The interaction of a binary/ternary interactive mixture of hydrophobic-hydrophilic materials on the drug distribution and drug release performance in the tablet formulation

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Abstract. The aim of this research was to optimize and determine an interaction of a binary/ternary mixture of hydrophobic-hydrophilic materials (H-HM) on the drug distribution, tablet characteristics, and drug release performance. The interactive mixture (IM) between carrier and H-HM was conducted using a carrier, Pruv and Cab-O-Sil as hydrophilic materials, magnesium stearate as a hydrophobic material, and a micronized nifedipine as a drug model. These interactions between binary and ternary mixtures of H-HM were assessed by a simplex centroid design (SCD) approach. The homogeneity of IM between drug and carrier was achieved at more time of mixing time. Unique effects and interactions of H-HM were observed on the drug distribution and drug release. Furthermore, the SCD had successfully determined the optimum design space of IM in the ternary mixture of H-HM.

1. Introduction
In the solid oral dosage form e.g. a tablet formulation, a mixing or blending is a fundamental process to ensure the homogeneity of the drug and achieve a high product quality. The objective of mixing is a less variation of the drug content in each unit of dosage form i.e. a homogenous mixture [1–3]. Furthermore, the mixing process of a very small particle involve the interactive mixture (IM) to obtain a good homogeneity. It is a mixture usually using an interactive constituent (a fine particle of drug) and a carrier. The mixing mechanism based on adhesive and interparticles forces, that is a fine or ultrafine drug adhere in to the surface of carrier [4–6].

A lubricant is used to reduce the friction or enhance the powder flow by reducing the interparticle friction [7,8]. The difference of lubricant properties affects the final product of a dosage form [4]. Magnesium stearate (MgSt) had negative effects on reducing the drug release and prolong the disintegration time due to its hydrophobicity [8]. The addition of MgSt in the final mixture retarded the drug release [9,10]. Enhancement of MgSt concentration enhance those negative effects although easy in the compression process due to a proper tablet ejection [10,11]. MgSt at concentrations 0.1 and 5% not significantly affected on the tensile strength and tablet crushing strength [10]. MgSt increased the drug distribution depending on the MgSt concentration and particle size [12].

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Sodium stearyl fumarate (SSF) as a hydrophilic material has been used as a pharmaceutical lubricant [11,13]. It has some advantages include a less interaction or compatible with other excipients, no reduce bioavailability effect, and enhance a tablet appearance [13]. Colloidal silica is a hydrophilic material that is used as a flowing agent to enhance flow of the powder or granule. This material is very small and has tendency to form an agglomerate [14]. A combination between colloidal silica and MgSt did not has significant effect on the drug release (13).

A design of experiment (DoE) offers several advantages, those are to reduce number of runs, to elucidate and assess the effect and interaction of factors, and to obtain the design space [15–17]. The aim of this study was to assess and elucidate effects and interactions of single, binary or ternary mixtures of MgSt, Pruv, Cab-O-Sil (COS) on the drug distribution, tablet characteristics, and drug release performance. The most optimum combination can be determined by a quality by design (QbD) approach using a simplex centroid design (SCD).

2. Experimental
2.1. Material
Nifedipin (Nif) micronized form (Lot No. 400196067; $d_{10} = 1.5 \mu m$, $d_{50} = 6.7 \mu m$, and $d_{90} = 9.8 \mu m$) was obtained from Dexa Medica (Palembang, Indonesia), Pruv ($d_{10} = 1 \mu m$, $d_{50} = 9 \mu m$, and $d_{90} = 29 \mu m$) was gift from JRS Pharma (Rosenberg, Germany), (COS) $d_{50} = 16 \text{ nm}$ (Cabot; Jiujiang, China), MgSt $d_{50} = 36 \mu m$ (Peter Greven; Germany), lactose (DFE Pharma; Foxhol, the Netherlands), Avicel PH101 (FMC Biopolymer, NJ, USA), Plasdone K30 (Shin-Etsu, Tokyo, Japan). All of the ingredients were used as receipt and pharmaceutical grade.

2.2. Preparation of carrier
Lactose 70% and Avicel 30% were mixed for 15 min at 25 revolution per minute (rpm). Plasdone K30 3\% (w/v) in ethanol 50\% (v/v) was used as a binder and added until the elastic mass was achieved. The mass was passed through a 20 mesh sieve (850 μm) and dried in the oven at 60°C for 4 h or the loss on drying below 2%. The used granule as carrier was passed through a 30 mesh sieve (600 μm) and retained on 50 mesh sieve (300 μm).

2.3. Homogeneity test of binary mixture between drug and carrier
The drug of 5\% and the carrier 95\% was mixed at 25 rpm. The sample was collected in the 3 different places at 100, 200, 300, 500, 800, 1200, and 1600 revolution (rev). The samples were determined on the Nif content spectrophotometrically at 238 nm and calculated the relative standard deviation (RSD) of the Nif content. The homogeneity was interpreted by a RSD.

2.4. Tablet formulation
A 13 runs was constructed depending on a quadratic equation using a SCD. The lubricant mixture was used at total level of 1%, 5% drug and 94% carrier. The Nif and carrier were mixed at 1600 rev, then lubricants were added to the mixture and mixed at 100 rev. The flow characteristic of the final mixture was assessed by a flow time through the funnel. The mixture were compressed using a single punch tablet (a flat-face punch diameter 8 mm) at a similar compression force.

2.5. Tablet characterization
The Nif was individually determined using spectrophotometer UV-Vis. The drug distribution was described by the RSD of 10 tablets. Tablet crushing strength (CS) was conducted using a Gouming YD-1 hardness tester (Tianjin, China) (20 tablets). The tablet disintegration test (DT) was determined using a Gouming DT-1 disintegration tester (Tianjin, China).

2.6. Drug release
The drug release was determined using an Electrolab TDT 08L (Electrolab, India) dissolution tester type apparatus II with 900 ml of HCl 0,1N as a dissolution medium, the temperature maintained
at 37±0.5°C and a stirring rate of 50 rpm. Aliquots of 5 mL were withdrawn at a determined time by a replacement of same medium. All the samples were analyzed spectrophotometrically. The model dependent approach was applied to compare the drug release profiles. The dissolution efficiency (DE) was used and calculated using following equation.

\[
DE = \frac{\int_{0}^{T} y \, dt}{100T} \times 100\%
\]

Here \(y\) is an amount of the drug released in time “\(t\)" and \(T\) is a total time. The DE was calculated depending on the drug released over 60 min (DE_{60min}).

2.7. Data analysis
The obtained data were analyzed using a Design Expert® software version 7.1.5 (Stat-Ease Inc., Minneapolis, MN, USA). Several statistical parameters were used to evaluate the equation fitting i.e the determination coefficient (R²), adjusted determination coefficient (Adj. R²), predicted determination coefficient (Pred. R²), adequate precision (adeq. prec) and predicted residual error sum square (PRESS). The optimized formulae was determined by critical quality attributes (CQAs) depending on quality target product profile (QTPP) that are presented in Table 1.

| Parameters | QTPP                     | Priority level |
|------------|--------------------------|----------------|
| Flow Rate  | more than 10 g/s         | +++            |
| RSD        | less than 5%             | +++++          |
| CS         | more than 40N            | +++            |
| DT         | less than 300 s          | +++            |
| DE_{60min} | more than 30%            | +++++          |

3. Results and Discussion
3.1. Preparation of carrier
In the IM, a granule size plays a fundamental role in the drug distribution and homogeneity [4,5]. A sufficient granule size promote a single layer of drug thus avoid the segregation of drug and carrier [18,19]. In the carrier preparation, the granule size was controlled. Hence, the particle size diameter was \(d_{10} = 377.5 \, \mu\text{m}, \, d_{50} = 468.6 \, \mu\text{m}, \, \text{and} \, d_{90} = 553.5 \, \mu\text{m},\) thus indicated the particle size normally distributed and had a narrow distribution of particle size. The granule had a flow rate of 14.50±1.05 g/s, bulk and tapped densities of 0.441±0.006 and 0.472±0.004 g/mL, respectively, an angle of repose of 21.86±0.84º and a compressibility index of 10.66±1.48%. According to these results, the granule had a good flow ability, thus can ensure the constant filling in the compression room.

3.2. Homogeneity mixture between drug and carrier
The homogeneity of mixture between drug and carrier was described by a RSD of Nif content. Figure 1 shows that the RSD pattern under different revolutions of mixing decreased exponentially. In the IM the drug as a guest substance adhere in the carrier strongly, thus avoid the segregation, an enhancement of mixing time enhanced the homogeneity [4,5,19]. In the initial mixing at a low revolution (100 – 500 rev), the RSD higher than that of revolution more than 800 rev. The desirable RSD was less than 5% that was achieved at 1600 rev.

3.3. DoE approach for assessing the effect of lubricant materials
A DoE approach using a SCD was helpful to elucidate the effect and interaction between hydrophilic and hydrophobic materials (HH-M). These effects and interactions could be knew by comparing the regression coefficient value and significant effects and interactions were showed by p-value (<0.05). Depending on the flow rate, an equation using a special cubic model, the linear mixture (MgSt, Pruv, and COS proportions) not significantly affected on the flow rate (p>0.05). Furthermore, these materials did not show a different effect due to small amount addition and we suggested that the flow characteristic was dominantly affected by the carrier. There was no a significant interaction in each material (p>0.05), meanwhile an interaction in the ternary mixture of lubricant materials showed
an enhancement of flow rate significantly (p<0.05). A contour plot (CP) of powder flow (Fig. 2(1)a) shows a unique effect on the mixture of lubricant materials. Fitting parameters of flow rate equation showed that the difference between adjusted and predicted $R^2$ was more than 0.2. Furthermore, the model could not be used to predict the flow rate adequately. In the mixing process, H-HM as lubricants coat the carrier and drug. Furthermore, those are be in place in the inter particles and affect the particle bonding consequently [20]. The particle bonding (CS) described by a MLRA of CS (Table 2). The linear mixture of equation had a significant effect on CS (p<0.05). The MgSt had more dominant effect on an increase the CS than Pruv and COS due to a reduction in ejection force. MgSt had a different mechanism in reduce the friction [9]. The interactions of MgSt – Pruv and MgSt-COS were not significant affecting on an increase the tablet CS (p>0.05). Although an interaction between Pruv and COS was statistically significant on an increase the tablet CS. The CP of tablet CS (Fig 2(1b)) was used to assess and elucidate the effect of H-HM on the interparticle bonding. Generally, the addition of H-HM promotes a reduce the tablet CS due to a reduction of the interparticle bonding that is caused by coating of H-HM on the surface of particle [4].

![Figure 1. RSD of drug distribution in the IM between drug and carrier as a function of revolution. This point was calculated using quintuplicate replications.](image)

The drug homogeneity is ensure the drug distribution be spread evenly in all samples. The lower RSD the more homogeneous mixture, in other word the RSD is less than 5%. The homogeneity of a binary mixture between Nif and carrier was achieved at 1600 rev of mixing process. The addition of lubricant materials could promote an alteration of homogeneity i.e. the RSD depending on their interactions between Nif, carrier, and lubricants. The RSD of all formulations ranged from 1.27 to 7.85%. This indicated that the addition of H-HM altered the drug homogeneity or induced a segregation. Depending on a quadratic equation of RSD, the linear mixture was significant affecting on the RSD. The Pruv had a better effect on drug distribution than MgSt and COS. Those were affected by particle size and interaction i.e. a competition between drug and lubricant that caused a redistribution of the adhered drug on the carrier. Interactions of MgSt-Pruv and COS – Pruv enhanced the RSD not significantly (p>0.05), although an interaction between MgSt and COS reduced the RSD significantly (p<0.05). The CP of RSD (Fig. 2(1c)) showed that Pruv had the lowest RSD and MgSt had the highest RSD, and the RSD changed as function of proportion of the mixture.

The quadratic model of DT was constructed using a logarithmic transformation to obtain the best fitting and a normally distributed data. The linear mixture was significant (p<0.05). Among the others materials, MgSt was 10 fold longer DT than Pruv and 35 fold than COS. All interactions between H-HM increased the DT significantly (p<0.05). Fig 2(2a) describes the DT pattern in a change of lubricant proportion in the mixture. The highest DT was obtained at high proportion of MgSt, and decreased logarithmically with decreasing the MgSt proportion. The lowest DT was achieved at the highest proportion of COS due to its hydrophilicity.

The drug release for all formulation are presented in Figure 3. Nif was chosen as a drug model due to practically insoluble in water, therefore it was very sensitive if a small amount of H-HM was added. The formulation with a hydrophobic material i.e MgSt (runs 1) showed that had lower drug released than a hydrophilic material about 20 and 80% during 60 min, respectively. This phenomenon was caused by coating the carrier and drug thus inhibit a water penetration and avoid or retard the disintegration process thus decreased the drug release. A binary blend reduced the drug released when
compared to a single component of lubricant. The effect of material hydrophobicity was more dominant in these combinations so it reduced the drug release. A tertiary mixture of lubricant was a preferable combination except the high proportion of MgSt. An over blended or lubrication cause a problem that is associated by disintegration process and drug release [3,8].

Table 2. Statistical parameter of simplex centroid design

| Statistics | Flow rate (g/sec) | RSD (%) | CS (N) | Log(DT) (sec) | DE_{60min} (%) |
|------------|------------------|---------|--------|----------------|----------------|
|            | Coef. | p-value | Coef. | p-value | Coef. | p-value | Coef. | p-value | Coef. | p-value |
| A          | 16.86 | 7.11    | 80.90 | 3.10  | <0.00  | 16.74 |
| B          | 18.37 | 0.902*  | 1.99  | 99.95 | 0.000  | 53.19 |
| C          | 16.57 | 5.60    | 30.54 | 1.56  | 57.42  |
| AB         | 2.85  | 0.879*  | 5.61  | 1.102*| 39.46  | 0.157*| 2.43  | 0.008  | -68.69 |
| AC         | 5.62  | 0.765*  | 0.099 | 40.48 | 0.148* | 3.00  | 0.003  | -99.09 |
| BC         | 0.58  | 0.975*  | 5.73  | 0.097*| 63.51  | 0.038 | 2.45  | 0.008  | -118.06 |
| ABC        | 535.71| 0.006   | -     | -     | -     | -     | 697.13| 0.005  |
| Model      | -     | 0.0289  | -     | 0.003 | -     | 0.0001 | -     | 0.0007 |
| Lack of fit| -     | 0.0211  | -     | 0.049*| 0.1667*| 0.1107*| -     | 0.1433*

| R²         | 0.8455 | 0.8875 | 0.9286| 0.9593| 0.9576 |
| Adj. R²    | 0.6910 | 0.8071 | 0.8775| 0.9302| 0.9152 |
| Pred. R²   | -0.8149| 0.6344 | 0.7019| 0.8781| 0.4451 |
| PRESS      | 1177.48| 12.81  | 1141.75| 0.59  | 1990.37 |
| Adeq. Prec | 7.184  | 10.042 | 11.858| 15.659| 12.213 |

*: not significant term

The drug released of all formulations (Figure 3) was compared by DE, comparing all points and possibility depending on the area under curve. A special cubic equation was constructed to describe the DE. The linear mixture had significant effect on DE_{60min} (p < 0.05), thus a hydrophilic material had higher in an increasing the DE than a hydrophobic material. It was discussed above due to a hydrophobicity characteristic. The interaction of two material lubricants and a combination of three materials lubricant had a significant effect on reducing and increasing DE_{60min} (p<0.05), respectively. The interaction of two lubricant in order from high to low in reducing the DE was Pruv-COS>MgSt-COS>MgSt-Pruv. An interaction of three lubricants increased the DE_{60min} value. Although some problems could occur due to inadequate prediction. The adequate precision describe the ratio of signal

Figure 2. (1) Contour plot of powder flow (a), tablet CS (b), and RSD of drug content (c); and (2) contour plot of DT (a), DE_{60min} (b), and superimposed contour plot (c)

Figure 3. The Nif released from the tablet formulation using the mixture of hydrophilic and hydrophobic materials.
to noise, it more than 4 is the desirable model. The pattern of CP of DE_{60min} was similar to CP of DT, but the value had an inversely correlation with DT. The control strategy was obtained by combining the CP of each CQA depending on QTPP. A superimposed CP was achieved and presented in Fig 2(2)c. The key determining in the control strategy is presented in Table 1. The control strategy was a non-linear combination, therefore it could be minimize to obtain a linear combination. The desired formulation based on QTTP was achieved at a dominant Pruv region and combination of COS and MgSt.

4. Conclusion

The homogeneity of IM between drug and carrier needed more time to ensure the homogeneity. A H-HM has unique effects and interactions on the drug distribution, tablet properties and drug release. All of the interactions between H-HM reduced the dissolution performance. Furthermore, the optimized formulae was achieve at Pruv 100% or a combination between COS 84% and MgSt 16%.

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