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# The Antibiotic Potency of Amoxicillin-Clavulanate Co-Crystal

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**Abstract:** The antibiotic activity related to compositions of amoxicillin-clavulanate co-crystals heated compare to the physical mixtures against non-betalactam bacteria: *Sarcina lutea* sp. has been studied. Amoxicillin trihydrate-potassium clavulanate were mixed in molar ratios: 0:10; 1:9; 2:8; until to 10:0 and heated at 50°C along 30 min. Inhibition diameters of the co-crystals were compared to amoxicillin heated and inhibition diameters of the physical mixtures were compared to amoxicillin raw material as counterparts. The results showed the tendency of increasing potency of the co-crystals in molar ratios 3:7-3:7 with significantly improvement at molar ratios 4:6; 6:4; 8:2 and 9:1 which proved different profile from the physical mixture.

**Key words:** Amoxicillin, clavulanate, co-crystal, DSC, XRPD, SEM, antibiotic potency, non beta lactamase, *Sarcina lutea* sp.

## INTRODUCTION

Amoxicillin-clavulanate is antibiotic combination with broad spectrum activity and widely used in the world. Clavulanate was combined with amoxicillin to increase antibiotic potency by inhibit beta-lactamase enzyme (Malik *et al*., 2006; Dufour *et al*., 2005; Smith *et al*., 1998; Storm *et al*., 2004). However, there was a fact which showed that in the dosage forms, clavulanate also increase antibiotic potency of amoxicillin toward non-beta lactamase bacterial with un-explained mechanism (Smith *et al*., 1998; Storm *et al*., 2004; Quach *et al*., 2005). It was already founded about high variability of dosage forms quality and its pharmacokinetic profiles, beside low stability of and incompatibility of amoxicillin-clavulanate (Vree *et al*., 2003; Chadha *et al*., 2003; Vahdat and Sunderland, 2001). Chadha *et al*. (2003) have reported incompatibility of amoxicillin-clavulanate in the liquid dosage form and measure the interaction energy by solution calorimeter. Vahdat and Sunderland (2001) have presented amoxicillin-clavulanate instability even in the frozen condition. Vree *et al*. (2003) reported the high variability of the dosage form quality.

We have investigated the solid state interaction between amoxicillin-clavulanate on the reason that so much solid dosage forms of this antibiotic combination have been produced. Instead, this combination has tendency to build a co-crystal which has not been studied yet. Physically, amoxicillin and clavulanate have similar structure and similar 3-D arrangement which could co-arrange a new crystal lattice on a few ways (Cartensen, 2001; Vednere, 1990). Chemically, these compounds have p-Ka value with differences it value more than 3, the important criteria to arrange a co-crystal (Stahly, 2007). Recently, co-crystals formation becomes important issue because of its potency to develop new pharmaceutical beside useful to study the activity mechanisms which have not been solved (Stahly, 2007; Caira, 2007).

We have reported the results of preliminaries researches in several steps (Nugrahani *et al*., 2007a, f). The first step have reported that interaction between amoxicillin and clavulanate can be clearly observed under polarize microscope and measurable with solution calorimeter in NaOH. The interaction observed extremely at molar ratio 3:7; 5:5 and 7:3, respectively (Nugrahani *et al*., 2007a). In the next research it was showed that interaction at the same molar ratio also observed visually and measured distinctly with solution calorimeter in HCl 0.1 N and buffered phosphate 6.8 solution as a model of non-enzymatic gastrointestinal tract solutions (Nugrahani *et al*., 2007b). After that, it have concluded that the hydrates of amoxicillin tri-hydrate could be bounded to potassium clavulanate which

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predicted produced an intermolecular interaction (Nugrahani *et al*., 2007c). Then, the recent research showed that the binary system of amoxicillin tri-hydrate-potassium clavulanate after Freeze Drying (FD) showed significant interaction points at molar ratios 3:7; 5:5 and 6:4; followed by investigation to look the influence of the freeze dried binary system activity against the non beta-lactamase bacterial *Sarcina lutea* sp. The results showed that freeze dried system had lower potency compared to the physical mixture; but in general had higher potency than freeze dried amoxicillin itself (Nugrahani *et al*., 2007d, e).

Finally, it have been proved that solid of amoxicillin trihydrate-potassium clavulanate formed a solid solution system with heated in closed system at temperature 50°C for 30 min (Nugrahani *et al*., 2007f). The aim of this research was investigated the antibiotic potency of the solid solution system (simplified namely AC-H) against *Sarcina lutea* sp.

## MATERIALS AND METHODS

This study was performed in January-June 2007. The thermal analysis study by DSC was conducted in January-March 2007 in Research and Development Laboratory of PT Tempo Scan Pacific Cikarang Indonesia; while the co-crystal preparation and microbiology evaluation was conducted in May-June 2007 in Pharmaceutical and Microbiology Laboratory of School of Pharmacy ITB Bandung Indonesia. Powder X-ray diffractometry was conducted in Meaming Faculty ITB Bandung Indonesia and Scanning Electron Microscope analysis was conducted in The Centre Research of Geology Bandung Indonesia. In segu times along January-June 2007.

**Physical mixture and co-crystal preparation:** Amoxicillin tri-hydrate (ex. Sandoz batch. No. 243Z from PT Tempo Scan Pacific) and potassium clavulanate potassium clavulanate (ex. Fermic, Mexico, batch Ko. CKA-2967 from PT Tempo Scan pacific) sieved with 100 mesh sieves (Rietsch, Germany). Amoxicillin tri-hydrate weighed in 10 vials with each weight 50 mg. Furthermore, one vial was filled with amoxicillin tri-hydrate alone while 9 other vials added by clavulanate to get molar ratios of amoxicillin tri-hydrate: potassium clavulanate = 1:9; 2:8; 3:7; 4:6; 5:5; 6:4; 7:3; 8:2; 9:1. In another vial, 50 mg of clavulanate weighed. All of the mixtures were homogenized manually (in about 5 min). Powder in all those 11 vials homogenized with motor stirrer for 10 min in closed condition, furthermore, heated in oven at 50°C for 30 min then identified as AC-H co-crystals (Nugrahani *et al*., 2007f).

**DSC analysis:** All of the physical mixtures and co-crystal heated were analyzed by Differential Scanning Calorimeter (DSC-6, Perkin Elmer, USA). Approximately 2-5 mg of each samples were heated in open aluminium pan from 30-350°C at a scanning rate of 10°C $min^{-1}$ under a stream of nitrogen gas. Amoxicillin trihydrate alone, potassium clavulanate alone, amoxicillin trihydrate alone heated at 50°C for 30 min and potassium alone heated at 50°C for 30 min were measure by DSC as standard.

**X-ray powder diffractometer analysis:** The crystal structure were analyzed by X-Ray Powder Diffractometer (XRPD Philips PW1710 BASED, Netherland) under following condition: target/filter (monochromator) Cu, voltage 40 kV, current 30 mA, receiving slit 0.2 inches. The data were collected in the continue scan mode using a step size of 0.5 deg $min^{-1}$. The scanned range was 5-40°.

**SEM analysis:** The morphology of physical mixture 1:1 and co-crystal 1:1 were observed by SEM (Jeoul, Japan) in magnification 1000, 2500 and 7500x.

**Bacteria and detection of beta-lactamase produce:** *Sarcina lutea* ATCC-9341 was identified and then grown in slant agar (Oxoid CM003, USA). The bacteria tested by beta lactamase tester kit (Hardy Diagnostics Beta-Lactamase); showed no beta lactamase enzyme was produced.

**Inhibition determination:** All of AC-H co-crystals and AC-PM were dissolved in buffered phosphate pH 6.8 to make at the rate of 100 μg $mL^{-1}$ sample solutions in all sterile condition. Each of antibiotic solution was dropped 10 $\mu L^{-1}$ on sterile paper disc which planted on cold growth medium. Four mL *Sarcina lutea* sp. ATCC-9341 were grown in a Petri dish contented 21 mL nutrient agar (Oxoid CM003, USA). After that, sample solutions were dropped to paper discs on the Petri dish, let for 1 h in ambient temperature and then entered into incubator at temperature 37°C for 24 h incubation. Then, measure the inhibition diameter.

**Evaluation of technique reproducibility:** to evaluate co-crystal preparation reproducibility, the DSC analysis was done 3 times. While the microbiology test was done 6 times, average and determined by Standard Deviation calculation and then evaluated by Student t-test ($p = 0.95$) to compare the antibiotic potency of AC-PM systems with amoxicillin trihydrate raw material and AC-H systems with amoxicillin trihydrate heated.

## RESULTS AND DISCUSSION

The thermograms resulted from DSC analysis of AC-H 1:1 is showed in Fig. 1 with AC-PM counterparts. The thermograms of amoxicillin and potassium clavulanate before and after heated were also presented as standard. The thermogram profile of AC-H look different from AC-PM and then the diagram phase which were arranged from all molar ratios thermogram data also shows different form were showed in Fig. 2. The AC-H's phase diagram showed the solid dispersion profile in all molar ratios (Cartensen, 2001). XRPD analysis resulted diffraction pattern like showed in Fig. 3. The morphology of co-crystal was compare to the raw materials which were described in Fig. 4 these illustrations were obtained by SEM photography.

The inhibition diameters of amoxicillin-clavulanate physical mixtures (AC-PMs) were showed at Table 1, while the inhibition diameters of AC-H systems were showed at Table 2. The curves of log molar fraction versus inhibition of bacterial growth are showed in Fig. 5. The inhibition curve of AC-H profile looks different compare to the AC-PM inhibition curve.

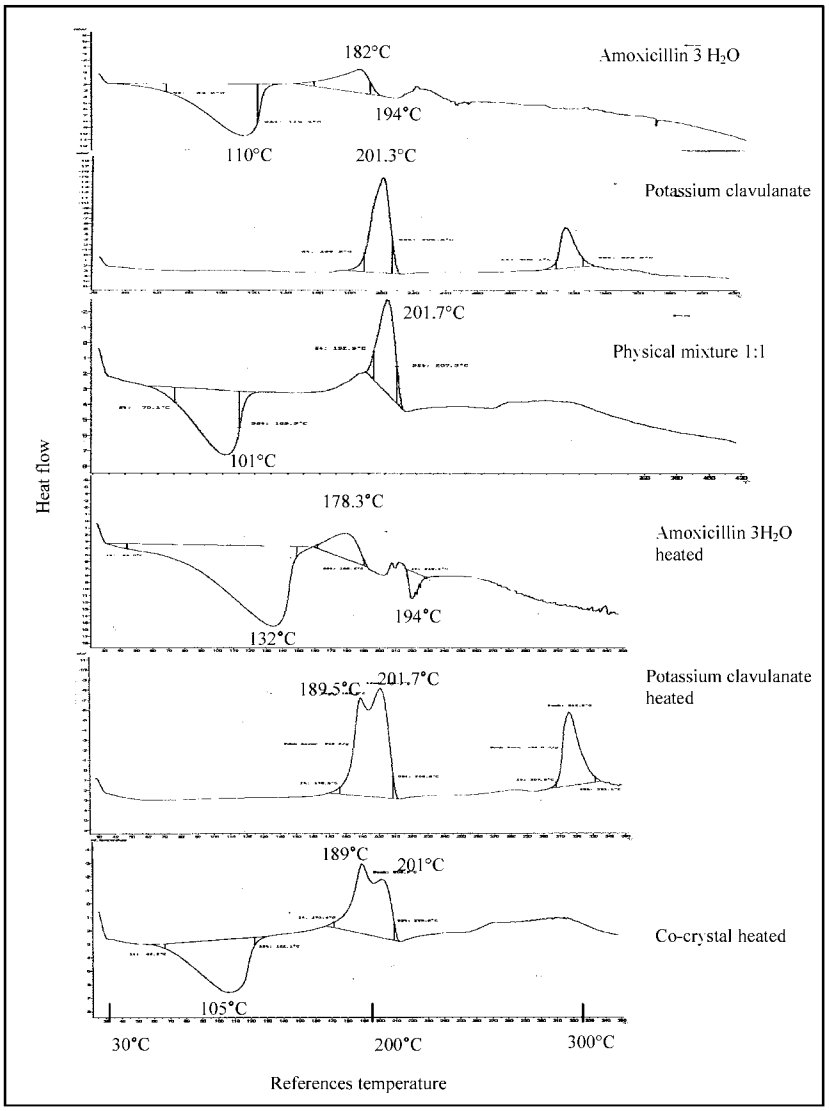


Fig. 1: Thermograms of amoxicillin trihydrate, potassium clavulanate, physical mixture 1:1 (AC-PM), heated amoxicillin, heated clavulanate and heated cocrystal 1:1 (AC-H)

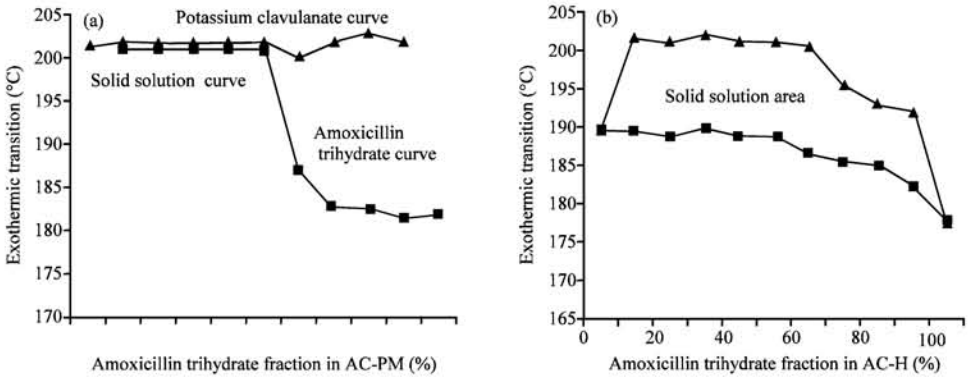


Fig. 2: (a) Phase diagram of AC-PMs and (b) Phase diagram of AC-Hs

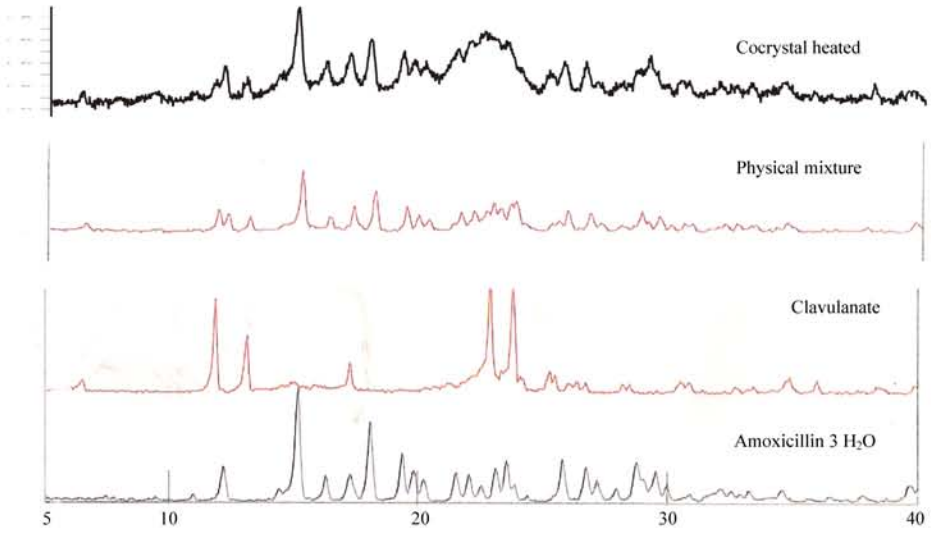


Fig. 3: X-ray powder diffraction patterns of amoxicillin trihydrate-potassium clavulanate physical mixture (AC-PM 1:1) and co-crystal heated (AC-H 1:1)

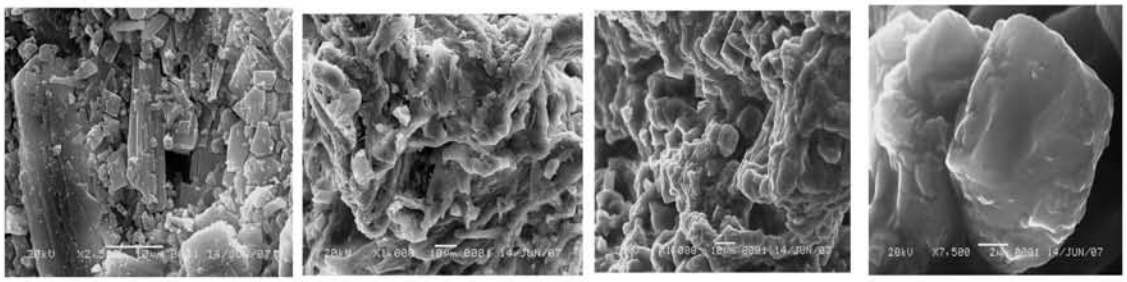

Fig. 4: SEM photographs of amoxicillin trihydrate (1000x), potassium clavulanate (2500x), co-crystal heated (1000x), co-crystal heated (7500x)

Table 1: Inhibition diameter of AC-PM

| Molar ratio of amoxicillin tri-hydrate: potassium clavulanate | Inhibition (cm) 1 | 2 | 3 | 4 | 5 | 6 | Average | SD | t-calculated compare to amoxicillin alone |
|---|---|---|---|---|---|---|---|---|---|
| 0:10 (Clavulanate alone) | - | - | - | - | - | - | - | - | |
| 1:9 | 2.40 | 2.40 | 2.35 | 2.25 | 2.20 | 2.25 | 2.31 | 0.0786 | 6.292 |
| 2:8 | 2.35 | 2.40 | 2.40 | 2.40 | 2.40 | 2.25 | 2.37 | 0.0553 | 5.750 |
| 3:7 | 2.40 | 2.40 | 2.35 | 2.40 | 2.40 | 2.40 | 2.39 | 0.0186 | 12.50 |
| 4:6 | 2.50 | 2.50 | 2.45 | 2.45 | 2.50 | 2.50 | 2.48 | 0.0236 | 16.23 |
| 5:5 | 2.60 | 2.70 | 2.60 | 2.70 | 2.70 | 2.70 | 2.67 | 0.0471 | 3.450 |
| 6:4 | 2.70 | 2.70 | 2.70 | 2.70 | 2.70 | 2.70 | 2.70 | 0.0000 | 3.550 |
| 7:3 | 2.50 | 2.70 | 2.70 | 2.60 | 2.70 | 2.70 | 2.65 | 0.0764 | 2.420 |
| 8:2 | 2.70 | 2.70 | 2.70 | 2.60 | 2.60 | 2.70 | 2.67 | 0.0471 | 3.467 |
| 9:1 | 2.70 | 2.90 | 2.70 | 2.70 | 2.70 | 2.77 | 2.77 | 0.0943 | 0.870 |
| 10:0 (Amoxicillin alone) | 2.90 | 2.90 | 2.80 | 2.80 | 2.90 | 2.90 | 2.87 | 0.0471 | |

Table 2: Inhibition diameter of AC-H

| Molar ratio of amoxicillin tri-hydrate: potassium clavulanate | Diameter inhibition (cm) 1 | 2 | 3 | 4 | 5 | 6 | Average | SD | t-calculated compare to amoxicillin alone |
|---|---|---|---|---|---|---|---|---|---|
| 0:10 (Clavulanate alone) | - | - | - | - | - | - | - | - | |
| 1:09 | 1.95 | 1.85 | 1.90 | 1.87 | 1.82 | 1.92 | 1.89 | 0.0435 | 11.59 |
| 2:08 | 2.20 | 2.10 | 2.00 | 2.12 | 1.92 | 2.30 | 2.11 | 0.1242 | 2.278 |
| 3:07 | 2.59 | 2.55 | 2.46 | 2.45 | 2.50 | 2.60 | 2.53 | 0.0591 | 1.630 |
| 4:06 | 2.61 | 2.59 | 2.66 | 2.60 | 2.58 | 2.55 | 2.60 | 0.0334 | 4.400 |
| 5:05 | 2.54 | 2.54 | 2.46 | 2.47 | 2.44 | 2.50 | 2.49 | 0.0385 | 1.710 |
| 6:04 | 2.70 | 2.64 | 2.67 | 2.65 | 2.56 | 2.67 | 2.65 | 0.0437 | 5.000 |
| 7:03 | 2.55 | 2.55 | 2.39 | 2.55 | 2.50 | 2.34 | 2.48 | 0.0845 | 2.300 |
| 8:02 | 2.56 | 2.58 | 2.59 | 2.60 | 2.65 | 2.50 | 2.58 | 0.0451 | 3.860 |
| 9:01 | 2.73 | 2.73 | 2.77 | 2.75 | 2.82 | 2.76 | 2.76 | 0.0306 | 10.68 |
| 10:00 (Amoxicillin alone) | 2.42 | 2.41 | 2.41 | 2.44 | 2.42 | 2.41 | 2.42 | 0.0107 | |

The data listed in Table 1 show that the averages of inhibition diameter of AC-PM in the molar ratios 1:9 until 4:6 were similar and after that there were a little increase at molar ratio of 5:5 until 9:1. Compare to amoxicillin trihydrate raw material, all AC-PM systems were significantly lesser with calculated t-value higher than t-table (t-table = 2.571; p = 0.05), as have been described in table 1 and shown in Fig. 6. AC-PM-0, the pure single clavulanate solution do not show any inhibition. In general, the inhibition diameters of AC-PM systems 1-4 were lesser than AC-PM 5-10.

AC-H systems inhibition diameters against *Sarcina lutea* sp. were shown in Table 2. This table shows that after molar ratio 3:7 the inhibitions diameters tend to increase. The statistical significant differences were showed at the molar ratios = 4:6, 6:4; 8:2 and 9:1 which have t-value higher than t-table (p = 0.05).

Thermogram of AC-PM and AC-H in molar ratio 5:5 or 1:1 were selected to explain the interaction between amoxicillin-clavulanate. From thermograms obtained by DSC analysis (Fig. 1), amoxicillin trihydrate and potassium clavulanate after heated at 50°C for 30 min showed have different profile and temperature transition. Amoxicillin alone before heated has important transition temperature at 110 (endothermic), 182 (exothermic), 194°C (endothermic) and after heated the temperature change to 130, 178 and 194°C. The first endothermic curve is anhydration, the exothermic showed re-crystallization from trihydrate to anhydrate and the last endothermic indicate melting point. Potassium clavulanate before heated has important exothermic transition temperature at 201.3°C (the second exothermic curve can be ignored because it is Avicel's curve which used to disperse clavulanate). After heated, clavulanate has 2 peaks at 189.5 and 201.7°C. The physical mixture 5:5 or 1:1 (AC-PM) showed that the exothermic curve of amoxicillin and clavulanate overlaid to be 1 curve at 201°C while the co-crystal (AC-H) overlaid and arrange 2 peaks at 189 and 201°C. The arrangement from 2 different peaks become one peak could indicate co-arrangement phenomenon in the type of solid solution (Vednere, 1990; Cartensen, 2001).

All of data obtained from DSC then used to arrange a phase diagram which yielded different phase diagram compare to the physical mixtures (Fig. 2a, b). AC-PM arranged a solid dispersion or co-crystallization at 201°C in molar ratio of amoxicillin: clavulanate = 1:9 until 5:5, but the heated systems have arranged co-crystals in all composition. It was expressed that amoxicillin-clavulanate after mixing and heating could form a new arrangement powder co-crystal in all molar ratios or composition.

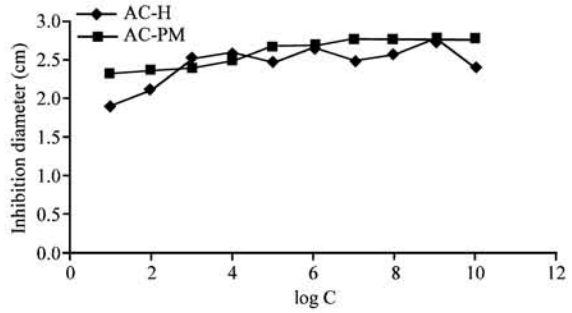


Fig. 5: The curve log concentration versus inhibition diameter of AC-PM and AC-H

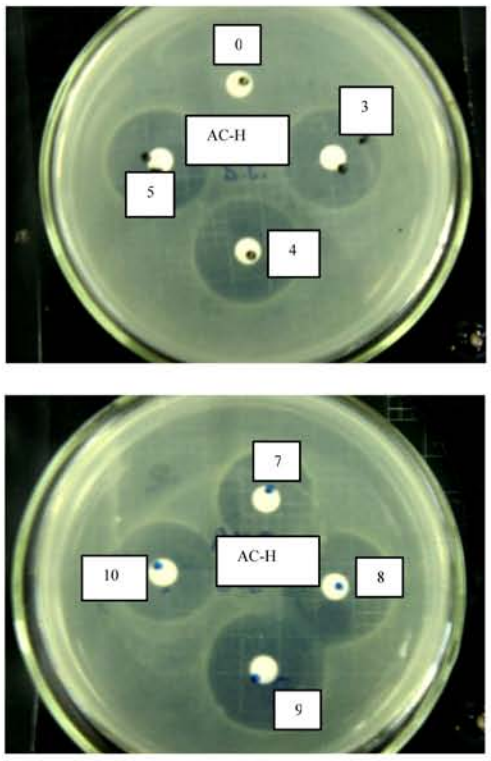


Fig. 6: Inhibition diameter AC-H against *Sarcina lutea* sp. in the ratios = 0:10 (clavulanate alone), 3:7 (3), 4:6, 5:5 (5), 7:3 (7), 8:2 (8), 9:1 (9), 10:0 (amoxicillin alone)

XRPD analysis was conducted to investigate the lattice structure and solid phase of amoxicillin-clavulanate. Figure 3 showed that the physical mixture and co-crystal have similar pattern with amoxicillin alone. Figure 4 which show SEM observation results, could explain this phenomena. Physically, clavulanate was more amorphous than amoxicillin trihydrate. After heated, clavulanate dispersed on amoxicillin surface but it still could diffract x-ray beam because of its low crystallinity, so the diffraction pattern still shows like amoxicillin alone. Co-crystals usually formed in some kind of non-covalent bonding, included hydrogen bonding formation and could change the physicochemical properties and the antibiotic potency (Stahly, 2007; Bettinetti *et al.*, 2000; Hickey *et al.*, 2007; Caira, 2007).

In this report, the changes of potency is related to phenomenon which showed that amoxicillin-clavulanate enhanced the potency against non beta lactamase bacteria with unknown mechanism (Storm *et al.*, 2004; Smith *et al*., 1998; Quach *et al.*, 2005). The co-crystal as a physical intermolecular interaction examined for its inhibition diameter against *Sarcina lutea* sp., a non beta lactamase bacteria, compared to the AC-PM counterparts.

The inhibition diameters of AC-PM 1-4 were lesser than AC-PM 5-10 caused at much of clavulanate which freely dissolved and covered the surface of bacterial *Sarcina lutea* sp., physically inhibit amoxicillin tri-hydrate activities. Figure 3 shows the lesser inhibition of molar ratio 1 and 2 than amoxicillin, increase at composition 3 (molar fraction: 3:7) and increase once again at composition 5 (molar fraction: 5:5). Different from AC-PM data, the inhibition diameter of AC-H since molar ratio 3:7 until 9:1 tended to show the higher potency compare to amoxicillin alone.

These phenomena occur in the reason as follows: after heating, hydrogen bonding between amoxicillin tri-hydrate with potassium clavulanate was formed and modifies the amoxicillin tri-hydrate polarity. At the molar ratios 1:9 and 2:8 (composition 1 and 2) the solid phase were dominated by potassium clavulanate which covered the existence of amoxicillin tri-hydrate that caused potency decrease, but began in molar ratio 3:7 the amoxicillin tri-hydrate was starting to dominate the solid solution and improve the antibiotic potency. From the preliminary researches, the interaction has been proven attain an equivalent point at 5:5 (Nugrahani *et al*., 2007a-d). In this research, the compositions 3:7; 5:5 and 7:3 are indicated as transition points which showed lesser potency than other co-crystal heated but still higher than amoxicillin heated alone. While the molar ratios 4:6; 6:4; 8:2 and 9:1 showed significantly higher than amoxicillin alone. Confirm to preliminary data have been reported, it conclude that interaction of amoxicillin-clavulanate were occur at 3:7-7:3 molar ratio and the interaction might change the antibiotic potency.

This research proved that amoxicillin-clavulanate heated at 50°C at 30 min influence the antibiotic activity against non-beta lactam bacteria *Sarcina lutea* sp. That is not a high level energy, which could be equal with the energy involved in the milling, granulating, compacting and the storing.

## CONCLUSION

Physical interaction between amoxicillin tri-hydrate and potassium clavulanate improve its antibiotic activity against non-beta lactamase bacterial, *Sarcina lutea* sp. The result can be used as information to knowing the mechanism of amoxicillin-clavulanate synergism to non-beta lactam bacteria. This research should continue with studying the interaction between the binary system interaction structures with the membrane cell of bacterial.

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## REFERENCES

Bettinetti, G., M.R. Caira, A. Callegari and M. Merli, 2000. Structure and solid state a chemistry of anhydrous and hydrated crystal form of trimethoprim-sulfamethoxypyridazine 1:1 molecular complex, 2000. J. Pharm. Sci., 89 (4): 478-489.

Caira, M.R., 2007. Sulfa drugs as model co-crystals former. Mol. Pharm., 4 (3): 310-316.

Cartensen, J.T., 2001. Advanced Pharmaceutical Solids. Taylor and Francis, New York, pp: 175-176.

Chadha, R., N. Kashid and D.V.S. Jain, 2003. Microcalorimetric evaluation of the *in vitro* compatibility of amoxicillin/clavulanic acid and ampicillin/sulbactam with ciprofloxacin. J. Pharm. Biomed. Anal., 30: 1515-1522.

Dufour, V., L. Millon, J.F. Faucher and E.B. Robinet *et al.*, 2005. Effects of a short-course of amoxicillin/ clavulamic acid on systemic and mucosal immunity in healthy adult humans. Int. J. Immunopharmacol., 5: 917-928.

Hickey, M., M.L. Peterson, E.S. Manas, J. Alvarez, F. Haeffner and O.R.N. Alarson, 2007. Hydrates and solid-state reactivity: A survey of b-lactam antibiotics. J. Pharm. Sci., 96 (5): 190-199.

Malik, Z.A., N. Litman and H.M. Adam, 2006. Ampicillin and Amoxicillin. Pediatr. Rev., 27: 434-436. downloaded from: http://pedsinreview. aappublications.org/cgi/content/full/27/11/434.

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007a. Cold contact method for detection amoxicillin-clavulanate interaction. International Conference of Chemical Sciences, Seminar and Proceeding, Jogja-Indonesia.

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007b. *In vitro* detection of amoxicillin-clavulanate interaction in gastrointestinal liquid pH. Med. Maranatha J., (In Press).

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007c. Isolation and characterization of freezedried amoxicillin-clavulanate co-crystals. Indian J. Pharm. Sci., (In Press).

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007d. Study of amoxicillin-clavulanate solid interaction. Malaysian J. Pharm. Sci., (In Press).

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007e. The influence of freeze drying process for amoxicillin-clavulanate binary system's antibiotic potency against non beta lactam bacteria: *Sarcina lutea* sp., Med. Maranatha J., (In Press).

Nugrahani, I., S. Asyarie, S.N. Soewandhi and S. Ibrahim, 2007f. The Co-crystal Amoxicillin-Clavulanate. Dissertation Research Report, School of Pharmacy, Institute Technology Bandung, Indonesia.

Quach, C., J. Collect and P.J. LeLorier, 2005. Effectiveness of amoxicillin, azithromycin, cefprozil and clarithromycin in the treatment of acute otitis media in children: A population-based study. Pharmacoepidemiol. Drug Saf., 14: 163-170.

Smith, G.M., B. Dlocombe, K.H. Abbot and L.W. Mizen, 1998. Activity of amoxicillin-clavulanate against penicillin-resistant *Streptococcus pneumoniae* in an experimental respiratory infection model in rats. Antimicrob. Agents Chem., 42 (4): 813-817.

Stahly, G.P., 2007. Diversity in single and multiple-component crystals. The search for and prevalence of polymorphs and cocrystals. Crystal Growth Des., 7 (6): 1007-1026.

Storm, K.H., C.P. Conley and J.A. Roush, 2004. Composition Comprising Amoxicillin and Potassium Clavulanate. US. Patent No. 6.783.773 B1.

Vahdat, L. and V.B. Sunderland, 2001. Kinetics of amoxicillin and clavulanate degradation alone and in combination in aqueous solution under frozen conditions. Int. J. Pharm., 342: 95-104.

Vednere, K.M., 1990. Co-Precipitates and Melts. In: Encyclopedia in Pharmaceutical Technology, Swarbrick, J. and J.C. Boyle (Eds.). 3, Marcel Dekker, New York, pp: 337-350.

Vree, T.B., E. Dammers and P.S. Exler, 2003. Identical pattern of highly variable absorption of amoxi-clav. J. Antimic. Chem., 51: 373-378.