tablets. The three groups induced pain using 0.01 mL/g body weight of 0.6% acetic acid. The significant difference in the amount of writhe of the three groups ($P < 0.05$) indicated that $3CH_2Cl$ still has analgesic activity despite the presence of tablet excipients.

Conclusion

The polynomial coefficient values of the two models show that the SLS, CS, and SLS-CS combinations increased the parameter values of flow time, Carr index, hardness, and disintegration time. The SLS-CS combination decreased the friability value and the drug release parameters. The optimum tablet formulas of $3CH_2Cl$ tablet were $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and adjusted with SDL until 800 mg total weight. Quality predictions of tablet mass were flow time (9.07 seconds); Carr index (25.33%). Quality tablets predictions are hardness (9.44 kp), friability (0.37%), disintegration time (5.22 minutes), and drug released 60 minutes (80%). The SLS was to increase the solubility particles of $3CH_2Cl$ and excipient. The CS had accelerated the disintegration of tablets into particles. The tablet dosage form of $3CH_2Cl$ is an innovative formulation and a new alternative to the future analgesic drug.

Associated Content

Supporting Information

Tablet dosage calculation; the release of $3CH_2Cl$ from the tablets; statistical analysis of $3CH_2Cl$ tablets; the kinetics profile of the release of $3CH_2Cl$ from TA, TB, TC, and T Opt. tablets.

Acknowledgment

The authors thank the Research and Community Service Institute of Widya Mandala Catholic University, Surabaya, Indonesia was supporting grants (5230/WM01/N/2021). The authors also would like to thank Khaterine Irene Phuk, Sherlilyta Stiara Dewi, Angela Tiffany, and Meidelin Ribka Abiati for their assistance during the experiment.

Declarations

Competing interest statement

The authors declare no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: Designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Kuncoro Foe, Yudy Tjahjono, Caroline, Senny Yesery Esar, Maria Annabela Jessica: performed the experiments, analyzed, and interpreted the data.

Statement of Human and Animal Rights

Experiments using experimental animals (mice) have been declared to meet the ethical requirements from the Research Ethics Commission of the Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta, Indonesia with No. 001/EC-FKH/Ex./2022 dated January 14, 2022.

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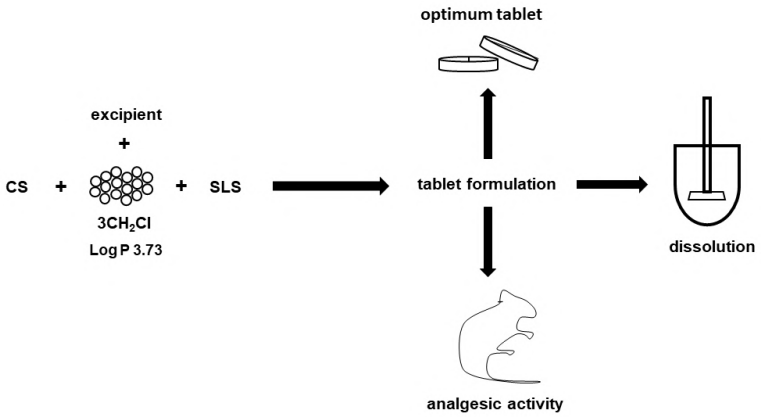

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Response to revisions requested

Revisions requested

1. Please remove the track changes and color from your MS and SI file text.

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Thank you for the suggestions. We have removed track and color changes from MS and SI file text. Here we attach an example of a change.

MS

Before revision

Determining the drug release of $3CH_2Cl$ tablets

Drug release from each tablet is shown in Table 2 and a detailed profile in Figure 1 (detail see supporting information Table S1). Tablets TC with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. ~~Tablets with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas.~~ The TC formula tablets contained the highest SLS, reducing the surface tension between the $3CH_2Cl$ particles and the dissolution medium. The simplex lattice design method with a linear model resulted in the coefficient values as presented in Table 3, where SLS (84.28) was the most dominant in increasing drug release, followed by CS (58.65). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (85.04) and CS (59.41) increased the release of $3CH_2Cl$. The quadratic model resulted in an SLS-CS combinations coefficient (-9.10), indicating that the SLS-CS combinations decreased the solubility of $3CH_2Cl$.

After revision

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SI

Before revision

Figure S4. The kinetics profile of the release of $3CH_2Cl$ from T Opt. tablets with various model kinetic. Based on the profile, the point of observation is most similar to the Higuchi model prediction line with a value of Rsqr_adj 0.9979; MSE_root 1.2986; and AIC 14.8858.

After revision

Figure S4. The kinetics profile of the release of $3CH_2Cl$ from T Opt. tablets with various model kinetic. Based on the profile, the point of observation is most similar to the Higuchi model prediction line with a value of Rsqr_adj 0.9979; MSE_root 1.2986; and AIC 14.8858.

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Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

After revision

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

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Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
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Manuscript ID Number

ao-2022-031476.R2

Manuscript Title

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Journal Title

ACS Omega

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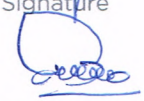
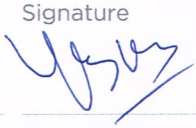
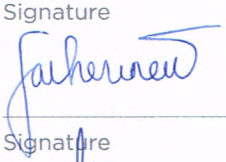
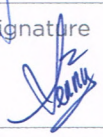
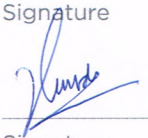
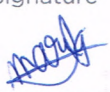
Kuncoro Foe		11/08/2022
Yudy Tjahjono		11/08/2022
Caroline Caroline		11/08/2022
Senny Yesery Esar		11/08/2022
Hendy Wijaya		11/08/2022
Maria Annabella Jessica		11/08/2022

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

Journal:	*ACS Omega*
Manuscript ID	ao-2022-031476.R3
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Pharmacy Foe, Kuncoro; Widya Mandala Catholic University Surabaya Tjahjono, Yudy; Widya Mandala Catholic University Surabaya, Pharmacy Caroline, Caroline; Widya Mandala Catholic University Surabaya, Pharmacy Esar, Senny; Widya Mandala Catholic University Surabaya, Pharmacy Wijaya, Hendy; Widya Mandala Catholic University Surabaya, Pharmacy Jessica, Maria ; Widya Mandala Catholic University Surabaya, Pharmacy

Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models

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Abstract

Purpose: This research to determine the effect of sodium lauryl sulfate (SLS) as surfactants, croscarmellose sodium (CS) as a disintegrating agent, and SLS-CS combinations on 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) (log P = 3.73) tablet formulations. In addition, this study aims to determine the optimum of the $3CH_2Cl$ tablet formula.

Methods: The tablets are manufactured through direct compression according to the simplex lattice design. The optimal SLS and CS concentration was determined in-vitro using linear and quadratic models to achieve better tablet disintegration and dissolution.

Results: The same linear and quadratic coefficient profiles of SLS and CS indicate that the combined coefficient of SLS-CS with a quadratic model can be used to predict the effect of the SLS-CS combination. Based on the linear model coefficients, SLS and CS increase the value of flow time (9.35; 7.65), Carr index (26.17; 21.17), hardness (9.84; 7.44), friability (0.38; 0.31), disintegrating time (5.74; 2.62), and drug release (84.28; 58.65). The quadratic model coefficient shows that SLS-CS combinations increase flow time (0.60), Carr index (2.00), hardness (1.00), and disintegrating time (1.04). Meanwhile, SLS-CS combinations decrease friability (-0.02) and drug release (-9.10).

Conclusion: SLS, CS, and SLS-CS combinations affect the quality of tablets mass and tablets. The optimum tablet formula was $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and SDL (ad 800 mg). The $3CH_2Cl$ has analgesic activity despite the presence of tablet excipients. The $3CH_2Cl$ tablet is an innovative formulation and new alternative to the future analgesic drug.

Introduction

The 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid ($3CH_2Cl$) is a new compound synthesized from acetylsalicylic acid and 3-chloromethyl benzoyl chloride.[1,2] $3CH_2Cl$ is very potential as an analgesic, an anti-platelet aggregation, and an anti-inflammation drug.[1,2] A previous study reported that the active compound of $3CH_2Cl$ could significantly reduce the nociceptive response in mice.[2] The C_{max} value of $3CH_2Cl$ is 0.57 µg/mL. It indicates the ability of $3CH_2Cl$ to distribute and perfuse widely into the very deep interstitial and intracellular parts of the tissue. However, the lipophilic value of $3CH_2Cl$ (log P) is 3.73.[3] While the optimal log P value of water-soluble compound during tablet formulation is theoretically between 2-3,[4] the reported log P value of $3CH_2Cl$ indicates the difficulties of this active compound for water-solubility.

Tablet form is one of the candidates in $3CH_2Cl$ formulation. Tablets may inhibit the hygroscopic character of $3CH_2Cl$ when stored. Tablet formulation requires the addition of several compounds such as surfactants to overcome the lipophilic character of the $3CH_2Cl$. Tablet formulation also needs a disintegrant to accelerate the dissociation of $3CH_2Cl$. The surfactants and disintegrant agents commonly used in the tablet formulation are sodium lauryl sulfate (SLS) and croscarmellose sodium (CS). The SLS has several characteristics, such as the hollow surface of the particles, easily soluble, and slight oily fatty.[5] The surface of CS has several characteristics such as a thread-root-like form, water-insoluble, and rapidly swells when hydrates.[5] The SLS is expected to accelerate the hydration of the tablet surface and increase the solubility of $3CH_2Cl$ and excipient particles. The CS is expected to accelerate the disintegration of tablets. However, the effect and the optimal amount of SLS and CS for the tablet formulation of $3CH_2Cl$ remain unclear. The novelty of this experiment is the tablet formulation of $3CH_2Cl$ using SLS as a surfactant and CS as a disintegrating agent in tablets. SLS and CS overcome $3CH_2Cl$ lipophilic problems on tablet disintegration and dissolution.

This formulation is an innovation of $3CH_2Cl$ made in tablets and new alternatives to the future analgesic drug.

This experiment aimed to determine the effect of SLS, CS, and SLS-CS combinations for the formulation of $3CH_2Cl$-tablet. In addition, this study aims to determine the optimum of the 3CH2Cl tablet formula. The effect of SLS, CS, and SLS-CS combinations was analyzed using linear and quadratic models following the simplex lattice design. It is believed that CS can accelerate the disintegration of tablets, while SLS increases hydrated tablets and the solubility of $3CH_2Cl$. This manuscript demonstrated that the tablet form of $3CH_2Cl$ using CS and SLS exerts an analgesic activity in mice writhing test. $3CH_2Cl$-tablet provides a new form of drug, which is a potential for an analgesic drug.

Material and methods

Raw materials and chemicals

Experiments using quality materials such as pro-analytical (p.a.), pharmaceutical grade (p.g.), and food grade (f.g.): salicylic acid (p.g.) (PT. Brataco, Indonesia), 3-chloromethyl benzoyl chloride (p.a.) (Sigma-Aldrich, GmbH, USA), pyridine (p.a.) (Merck KgaA, Darmstadt, Germany), ethanol (p.a.) (Merck KgaA, Darmstadt, Germany), neusilin (p.g.) (Gangwal Chemicals, India), croscarmellose sodium (p.g.) (FMC Biopolymer, USA), microcrystalline cellulose (p.g.) (Flocel 102, Gujarat Microwax PVT. LTD, India), spray-dried lactose (p.g.) (Foremost Farm, USA), sodium hydroxide (p.a.) (Merck KgaA, Darmstadt, Germany), potassium dihydrogen phosphate (p.a.) (Merck KgaA, Darmstadt, Germany), and distilled water (f.g.) (Brataco Chemical, Indonesia).

Synthesis and characterization of $3CH_2Cl$

Salicylic acid (1.8 mmol), 3-chloromethyl benzoyl chloride (7.2 mmol), pyridine (1.7 x 10^{-6} mmol), and acetone (14.8 x 10^{-6} mmol) were mixed homogeneously in Erlenmeyer. The mixture was microwave irradiated for 5 minutes with a Millstone Organic Synthesis Unit (MicroSYNTH). The mixture was then placed in a microwave oven (600 Watt, 1 minute). Afterwards, the mixture was evaluated with ferric chloride ($FeCl_3$) and thin-layer chromatography (TLC) (silica gel F254 stationary phase and n-hexane: ethanol (1:2) mobile phase). This test is to identify the salicylic acid in the mixture. At the beginning, pasta was prepared and then turned into a solution when irradiated by microwaves, and the final product was solid. The synthesis procedure followed the previous experiment, and the stability of $3CH_2Cl$ was proven.[1,2] Based on these reasons, the compound $3CH_2Cl$ can be used for tablet formulation.

Preparation of tablets

The tablet ingredients were weighted using the formula (Table 1) and the direct compression method. The process began by mixing $3CH_2Cl$ with Ne using a mortar and stamper until homogeneous. The mixture was transferred to a cubic mixer and added with SLS, CS, MCC, and SDL to rotate for 2 minutes at 100 rpm (Erweka). The homogeneous tablet mass was to test flowability and compressibility. The homogeneous tablet mass was compressed to form tablets (800 mg) with a single punch machine (Jenn Chian Machinery, Taiwan). Tablets were evaluated for hardness, friability, disintegration time, and drug dissolution.

Table 1. Detailed of experimental formula and prediction of optimum formula

Component	Unit	Formula			
		TA	TB	TC	T Opt.
$3CH_2Cl$	[mg]	300.00	300.00	300.00	300.00
Ne	[%]	9.38	9.38	9.38	9.38
	[mg]	75.00	75.00	75.00	75.00
SLS	[%]	0.50	0.75	1.00	0.92
	[mg]	4.00	6.00	8.00	7.36
CS	[%]	4.00	3.00	2.00	2.33
	[mg]	32.00	24.00	16.00	18.64
MCC	[%]	5.00	5.00	5.00	5.00
	[mg]	20.00	20.00	20.00	20.00
SDL ad	[mg]	800.00	800.00	800.00	800.00

Flow time

The mass of the tablet was weighed at 100 g and placed on a flowability tester funnel (Erweka, Germany). The funnel valve opened to drain the tablet mass and determine the flow time parameter. The cone of the tablet mass was scanned by infrared to determine the parameter of the angle of repose.

Compressibility

The glass measuring tube (100 mL) was weighted and recorded. Then, tablet mass was inserted to a glass measuring tube (100 mL) inclined (35^0-40^0). The glass measuring tube filled with the tablet mass was weighed and recorded. The glass measuring tube loaded the tablet mass was placed on a density tap volumeter (Erweka, Germany) and tapped 500 times. The initial and final volumes of tablet mass were recorded to determine the bulk density and tap density. Bulk density is the ratio of the tablet mass to the initial volume, while tap density is the ratio between the tablet mass and volume. Determination of the Carr index value follows Equation 1.[6]

$$Carr\ index\ (\%) = \frac{tap\ density - bulk\ density}{tap\ density}\ x\ 100\% \qquad \text{Equation 1}$$

Table 2. Evaluate of tablets mass, tablets, and dissolution on formulations of $3CH_2Cl$

Tablet code	SLS [mg]	CS [mg]	Flow time [s]	SD	Carr index [%]	Hardness [kp]	SD	Friability [%]	Disintegrating time [min.]	Drug release [%]	SD
TA	4.00	32.00	7.63	0.06	21.00	7.36	0.77	0.31	2.53	59.41	0.95
TB	6.00	24.00	8.60	0.10	24.00	8.81	0.97	0.34	4.35	69.95	1.00
TC	8.00	16.00	9.33	0.06	26.00	9.76	0.59	0.38	5.65	85.04	1.05
T Opt.	7.36	18.64	9.10	0.10	25.00	9.48	0.52	0.36	5.25	81.53	0.86
P Opt.	7.36	18.64	9.07	-	25.33	9.44	-	0.37	5.22	80.00	

The quality evaluation of tablets mass, tablets, and dissolution of each formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Hardness

Tablets (6) were randomly selected from all tablets[7,8] and placed in a hardness tester (Schleuniger, Netherlands). The tablet was pressed by a metal rod until the tablet cracked or broke. The hardness of the tablet can be read on the monitor hardness tester.

Friability

Tablets were randomly selected up to a total weight of more than 6500 mg.[7,8] All tablets were dust-free for careful weighing (Wo). The tablets were rotated on a drum friability tester (Erweka, Germany) for 4 minutes at 25 rpm. The tablets were dust-free and carefully reweighed (W1). The value of tablet friability is the difference between the total weight of the initial tablet and the total weight of the final tablet compared to the total weight of the initial tablet. Determination of the friability value follows Equation 2.

$$friability\ (\%) = \frac{Wo - W1}{Wo}\,100\% \qquad \text{Equation 2}$$

Disintegration time

Tablets (18) were selected, and six of which were randomly selected.[7,8] Tablets were placed in each tube of the disintegration tester (Erweka Z3, Germany). The cylinder moved up and down in the chamber containing distilled water at 37^0C and 900 mL. Disintegration time is the time required by six tablets for no particles/fragments to remain in the mesh in each tube.

Dissolution

Each tablet was placed in a vessel of dissolution tester (Electrolab TDT-08L, India) containing phosphate buffer medium pH 6.8 (37 ± 0.5 C; 50 rpm; 900 mL) using the basket method for 60 minutes.[9,10] A sampling of the release of $3CH_2Cl$ (5 mL) was done at 10, 20, 30,

45, and 60 minutes. The concentration of the dissolved active compound was analyzed using UV-VIS spectrophotometer (Hitachi U-1900, Japan) at the maximum wavelength.

Optimization

The optimization of the tablet formula was generated using the simplex lattice design with a two-factor method. The working concentration of SLS is 0.5%-1%, and CS is 2%-4%. The experiment used three formulas (Table 1) with the proportion of 0.50:4.00 (called TA), TB 0.75:3.00 (called TB), TC 1.00:2.00 (called TC), 0.92:2.33 (T Opt.), Flow time, Carr index, hardness, disintegrating time, and drug release were used as the optimization parameters. The optimization response was analyzed *in-silico* (Design Expert ver.10) to predict the tablet formula of $3CH_2Cl$.

Release kinetics of $3CH_2Cl$ from tablet

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using the following equations 3-6:[11–14]

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 3

Qt: the amount of drug dissolved at the time (t) [mg], Qo: the initial drug [mg], and Ko: constant drug release [mg/minute^{-1}].

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 4

Qt: the amount of drug [mg], K_H: Higuchi constant [mg/minute$^{1/2}$], and t: time [minute].

Korsmeyer-Peppas $: Q_t/Q_\infty = K_k.\ t^n$ Equation 5

Q_t/Q_∞: fraction of drug released [mg], K_k: Korsmeyer-Peppas constant [mg/minute^{-1}], and n: diffusion exponential.

Weibull $: \log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 6

(1-m): fraction of insoluble drug [mg], Ti: the lag time before dissolution, a: initial fraction of drug [mg], b: shape parameter obtained from the slope of the obtained curve.

The release kinetics of $3CH_2Cl$ from each tablet formula was analyzed using DDSolver software.

Analgesic activity by writhing test

In this study, 2-3 months male mice (*mus musculus*) weighed about 20-25 grams were used to measure the analgesic activity. The writhing test consisted of control groups, active compound group, and comparator group. Each group consisted of 6 mice. Pain were generated using intraperitoneal injection (0.01 ml/g body weight) of 0.6% acetic acid.[15] The successful induction of pain was characterized by writhing reactions in mice, such as stretching, the extension of the hind legs, and stomach contraction. For the negative control, mice were given a mixture of excipient and 3% PGA orally, followed with intraperitoneal acetic acid injection after 30 minutes. The active compound (1.23 mg/20 g body weight) or the comparator (2.05 mg/20 g body weight) was given in another group. The writhing behavior was observed within 10 minutes.

Result and discussion

Characterization of $3CH_2Cl$

Infrared spectra show the ester peak C=O at 1732.10 cm^{-1}, while the peak C-O at 1298.22 cm^{-1}, 1279.16 cm^{-1}, and 1262. 18 cm^{-1}. The carboxylate peak C=O appeared at 1694.90 cm^{-1}, while C-O at 1262.18 cm^{-1}. The peak C=C was aromatic at 1606.29 cm^{-1}, and the peak C-Cl at 704.24 cm^{-1}. The Rf value of thin layer chromatography $3CH_2Cl$ compound in the mobile phase of ethyl acetate:ethanol (1:2) is 0.91; n-hexane:ethanol (1:2) is 0.82; and chloroform:ethanol (4:1) was 0.87. The melting point value of $3CH_2Cl$ is at 109-111°C.

Formulation of $3CH_2Cl$ tablets

The $3CH_2Cl$-tablet formula was used excipients Ne, SLS, CS, MCC, SDL. Ne was used to prevent the coagulation of $3CH_2Cl$.[16–18] The SLS-CS combination improved the flowability of $3CH_2Cl$. SLS can accelerate the tablet hydration through disintegration or dissolution media. SLS also lowered the surface tension of $3CH_2Cl$ particles with a hydrating medium, thereby accelerating the solubility of the particles.[19–21] CS can swell when interacting with a hydrating-medium so that the surrounding particles were pushed, resulting in the tablet disintegration.[22–24] The MCC was used as a tablet filler for excellent tablet compatibility, while SDL was used as a high-density filler to adjust the tablet with optimal thickness.[25–27] Both MCC and SDL were ideal excipients for the direct compress method.

Determining the flow time value of $3CH_2Cl$ tablet mass

The flow time values of the three tablet mass formulas are shown in Table 2. All formula has a flow time value of less than 10 seconds. It means the tablet mass can move freely and fill the tablet machine dies.[6] The TA (7.6 seconds) formula has the fastest flow time, followed by TB (8.6 seconds) and TC (9.3 seconds) formula. The coefficient value (Table 3) from the simplex lattice design method with a linear model shows that SLS (9.35) was dominant in increasing tablet mass flow time, followed by CS (7.65). The linear model coefficient is acceptable based on statistical analysis (see supporting information Table S2). The ANOVA results from the quadratic model show a coefficient profile similar to the linear model, where the coefficients of SLS (9.30) and CS (7.60) increased the tablet mass flow time. Through a quadratic model, the combination coefficient of SLS-CS (0.60) shows that the SLS-CS combinations increased the flow time, but the SLS-CS combinations were not as dominant as SLS and CS.

Table 3. The polynomial coefficient of each parameter quality of tablets mass and tablets

Component	Flow time		Carr index		Hardness		Friability		Disintegrating time		Drug release	
	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic	linear	quadratic
SLS	9.35	9.30	26.17	26.00	9.84	9.76	0.38	0.38	5.74	5.65	84.28	85.04
CS	7.65	7.60	21.17	21.00	7.44	7.36	0.31	0.31	2.62	2.53	58.65	59.41
SLS-CS		0.60		2.00		1.00		-0.02		1.04		-9.10

Polynomial coefficients according to the simplex lattice design with the linear and quadratic system. The tablet formula used contains SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), and TC (1.00:2.00).

The hollow form of SLS particles caused the surface of the particles to become rough, which might inhibit the movement and increase the flow time of the tablet mass. The shape of CS particles, such as thread roots, made the particles difficult to move and increases the flow time. In addition, this character can inhibit the movement of other particles of the tablet mass component. The screw root shape of the CS particles can fill the hollow of the SLS particles so that the combination particles have a flatter surface and reduce the resistance to movement of the tablet mass.

Determining the Carr index value of $3CH_2Cl$ tablet mass

The Carr index values of the three tablet mass formulas are shown in Table 2. The TA and TB formulas have a Carr index value of less than 25%, indicating that the tablet mass was good enough to flow and move slightly and to achieve a stable arrangement in the dies chamber of the tablet machine. The TC formula has a Carr index value of more than 25%, indicating that the tablet mass can flow. The particles required more movement to achieve a stable arrangement in the tablet machine dies space. The simplex lattice design-method linear model could generate the coefficient values as presented in Table 3. Meanwhile, SLS (26.17) was the most dominant in increasing the Carr index, followed with CS (21.17). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). Quadratic model ANOVA had a coefficient profile similar to the linear model. The coefficients of SLS (26.00) and CS (21.00) increased the Carr index of the tablet mass. The quadratic model resulted in the SLS-CS combinations coefficient (2.00), showing that SLS-CS increases the Carr index. The SLS-CS combinations were less dominant than SLS and CS.

The Hollow SLS particles caused brittle particles. Therefore, when particles were subjected to mechanical stress, the particles could break into smaller sizes. The small SLS particles were difficult to flow while producing much porosity in a stable arrangement. The

screw root shape of CS particles caused the tablet mass to be difficult to move and have large porosity in a sturdy structure. The CS particles that fill the cavity of SLS particles can improve the surface morphology of the particles. Still, the remaining part of the CS particles outside the hollow can break into fine particles. Smaller CS particle size can inhibit tablet mass flow.

Determining the hardness of $3CH_2Cl$ tablets

The tablet hardness of each formula is shown in Table 2. The TC tablets were the hardest than TA and TB tablets. TC formula tablets had the strongest interlocking between particles among other formula tablets. The simplex lattice design method with a linear model produced the coefficient values (Table 3), while SLS (9.84) was the most dominant in increasing the tablet hardness, followed by CS (7.44). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. SLS (9.76) and CS (7.36) coefficients increased tablet hardness. The quadratic model produced an SLS-CS combination coefficient (1.00), indicating the SLS-CS combinations increased tablet hardness.

The $3CH_2Cl$, Ne, SLS, and CS particles filled random porosity between MCC and SDL particles. When the tablet mass was compressed, a tablet with solid interlocking and little porosity was formed. The cavity of SLS particles broke when compressed into tablets. Tablets had strong interlocking between particles and little porosity. The screw root shape of the CS particles caused the interlocking between the particles in the tablet to become elastic withstand mechanical stress. The CS particles that filled the SLS particle cavity caused the combination particles to become stronger and more elastic. The resulting tablet had strong interlocking and can withstand mechanical stress.

Determining the friability of $3CH_2Cl$ tablets

The tablet friability of each formula is shown in Table 2. The tablet orders of the most friable were TC, TB, and TA tablets. Although the tablet formula TC was the hardest, the tablet TC was the most brittle because the interlocking between the particles on the tablet surface cannot withstand mechanical movements. The simplex lattice design method with a linear model produced the coefficient values presented in Table 3, where SLS (0.38) was the most dominant in increasing tablet friability, followed by CS (0.30). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (0.38) and CS (0.31) increased tablet friability. The quadratic model resulted in an SLS-CS combinations coefficient (-0.02), indicating that the SLS-CS combinations decreased tablet friability.

The tablet constituent particles on the tablet surface and the interlocking which were not strong can be released when subjected to mechanical movement. SLS particles were at risk of breaking and forming fine particles when compressed because SLS particles are hollow. If the fine particles are on the tablet surface, the fine particles are released when receiving mechanical movement. The screw shape of the CS particles on the tablet surface was difficult for the particles to maintain interlocking when receiving mechanical movements. Particle combination between SLS and CS particles on the tablet surface can support interlocking with other particles that make up the tablet to withstand mechanical movements.

Determining the disintegration time of $3CH_2Cl$ tablets

The tablet disintegration time for each formula is shown in Table 2. The TA tablets were the fastest to disintegrate than TB and TC tablets. TA formula tablets contained the highest CS so that the more CS particles hydrate and swollen, caused the tablet to disintegrate quickly. The simplex lattice design method with a linear model produced the coefficient values

(Table 3). SLS (5.74) was the most dominant ingredient in increasing tablet friability, followed by CS (2.62). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (5.65) and CS (2.53) increased tablet disintegration time. The quadratic model resulted in an SLS-CS combination coefficient (1.04), indicating that the SLS-CS combination increased the tablet disintegration time.

Changes in SLS particle size and the formation of fine particles when the tablet mass was compressed caused the tablet to have a dense porosity. The disintegrating medium was difficult to penetrate the tablet and slow down the disintegration. CS particles can function as disintegrants if particles are hydrated and swell. CS particles needed time to hydrate and swell all the particles so that the tablet disintegrates longer. The SLS-CS combinations particles narrowed the porosity of the tablet so that there was less passage for the disintegrating medium. In addition, tablet hardness increased the disintegration time because the hard tablet had narrow porosity, so the disintegrating medium was difficult to penetrate the tablet.

Determining the drug release of $3CH_2Cl$ tablets

Drug release from each tablet is shown in Table 2 and a detailed profile in Figure 1 (detail see supporting information Table S1). Tablets TC with the release of $3CH_2Cl$ were the highest, followed by tablets with TB and TA formulas. The TC formula tablets contained the highest SLS, reducing the surface tension between the $3CH_2Cl$ particles and the dissolution medium. The simplex lattice design method with a linear model resulted in the coefficient values as presented in Table 3, where SLS (84.28) was the most dominant in increasing drug release, followed by CS (58.65). The linear model coefficient was acceptable based on statistical analysis (see supporting information Table S2). The quadratic ANOVA model had a coefficient profile similar to the linear model. The coefficients of SLS (85.04) and CS (59.41)

increased the release of $3CH_2Cl$. The quadratic model resulted in an SLS-CS combinations coefficient (-9.10), indicating that the SLS-CS combinations decreased the solubility of $3CH_2Cl$.

Hollow SLS particles can accelerate the solubility of SLS. The dissolved SLS particles reduced the surface tension of the $3CH_2Cl$ particles with the dissolution medium. Swelling CS particles forced the tablet to disintegrate into tiny particles, thereby increasing the surface area of the $3CH_2Cl$ particles in contact with the dissolution medium. SLS-CS combination particles have a narrow porosity, so the medium was difficult to hydrate other particles and inhibits the solubility of $3CH_2Cl$ particles.

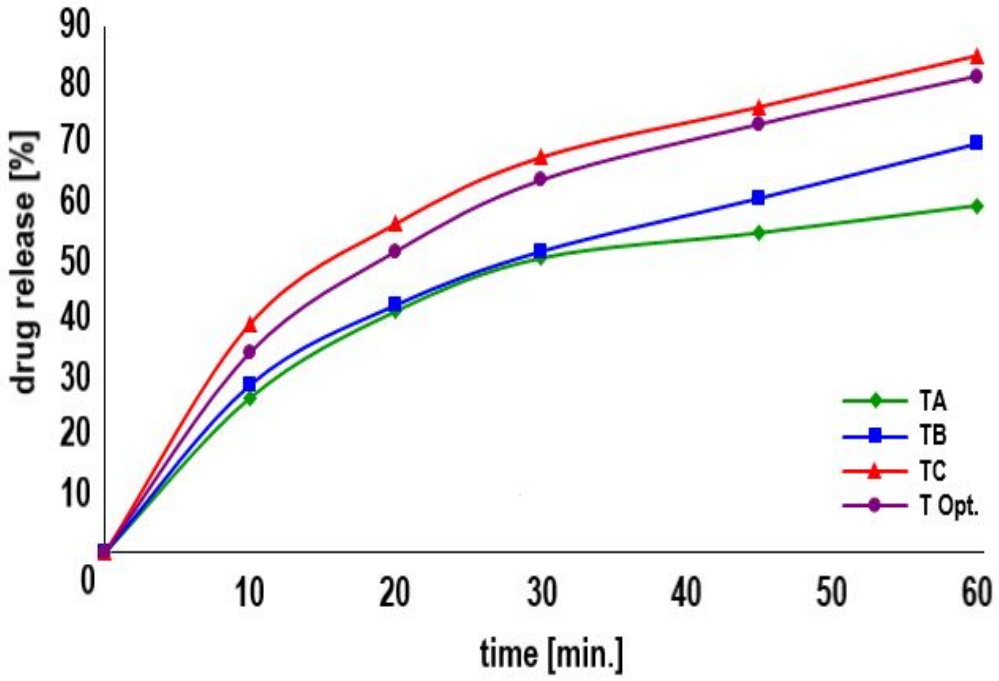

Figure 1. Dissolution profile of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33).

Simplex lattice design and ANOVA of $3CH_2Cl$ tablets

This experiment used the simplex lattice design because the optimization factor for the concentration of SLS and CS is an internal factor of the tablet formula, without any external factors. Linear and quadratic models were used to support each other in predicting the effect of SLS, CS, and a combination of SLS-CS (Table 3 and Figure 2). ANOVA from a linear model can provide R-Squared, Adj R-Squared, Pred R-Squared, and Adeq Precision values to evaluate the model's acceptability. The coefficient of the polynomial equation of the linear model is accepted if the difference between R-Square and Pred R-Square is less than 0.2 and Adeq Precision is more than 4. Thus, the polynomial coefficients can be used to predict the effect of SLS and CS. The weakness of the linear model is that it cannot predict the impact of the combination of SLS with CS. The quadratic model can produce polynomial coefficients for the influence of SLS, CS, and SLS-CS combinations. However, the quadratic model cannot represent ANOVA parameters like a linear model because of the limited experimental formulas. The effort to maximize these two models in predicting the effect of SLS, CS, and SLS-CS combinations by analyzing the similarity of SLS and CS coefficients is critical. The profiles of the SLS and CS coefficients from the two models are similar. In that case, the coefficient values of the SLS-CS combination in the quadratic model can be used to predict the effect of the SLS-CS combination. The profiles of SLS and CS were similar, so that the coefficient values of SLS-CS combined in the quadratic model can be used to predict the effect of the SLS-CS combination on the tablet formulation parameter of the $3CH_2Cl$. Both models are beneficial for experiments using a limited number of formulas due to the availability of $3CH_2Cl$ synthesized by laboratory capacity. Prediction of the optimum formula in this experiment was done numerically according to a linear model. Predicted (P Opt.) and verified (T Opt.) optimum tablet formulas are presented in Table 2.

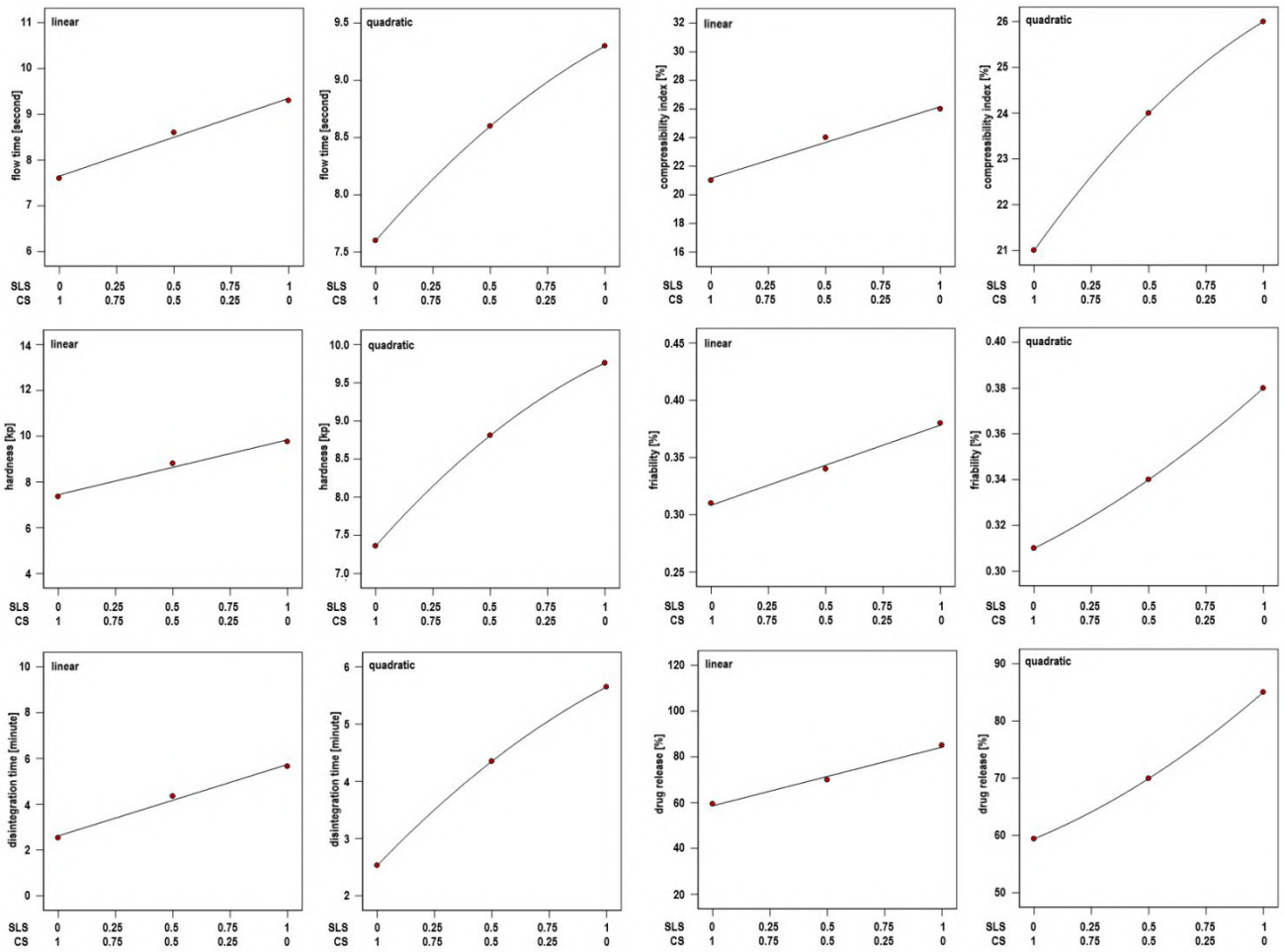

Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

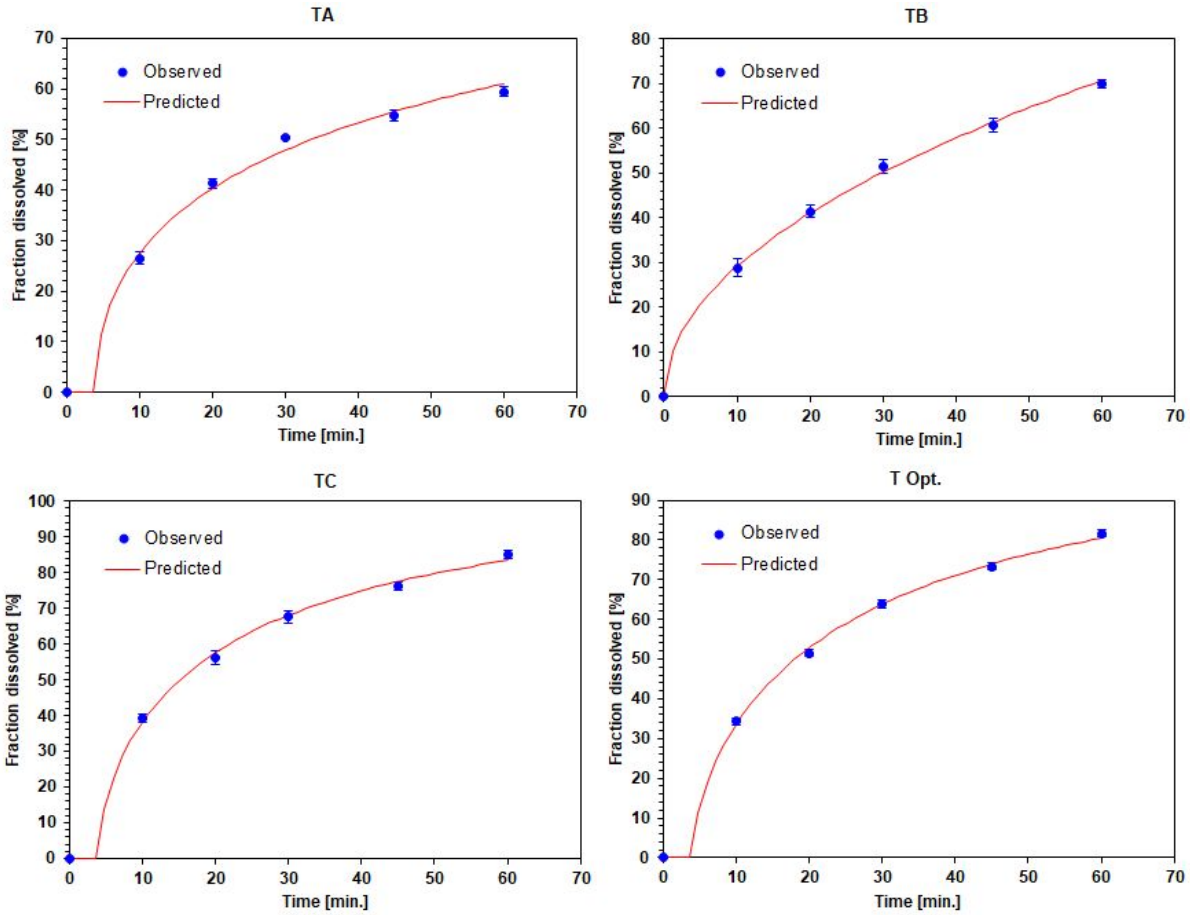

Figure 3. The kinetics profile of the release of $3CH_2Cl$ from tablets containing SLS [%] and CS [%]: TA (0.50:4.00) (Weibull), TB (0.75:3.00) (Higuchi), TC (1.00:2.00) (Weibull), and T Opt. (0.92:2.33) (Weibull).

Release kinetics of $3CH_2Cl$ tablets

The release kinetics models of $3CH_2Cl$ from tablets were analyzed using DDSolver. Rsqr_adj shows the correlation between dissolution time and release of $3CH_2Cl$. MSE_root determinated the correlation analysis correction, while AIC demonstrated the suitability of the equation for determining the release kinetics model.[28–31] The results of the DDSolver analysis are shown in Table 4 and Figure 3 (detail see supporting information Figure S1-S4).

The TA and TC formulas following the Weibull release kinetics model show that $3CH_2Cl$ was released from the tablet without any delay. The presence of SLS lowered the

surface tension of $3CH_2Cl$ with the dissolution medium so that the particles dissolved quickly. This was also supported by the presence of CS, which accelerates the disintegration of tablets into granules or particles thereby expanding the surface of the particles to dissolve.

The Higuchi release kinetics model of TB formula shows that the release was influenced by the diffusion mechanism of $3CH_2Cl$ out of the tablet. SLS on the tablet surface accelerated hydrating and was followed by the formation of a hydration layer so that the particles dissolve and leave the tablet. CS served as a disintegrating agent after hydrating and swelling. This condition took time, so that $3CH_2Cl$ was allowed to dissolve and diffuse before the CS can function.

Table 4. Evaluation of the release kinetics of $3CH_2Cl$

Formula code	Parameter	First order		Higuchi		Korsmeyer-Peppas		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	
TA	Rsqr_adj	0.8545	0.02	0.9721	0.01	0.9779	0.01	0.9907	0.01	Weibull
	MSE_root	8.4740	0.47	3.6791	0.57	3.2431	0.75	2.0408	0.80	
	AIC	37.2882	0.67	27.1910	1.89	26.2323	2.67	20.5635	4.56	
TB	Rsqr_adj	0.9475	0.01	0.9966	0.00	0.9961	0.00	0.9917	0.00	Higuchi
	MSE_root	5.7427	0.56	1.4227	0.47	1.5214	0.53	2.2621	0.46	
	AIC	32.5953	1.14	15.3644	4.53	16.8557	4.27	22.229	2.35	
TC	Rsqr_adj	0.9578	0.01	0.9885	0.00	0.9949	0.00	0.9963	0.00	Weibull
	MSE_root	6.3475	0.45	3.3264	0.47	2.221	0.13	1.8553	0.28	
	AIC	33.8125	0.87	26.0793	1.49	21.8932	0.65	19.9178	1.81	
T Opt.	Rsqr_adj	0.9686	0.01	0.9926	0.00	0.9925	0.01	0.9979	0.00	Weibull
	MSE_root	5.2892	0.42	2.5394	0.52	2.5334	0.39	1.2986	0.53	
	AIC	31.6188	0.97	22.6583	2.61	23.2554	0.57	14.8858	5.82	

The release kinetics of $3CH_2Cl$ from each tablet formula containing SLS [%] and CS [%]: TA (0.50:4.00), TB (0.75:3.00), TC (1.00:2.00), and T Opt. (0.92:2.33). The model selection was high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC).

The $3CH_2Cl$-tablet showed analgesic activity in mice writhing test

This experiment was conducted using a T Opt. tablet to determine the effect of excipients on the analgesic activity of $3CH_2Cl$. The results of the analgesic activity test of $3CH_2Cl$ are presented in Figure 4. The control group produced a very high amount of writhing-

response (78.83 ± 4.17), indicating the success of pain induction using 0.6% acetic acid (dose of 0.01 mL/g body weight). The number of writhes of the T Opt. group (18.17 ± 3.19) was less than the control group, showing that the $3CH_2Cl$ can suppress pain. The analgesic activity of the $3CH_2Cl$ was more effective than that of the comparison compound because the $3CH_2Cl$ had less amount of writhe than the comparison compound (52.83 ± 3.87). The significant difference in the amount of writhe of the three groups ($P < 0.05$) shows that the $3CH_2Cl$ had analgesic activity despite presence tablets excipients.

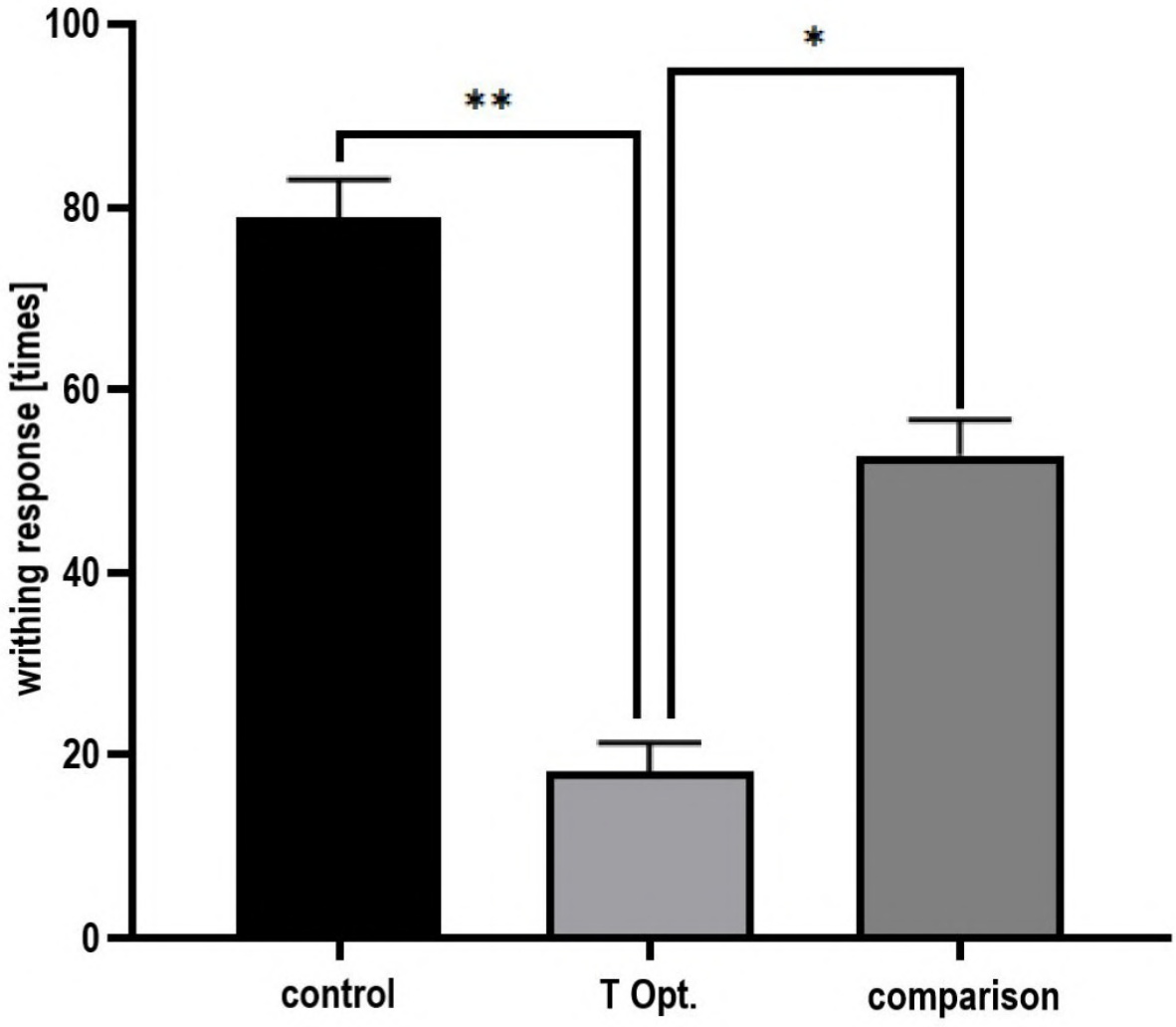

Figure 4. Analgesic activity of $3CH_2Cl$.

The control group is mice given excipient tablets. The active compound group in mice was assigned $3CH_2Cl$ tablets. The comparison group was mice given acetylsalicylic acid tablets. The three groups induced pain using 0.01 mL/g body weight of 0.6% acetic acid. The significant difference in the amount of writhe of the three groups ($P < 0.05$) indicated that $3CH_2Cl$ still has analgesic activity despite the presence of tablet excipients.

Conclusion

The polynomial coefficient values of the two models show that the SLS, CS, and SLS-CS combinations increased the parameter values of flow time, Carr index, hardness, and disintegration time. The SLS-CS combination decreased the friability value and the drug release parameters. The optimum tablet formulas of $3CH_2Cl$ tablet were $3CH_2Cl$ (300 mg), Ne (9.38%), SLS (0.92%), CS (2.33%), MCC (5%), and adjusted with SDL until 800 mg total weight. Quality predictions of tablet mass were flow time (9.07 seconds); Carr index (25.33%). Quality tablets predictions are hardness (9.44 kp), friability (0.37%), disintegration time (5.22 minutes), and drug released 60 minutes (80%). The SLS was to increase the solubility particles of $3CH_2Cl$ and excipient. The CS had accelerated the disintegration of tablets into particles. The tablet dosage form of $3CH_2Cl$ is an innovative formulation and a new alternative to the future analgesic drug.

Associated Content

Supporting Information

Tablet dosage calculation; the release of $3CH_2Cl$ from the tablets; statistical analysis of $3CH_2Cl$ tablets; the kinetics profile of the release of $3CH_2Cl$ from TA, TB, TC, and T Opt. tablets.

Acknowledgment

The authors thank the Research and Community Service Institute of Widya Mandala Catholic University, Surabaya, Indonesia was supporting grants (5230/WM01/N/2021). The authors also would like to thank Khaterine Irene Phuk, Sherlilyta Stiara Dewi, Angela Tiffany, and Meidelin Ribka Abiati for their assistance during the experiment.

Declarations

Competing interest statement

The authors declare no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: Designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Kuncoro Foe, Yudy Tjahjono, Caroline, Senny Yesery Esar, Maria Annabela Jessica: performed the experiments, analyzed, and interpreted the data. Hendy Wijaya: analyzed, and interpreted the data.

Statement of Human and Animal Rights

Experiments using experimental animals (mice) have been declared to meet the ethical requirements from the Research Ethics Commission of the Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta, Indonesia with No. 001/EC-FKH/Ex./2022 dated January 14, 2022.

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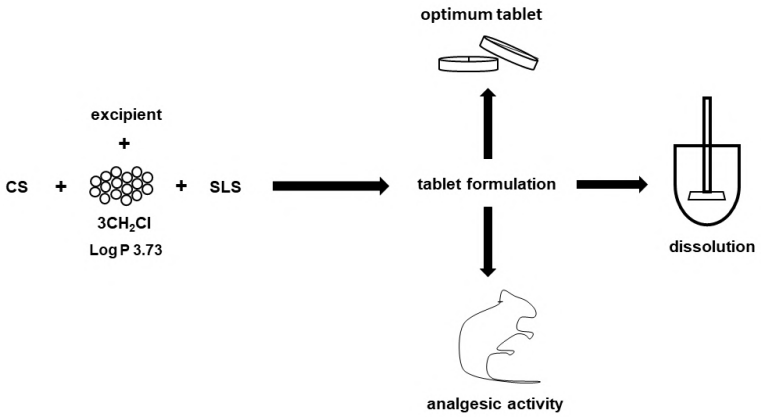

338x190mm (96 x 96 DPI)

Response to revisions requested

Revisions requested

1. Mark the corresponding author (Wuryanto Hadinugroho) with an asterisk in your manuscript and supporting information file.

   Response to revisions requested 1:

   Thank you for the suggestions. We have added an asterisk in your manuscript and supporting information files.

   MS

   Before revision

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2. Remove color from your manuscript file text (Figure 2 caption)

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   Thank you for the suggestions. We have removed the color from your manuscript file text (Figure 2)

   Before revision

   Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

   After revision

   Figure 2. Linear and quadratic system profiles of each tablet mass parameter, tablet, and dissolution on the formulation of $3CH_2Cl$ tablets.

Hadinugroho, Wuryanto ao-2022-031476.R3 - Manuscript Accepted 17-Aug-2022

Dari: ACS Omega (onbehalfof@manuscriptcentral.com)

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Tanggal: Rabu, 17 Agustus 2022 pukul 18.56 GMT+7

17-Aug-2022

Journal: ACS Omega
Manuscript ID: ao-2022-031476.R3
Title: "Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models"
Author(s): Hadinugroho, Wuryanto; Foe, Kuncoro; Tjahjono, Yudy; Caroline, Caroline; Esar, Senny; Wijaya, Hendy; Jessica, Maria
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Dr. Krishna Ganesh
Coeditor
ACS Omega
Phone: (202) 657-6323
Email: Ganesh-office@omega.acs.org

---

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Action required: Journal publishing agreement for ao-2022-031476

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Kepada: wuryanto.hadinugroho@ymail.com

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August 17, 2022

Journal: ACS Omega
Manuscript No.: ao-2022-031476
Title: Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models
Authors: Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica
Status: Manuscript Accepted - Signature for journal publishing agreement required

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August 18, 2022

Journal: ACS Omega

Manuscript No.: ao-2022-031476
Title: Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models
Authors: Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica
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Article ID: ao-2022-031476
Received Date: 26 May 2022
Journal: *ACS Omega*
Article: Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models
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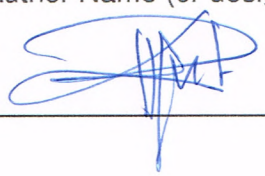
Contact Email Address: wuryanto.hadinugroho@ymail.com

Contact Postal Address: Kalisari Selatan no. 1 Pakuwon City, Surabaya, Indonesia

Corresponding Author Name (or designee): Wuryanto Hadinugroho.

Signature:  Date: 18-8-2022

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Dari: acsproof@acs.org

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Kamis, 25 Agustus 2022 pukul 18.39 GMT+7

August 25, 2022

Journal: ACS Omega
Manuscript No.: ao-2022-031476 (acsomega.2c03147)
Title: Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models .
Authors: Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica .
Manuscript Status: Accept - Review Proof

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August 30, 2022

Journal: ACS Omega
Manuscript No.: ao-2022-031476 (10.1021/acsomega.2c03147)
Title: Tablet formulation of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid by linear and quadratic models
Authors: Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica
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September 12, 2022

Journal: ACS Omega
Manuscript No.: ao-2022-031476 (10.1021/acsomega.2c03147)
Title: Tablet Formulation of 2((3-(Chloromethyl)benzoyl)oxy)benzoic Acid by Linear and Quadratic Models
Authors: Wuryanto Hadinugroho, Kuncoro Foe, Yudy Tjahjono, Caroline Caroline, Senny Yesery Esar, Hendy Wijaya, Maria Annabella Jessica .
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