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**Research Article**

# APPLICATION OF MONTMORILLONITE, ZEOLITE AND HYDROTALCITE NANOCOMPOSITE CLAYS-DRUG AS DRUG CARRIER OF SUSTAINED RELEASE TABLET DOSAGE FORM

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## ABSTRACT

Captopril is an angiotensin converting enzyme (ACE) inhibitor as antihypertensive treatment with half-life about 2h. Development of sustained-release dosage form can maintenance the drug concentration at therapeutic window in long period of time with constant release. Montmorillonite, zeolite and hydrotalcite nano-composites were used as drug carrier as sustained release dosage form. This study aimed to determine the drug release from nanocomposite of montmorillonite-drug, zeolite-drug and hydro-talcite-drug. Nanocomposite drug and carriers were made with the model drug was dispersed in carrier with matrix system. Matrices used montmorillonite, zeolite and hydrotalcite with concentrations of 20%, 30% and 40%. Characterization of matrices were done by testing the physical properties of the granules and drug release. Dissolution test using apparatus II USP model with speed rotation of 50rpm of, 900mL of HCl 0.1N as medium. The results were compared statistically with one way ANOVA 95% of interval confidence. The results showed that the difference of matrices and concentrations gave the difference effect in flow time, compact-tibility, $DE_{360}$, initial burst release and maintenance release ($p<0.05$). Nanocomposites between drug and nanoclays occurred after 60min were shown with decreasing the drug release rate. Nanocomposite was formed with the drug molecules adsorb on nanoporous of carrier material. Increasing of clays concentration improved the fluidity and compactibility, reduced the drug release.

**Key words:** Nanocomposite, clays, drug release

## INTRODUCTION

Captopril is a first active orally angiotensin converting enzyme inhibitor, the enzyme responsible to inhibits the formation of angiotensin II effectively for hypertensive treatment (Donald *et al.,* 1982). Given orally, captopril is absorbed rapidly, has a bioavailability of 75%. Peak concentration in plasma occur within an hour, and a half-life of about 2h. The oral dose of captopril ranges from 6.25 to 150mg twice or three times daily (Brunton *et al.,* 2008). Strategy in development of sustained release dosage form to maintain drug at therapeutic levels in the long term. Captopril sustained release dosage form is considered to provide benefits by reducing the frequency of drug administration, improve the patient compliance. Therefore the effectiveness of treatment can be achieved and reduce the side effect (Collet and Moreton, 2002).

Montmorillonite, zeolite and hydrotalcite are one type of natural clays. Montmorillonite consist of large layer and insoluble cation are bound weakly to the space between the layer (Wijaya *et al.,* 2004). Clays have three properties (swelling ability, cation/anion exchange and intercalation), with the abilities were developed as nano carriers of nanocomposite drug-clays for controlled release drug delivery (Hua *et al.*, 2010; Zheng *et al.,* 2007). Montmorillonite have average porous size (nanoporous) of about 15 Å (1.5nm) (Figure 1) which was called basal spacing (Ainurofiq *et al.,* 2010). Nanocomposite drug-clays naturally occur drug to be loaded into the nanoporous as nanocomposite (Suresh *et al.,* 2010). The natural montmorillonite and

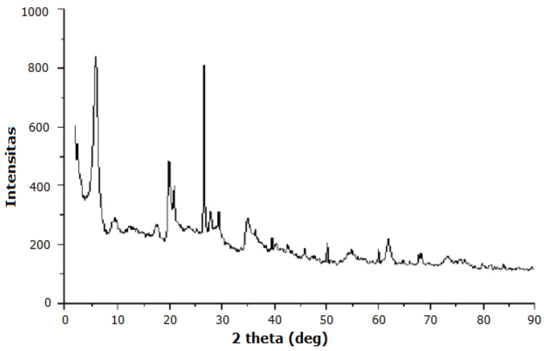


Figure 1. XRD pattern of natural montmorillonit with basal spacing 1.5 nm

pillarization of montmorillonite with various molecular weight of chitosan (small, medium, and high) could release the drug slowly from dosage form using a poorly soluble drug (theophylline) (Ainurofiq *et al.,* 2010).

Zeolite have cavity (porous) smaller than mesoporous material, and these characteristics can be used to achieve the more effective controlled release drug delivery. Pore size of nanoporous and mesoporous materials as the host determine the size of the drug molecules to be adsorbed into the pore. Adsorption and release of the molecules in the matrix is controlled by size selectivity. The pore size can provide better controlled drug release (Gonzales *et al.,* 2013). The nanocomposite of drug-zeolite, the composite combined with biodegradable polymers (chitosan, gelatin, and alginate) and the drug loaded in the nanoporous of zeolite provided prolong drug release (Zhang *et al.,* 2007).

Hydrotalcite (anionic clays) or layered double hydroxides are two dimensional material, these material is natural hydrotalcite with the brucite structure, where for each set of eight $Mg^{2+}$ cation, two are substituted by $Al^{3+}$. The positive charge in excess is balanced by carbonate anions hosted together with water molecules in the interlayer (Cavani *et al.,* 1991). The intercalation of these anions clays, and their high affinity to carbonate ion to acid dissolution is able to the loaded drug in the interlayer. The composite between drug (ketoprofen, sodium diclofenac, and chloramphenicol succinate) and hydrotalcite, the drug release slowly up to 24h (San Roman *et al.,* 2013).

This study aimed to determine the drug release (kinetic models and characteristics) from nanocomposite of nanoclays (zeolite, hydrotalcite and montmorillonite) with dispersion in matrix system using captopril as water soluble drug from sustained release tablet dosage form.

## MATERIAL AND METHODS

Captopril (Afine Chemicals, China), lactose (DFE Pharma, Germany), nature montmorillonite from Wonosegoro, Boyolali, Central Java, nature zeolite from Gunung Kidul, Yogyakarta, magnesium stearate (Bratachem, Indonesia), hydrotalcite (Sigma Aldrich, Singapore), hydrocloric acid p.a (Merck, Germany), $K_3[Fe(CN)_6]$ p.a (Merck, Germany), $FeCl_3$ p.a (Merck, Germany), demineralized water.

### Purification of montmorillonite

Montmorillonite had been purified from bentonite, coarse bentonite, were washed with demineralized water. The colloid phase was precipitated over night and dried in oven at temperature of 110°C and rewashed three times. Montmorillonite were sieved with 180 mesh sieve.

### Purification of zeolite

Zeolite were washed with demineralized water, and the colloid phase were precipitated for one night. The sediment were then over rewashed three times The residue were dried in oven at temperature of 100°C for 6h followed by refluxed with 500mL of HCl 0.1N and for 5h at temperature 90°C. The resulted material were washed with demineralized water until the neutral pH. Zeolite, eventually it was washed with 500mL of NaOH 0.75N to build the ratio proportion of silica and aluminum followed by demineralized water until the neutral pH. The precipitate were dried at 110°C for 6h. The dried zeolite were sieved with 180 mesh sieve.

### Preparation of captopril tablet

Tablets were formulated according to Table I. Wet granulation method was employed for formulation. All of the component in formula except lubricant (1% magnesium stearate) were mixed in the mixer for 16min 25rpm followed by addition of demineralized

Table I. Composition formula of captopril tablet

| Formula | Composition(mg) | | | | | |
|---|---|---|---|---|---|---|
| | Captopril | Zeolit | Hydrotalcite | Montmorillonite | Lactose | Mg stearat |
| F1 | 50 | - | - | - | 197.5 | 2.5 |
| F2 | 50 | 50 | - | - | 147.5 | 2.5 |
| F3 | 50 | 75 | - | - | 122.5 | 2.5 |
| F4 | 50 | 100 | - | - | 97.5 | 2.5 |
| F5 | 50 | - | 50 | - | 147.5 | 2.5 |
| F6 | 50 | - | 75 | - | 122.5 | 2.5 |
| F7 | 50 | - | 100 | - | 97.5 | 2.5 |
| F8 | 50 | - | - | 50 | 147.5 | 2.5 |
| F9 | 50 | - | - | 75 | 122.5 | 2.5 |
| F10 | 50 | - | - | 100 | 97.5 | 2.5 |

water to the blend until elastic mass of wet granules. Mass of wet granules were sieved with 16 mesh sieve. Wet granules were dried in oven at 40°C for 6h. The dried granules were mixed with magnesium stearate in mixer for 4min 25rpm. The granules were characterized by particle size distribution test with analytical sieving, moisture content, bulk density and tapped density. The mass of tablets were characterized by fluidity and compact-tibility test. The compactibility test was done with the deepness of upper punch of 5.3mm and the lower punch of 8.15 mm.

The tablet compression process, the weight of tablet was arranged at 250mg and the hardness was controlled at 10-12kg.

### Drug release

Drug release was determined using dissolution tester type apparatus II (paddle method), where 900mL of HCl 0.1N was used as dissolution medium maintained at 37±0.05°C at 50rpm for 6h. Aliquots of 10mL were withdraw at 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360min with replacement of 10mL of the fresh media. All the samples were analyzed directly at 202.4nm ($\lambda_{max}$ of captopril) using UV-Vis Hitachi U-2900 spectrophotometer.

### Drug release kinetics

Drug release kinetics is assumed to reflect different release mechanism of controlled release matrix system. Therefore, six kinetic models were applied to analyze the drug release data to find the best fitting equation. These models are zero-order release, first-order release, Hixcon-Crowell, Weibull, Higuchi release and Korsmeyer-Peppas. The release mechanism based on the exponential diffusion value (*n*) of Korsmeyer Peppas equation. The best fitting equation based on coefficient of determination ($R^2$), AIC (Akaike's Information Criterion) and RMSE (root mean square eror).

### Analysis of result

The results obtained were analyzed statistically, with normal distribution followed by one way ANOVA with 95% of confidence interval, if significant different followed by t-LSD test. The drug releases were computed by free open source software, KinetDS® (Mendyk *et al.,* 2012).

## RESULT AND DISCUSSION

According on the results of physical properties tablet mass (Table II), granule using matrix montmorillonit showed the best physical properties tablet mass between zeolite and hydrotalcite, by fluidity and compactibility. Increasing matrix concentration enhanced the physical properties of captopril granules. Granules have good fluidity if flow time of 100g of granules not more than 10s and the angle of repose is less than 30° (Fudholi, 1983). The fluidity was influenced by some factor such as moisture content, granules density, particle size distribution, porosity and cohesiveness interparticulate. The particle size distribution characteristic showed that fines (particle size less than 180μm) in granules not should be more than 10%.

Table II. Physical properties of captopril tablets mass (mean±SD)

| Formula | Bulk density (g/mL) | Tapped density (g/mL) | moisture content (%) | flow time (sec) | Compact-tibility (kg) | angle of repose (°) | fines (%) |
|---|---|---|---|---|---|---|---|
| F1 | 0.629±0.01 | 0.731±0.01 | 0.50±0.00 | 5.08±0.38 | 1.28±0.16 | 24.90±0.81 | 3.08±0.29 |
| F2 | 0.667±0.01 | 0.709±0.02 | 1.80±0.17 | 6.26±0.11 | 5.18±0.53 | 24.00±1.24 | 3.15±0.86 |
| F3 | 0.658±0.01 | 0.721±0.01 | 2.30±0.00 | 5.02±0.12 | 6.08±0.46 | 24.20±1.45 | 4.60±0.82 |
| F4 | 0.658±0.02 | 0.727±0.01 | 2.00±0.00 | 4.16±0.09 | 6.65±0.82 | 25.40±0.89 | 3.68±0.71 |
| F5 | 0.538±0.00 | 0.581±0.01 | 1.20±0.17 | 5.40±0.21 | 3.94±0.45 | 26.15±0.35 | 2.89±0.23 |
| F6 | 0.602±0.00 | 0.694±0.00 | 1.33±0.29 | 4.57±0.07 | 5.97±0.48 | 24.88±0.28 | 2.79±1.46 |
| F7 | 0.704±0.00 | 0.848±0.00 | 2.00±0.50 | 5.29±0.16 | 6.70±0.68 | 24.70±0.49 | 6.45±1.82 |
| F8 | 0.667±0.00 | 0.767±0.01 | 1.00±0.00 | 5.07±0.22 | 7.24±0.19 | 24.43±1.52 | 3.12±1.04 |
| F9 | 0.816±0.00 | 0.984±0.00 | 1.00±0.00 | 4.13±0.24 | 10.31±0.74 | 22.96±0.40 | 0.33±0.06 |
| F10 | 0.800±0.00 | 0.948±0.04 | 1.30±0.58 | 3.65±0.13 | 13.25±0.92 | 20.86±0.59 | 1.08±0.90 |

Tabel III. Physical properties of captopril tablet and the release rate (mean±SD)

| Formula | Hardness (kg) | Drug content (%) | $DE_{360}$ (%) | Initial burst release (mg/min) | Maintenance release (mg/min) |
|---|---|---|---|---|---|
| F1 | 4.52±0.28 | 96.29±2.85 | 90.64±3.42 | 0.8802±0.0083 | 0.0058±0.0019 |
| F2 | 10.15±1.19 | 99.19±1.07 | 83.90±2.15 | 0.6274±0.0270 | 0.0319±0.0109 |
| F3 | 10.21±0.23 | 100.85±4.34 | 74.15±1.61 | 0.4486±0.0114 | 0.0646±0.0052 |
| F4 | 10.42±0.57 | 97.99±3.96 | 56.59±5.76 | 0.3356±0.0414 | 0.0552±0.0037 |
| F5 | 11.46±0.78 | 96.92±4.33 | 81.22±2.26 | 0.5928±0.0594 | 0.0361±0.0058 |
| F6 | 10.98±0.72 | 96.29±4.23 | 68.34±2.90 | 0.4319±0.0253 | 0.0598±0.0105 |
| F7 | 10.44±0.98 | 101.88±3.11 | 69.62±3.82 | 0.4049±0.0251 | 0.0665±0.0063 |
| F8 | 11.39±0.74 | 99.43±0.86 | 68.96±5.48 | 0.5702±0.0564 | 0.0296±0.0023 |
| F9 | 11.32±0.78 | 98.58±1.14 | 65.62±3.04 | 0.4352±0.0189 | 0.0455±0.0031 |
| F10 | 11.54±0.65 | 100.00±1.22 | 60.64±0.90 | 0.4175±0.0145 | 0.0431±0.0047 |

Good flowability will produce uniform dosage form with constant filling granules in the compression room. The compactibility was showed by the tablet hardness after compaction, higher of compactibility of mass tablet then mass of tablet to be compressed with low pressure. Uniformity of dosage form was determined by the drug content of captopril tablet. Uniformity of dosage form as required in Indonesian Pharmacopecia IV, that the drug content not less than 85% and not more than 115% with the relative standard deviation not more than 6%. The controlled hardness of tablet was expected that the hardness will not affect the drug release form dosage form. Tablet without matrix showed that the hardness was not in accordance with the prescribed. Low compactibility and low of the moisture content caused tablet capping when compressed with high pressure and cannot formed compact mass with hardness of 10-12kg. Hardness of tablet without matrix with the maximum pressure without occurrence of capping and lamination.

Drug release profile (Figure 2) showed that the drug release form of captopril sustained release tablet dosage form. In the initial release occurred initial burst release or the drug release uncontrolled, the matrices cannot control the drug release and the drug cannot loaded in the nanoporous of clays maximally.

Composite between drugs and clays were formed maximally at 60 min that showed the lower drug release rate. Nanocomposites were formed with the drug molecules adsorb on nanoporous of carrier materials (zeolite, hydrotalcite and montmorillonite), then the loaded drug in the nanoporous have hydrogen bonding interaction between the drug molecules and nanoclays making the drug release slowly. Clay materials are naturally occurring

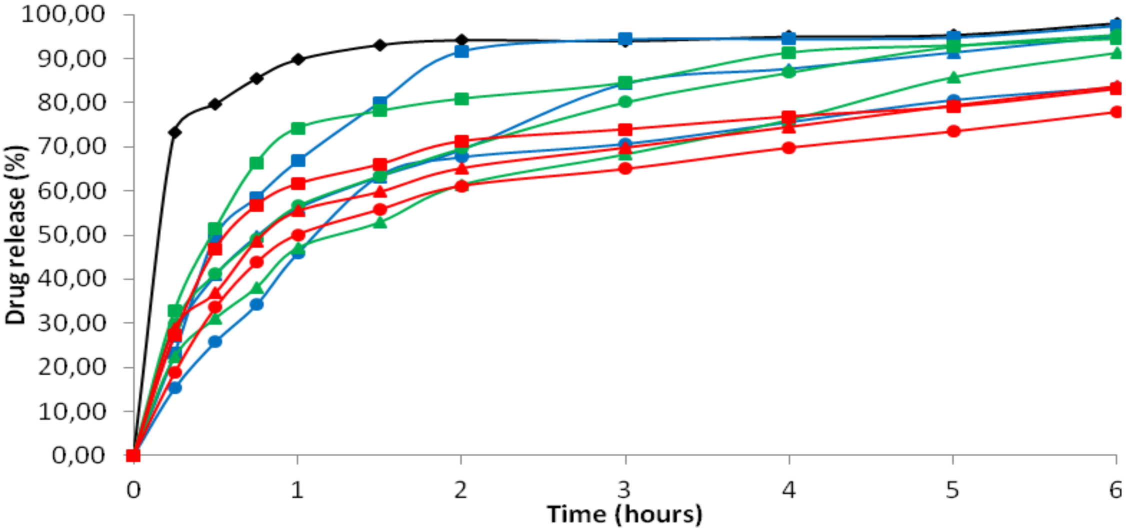


Figure 2. The drug release profile of captopril from dosage form ( — : without matrix, — : zeolite, — : hydrotalcite, — : montmorillonite, ■ : concentration 20%, ▲: concentration 30%, and ●: concentration 40%)

cationic/anionic exchangers and so they may undergo in exchange with basic drug in solution. Release rate of the drug decreased with enhancement of the matrix concentrations.

F4 showed the lowest drug release rate, and F7 showed the fastest between the other formulas. The drug release showed the exponential/parabolic curve showed by the β (shape parameter of Weibull's equation) <1, there are indicated that the initial release with higher slope in the initial. The drug release using 2 release models were initial burst release occurred at 0 until 60min and maintenance release that occurred at 60-360 min. Dissolution profile all formulas were compared with dissolution efficiency until 360 minutes ($DE_{360}$), initial burst release and maintenance release. The result showed significant different with value of $DE_{360}$ ($p<0.05$), initial burst release ($p<0.05$) and maintenance release ($p<0.05$). Release rate was determined by the profile pharmacokinetics approach of captopril with the rate of maintenance release more than 0.02mg/min and approach the steady state concentration (0.05mg/min) and the lowest initial burst release rate. Montmorillonit 40% has been required the lowest of initial burst release rate and the expected of pharmacokinetics profile approach (steady state). The release mechanism based on diffusion exponential of Korsmeyer-Peppas equation. The exponential (n) equation was determined the release mechanism, fickian diffusion ($n=0.45$), anamolius transport ($0.45<n<0.89$), case II transport ($n=0.89$), and super case II transport ($n>0.89$) (Colombo et al. 2007). The mechanism release all formula showed that the mechanism release not followed the Korsmeyer-Peppas equation. Exponential value less than 0.45, the mechanism of release was unclassified. The mechanism release using 2 model of drug release because the nanocomposite of drug and clays, the composites were not occurred in the initial time. The best kinetic models to describe the release kinetics and fitting the equation based on goodness of fitting that the highest of coefficient determination ($R^2$), the lowest of AIC, and the lowest of RMSE that showed the similarity between observed data and predicted data (equation model) (Motulsky & Chirtopoulos, 2003). The release kinetic was described by the Weibull's model. The drug release linear relation can be obtained for a log-log plot of –ln (1-m) versus time (t) (Costa and Lobo, 2001). Ketoprofen, sodium diclofenac and chloramphenicol succinate loaded in the mesoporous of anionic clays (hydrotalcite) showed the initial burst release in 1h and the

Tabel IV. Kinetic models of drug release captopril tablet

| Models | Statistic | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| zero-order | $R^2$ | 0.591 | 0.862 | 0.837 | 0.691 | 0.861 | 0.918 | 0.631 | 0.837 | 0.788 |
| | RMSE | 15.86 | 8.14 | 8.71 | 10.66 | 8.12 | 5.99 | 10.59 | 6.90 | 8.16 |
| | AIC | 82.91 | 68.95 | 70.32 | 74.36 | 69.51 | 62.82 | 74.22 | 65.64 | 69.02 |
| first-order | $R^2$ | 0.473 | 0.736 | 0.649 | 0.560 | 0.714 | 0.814 | 0.484 | 0.718 | 0.613 |
| | RMSE | 19.28 | 11.33 | 13.81 | 12.37 | 11.45 | 8.83 | 12.05 | 8.68 | 10.55 |
| | AIC | 86.21 | 75.58 | 79.54 | 77.33 | 75.79 | 70.60 | 76.80 | 70.25 | 74.16 |
| Higuchi | $R^2$ | 0.883 | 0.891 | 0.931 | 0.829 | 0.833 | 0.775 | 0.769 | 0.865 | 0.902 |
| | RMSE | 8.75 | 7.40 | 5.65 | 7.68 | 8.88 | 9.93 | 10.12 | 8.77 | 10.77 |
| | AIC | 69.65 | 65.69 | 61.66 | 71.17 | 70.70 | 72.94 | 77.67 | 70.46 | 64.57 |
| Hixson-Crowell | $R^2$ | 0.514 | 0.784 | 0.719 | 0.605 | 0.768 | 0.853 | 0.533 | 0.760 | 0.676 |
| | RMSE | 17.59 | 9.95 | 11.26 | 11.61 | 9.94 | 7.63 | 11.36 | 7.92 | 9.44 |
| | AIC | 84.37 | 72.97 | 75.45 | 76.06 | 72.96 | 67.67 | 75.62 | 68.41 | 71.92 |
| Weibull | $R^2$ | 0.938 | 0.994 | 0.966 | 0.975 | 0.987 | 0.976 | 0.896 | 0.985 | 0.953 |
| | $\beta$ | 0.812 | 0.690 | 0.766 | 0.606 | 0.679 | 0.640 | 0.505 | 0.506 | 0.563 |
| | RMSE | 3.45 | 1.67 | 3.76 | 2.78 | 2.52 | 2.80 | 5.12 | 2.03 | 3.20 |
| | AIC | 51.81 | 37.30 | 53.52 | 47.50 | 45.51 | 47.63 | 59.68 | 41.23 | 50.27 |
| Korsmeyer -Peppas | $R^2$ | 0.814 | 0.973 | 0.929 | 0.872 | 0.959 | 0.989 | 0.801 | 0.959 | 0.904 |
| | n | 0.412 | 0.380 | 0.576 | 0.297 | 0.422 | 0.368 | 0.302 | 0.321 | 0.395 |
| | RMSE | 2,66 | 3.33 | 5.17 | 8.16 | 3.91 | 2.03 | 6.83 | 0.310 | 4.41 |
| | AIC | 74.63 | 51.10 | 59.89 | 63.37 | 54.28 | 41.16 | 65.48 | 49.64 | 56.71 |

diffusional release mechanism (San Roman *et al.,* 2013). The nanocomposites of ofloxacin with montmorillonite-chitosan reduced the initial burst release and the kinetic release followed the Higuchi equation and first-order kinetic (Hua *et al.,* 2010).

## CONCLUSION

Montmorillonite, zeolite and hydrotalcite were used as matrices captopril tablet could release the drug form dosage form with the sustained release with initial burst release and maintenance release. Montmorillonit 40% as matrix showed that the lowest initial burst release and expected maintenance release.

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