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Original Article

PREPARATION, CHARACTERIZATION AND FORMULATION OF NANOCOMPOSITE MATRIX Na-MONTMORILLONITE INTERCALATED MEDIUM MOLECULAR WEIGHT CHITOSAN FOR THEOPHYLLINE SUSTAINED RELEASE TABLET

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ABSTRACT

Objective: The purpose of this study was to investigate Na-montmorillonite (Na-MMT) intercalated medium molecular weight (MMW) chitosan as an oral drug delivery vehicle for *In Vitro* release of theophylline sustained release tablet.

Methods: Montmorillonite (MMT) clay were synthesized into Na-MMT and treated with chitosan. Combination becomes synthesis of Na-montmorillonite intercalated MMW chitosan. Parameters tested including MMT characterization as well as already intercalated using XRD, FTIR and SEM. Tablets were prepared using the wet granulation method. The physical properties evaluation was conducted on granules and tablets. Dissolution test used apparatus II USP model with 100 rpm of speed rotation for 6 hours and phosphate buffer pH 7.2 as a medium. Absorbance of the sample was measured on a spectrophotometer.

Results: XRD spectra results showed 15.43 Å MMT basal spacing. Na-MMT was synthesized and distance between the layers value was 15.225 Å, this was because the smaller size of impurity cations than Na^+ cation. After intercalation with chitosan, distance between layers became wider to 15.94Å. Characterization results with FTIR spectra on MMT intercalated MMW chitosan exposed similarities with Na-MMT, small shift was occurred. This indicated that intercalation with chitosan did not change the structure of Alumina silicate MMT. However, the physical properties of the granule were not affected by any difference of components formula. Tablets physical properties still meet the reference requirements. Tablets with dissolution efficiency has different values with different composition formulas.

Conclusion: Characteristics of the MMT, Na-MMT, Na-MMT intercalated MMW chitosan did not change much. The intercalation process of Na-MMT with chitosan further accelerates drug release compared to MMT and exhibited a prolonged release as compared to the pure drug without MMT.

Keywords: Theophylline, Montmorillonite, Intercalated, Chitosan, Drug release.

INTRODUCTION

Clay minerals have been proposed as fundamental constituents of several modification of drug delivery systems, with different purposes and acting through various mechanisms. Based on their high retention capacities as well as swelling and colloidal properties, clays have been proposed as useful materials to modify drug delivery. Because of their swelling potential, clay minerals can be effectively used to delay (extended-release systems) drug release or even improve drug solubility [1].

MMT is a natural mineral consists of an insoluble large layer and weakly bound cations to the space between layers. Each layered hydrated aluminum silicate whose unit cell is composed of one Al-octahedral sheet (O) sandwiched between two Si–tetrahedral sheets (T). It possesses a net negative charge due to isomorphous ionic substitutions in the T–O–T structure. This charge is compensated by interlayer hydrated cations, which can be exchanged by a variety of organic molecules [1,2]. MMT is able to swell with the addition of large cations into the space between the layer of MMT [3,4,5]. Intercalated clay is a derivative of smektit which the cations have been exchanged by large cations and these cations serves as a pillar of support between MMT layer [6]. MMT is a smectite group clay and has a large specific surface area, good adsorption,and cation exchange capacity [7].

Intercalation is a process of atoms or molecules insertion into the interlayer of layered material without damaging the layer structure [6]. Intercalation into interlayer of silicate clay occured because of incoming intercalate (atoms or molecules that will be inserted) as cation or positively charged ions replaced cations in interlayer of clay for example Na^+, K^+, Ca^{2+}. These cations are generally not bound so it easily moved or exchanged with intercalate cations. This process was often called cation exchange.

Intercalation with inorganic polyhydroxy cations followed by heat treatment will form intercalated clays by metal oxides which typically have a high thermal stability [8,9]. Intercalation is insertion of a pillar agent into clay silicate interlayer so intercalated clay compound is obtained. Intercalation will increase the chemical and physical properties that include basal spacing (d_{001}), specific surface, porosity and acidity of MMT [10].

MMT is the most commonly used natural clays and has been successfully applied in numerous nanocomposite systems [11,12]. Some of MMT uses have been made to the controlled drug release [13-23]. Dispersion of chitosan on the MMT surface opens the functional groups that could potentially form a hydrogen bond with theophylline. Chitosan being a cationic, hydrophilic, nontoxic, biocompatible, and bioabsorbable polymer is a popular material for drug delivery applications [24]. Chitosan has also been used to prepare nanocomposites with MMT for prolonged release and biomedical applications [25,26]. In particular, chitosan chains have been described to intercalate with Na-MMT, because of their hydrophilic and cationic character, giving hybrid nanocomposite materials with interesting properties [27]. Other works showed that the ratio between MMT and chitosan was a crucial factor also in the case of nanocomposites prepared to control the release of the chemotherapeutic agent doxorubicin [28].

In this research work, an attempted has been done to design and evaluate drug release of theophylline sustained release tablet formulation using Na-MMT intercalated MMW chitosan. Theophylline was chosen as a model drug due to its efficiency to treat chronic obstructive pulmonary disease, and a narrow therapeutic index which requires regular monitoring of serum theophylline concentrations. In this way slow release forms of theophylline can be used to avoid adverse effects and promote its efficient use.

MATERIALS AND METHODS

Materials

Theophylline (Shandong Pharm, China), lactose, starch, methocel K15M (Hydroxypropylmetylcellulose HPMC type 2208 with 15,000 cps viscosity), buffer phosphate pH 7.2 liquid, natural montmorillonite obtained from Wonosegoro Boyolali Indonesia, Medium molecular weight (MMW) chitosan (200,000 cps viscosity) obtained from Aldrich Singapore, magnesium stearate, talc, aquadest, NaCl (E. Merck, Germany), $AgNO_3$ (E. Merck, Germany), NaOH (E. Merck, Germany), Acetic Acid (E. Merck, Germany).

Preparation and characterization of Initial Montmorillonite

MMT had been purified from bentonite which were obtained from Wonosegoro, Boyolali, Central Java, Indonesia. Rough bentonite were taken and washed with demineralized water, the colloid phase was precipitated one night. The sediment was dried at 110^0C in the oven (Memmert) for a day. This process was repeated for 5 times. Dried MMT then sifted with 180 mesh sieve, identified and characterized with X-Ray Difractometer (XRD) Shimadzu type 6000.

Synthesis of Na-Montmorillonite

MMT of 70 grams was added into 1.5 L Natrium Chloride 1M liquid. The suspension was stirred with magnetic stirrer for 24 hours in the temperature range of 55-60^0C. Sediment was separated from the suspension by decantation. Obtained sediment was washed with aquadest to remove the remaining chloride ion. To make sure that there is no longer chloride ion remaining on the clay surface, the water that used to wash the sediment was tested with $AgNO_3$ 1M liquid. If this test shows a negative result of $AgNO_3$, it means that it did not form white sediment of AgCl. Formed Na-MMT were dried at 100^0C in the oven.

Synthesis of Na-montmorillonite intercalated MMW chitosan

Composite manufacture with chitosan: clay ratio of 0.603:1.500; 1.206:1.500; 2.415:1.500; and 4.830:1.500 conducted with making a chitosan suspension of 4.83 grams into 750 ml 1% acetic acid, then stirred for 4 hours at room temperature. NaOH 4M was added into suspension until pH 4.9 reached using a pH meter (Hanna 8514). Next, 750 ml of clay suspension 2% (1.5 gram Na-MMT on 750 ml aquadest) added carefully at temperature of 50^0C. This mixture then stirred for 2 days, then washed with aquadest until free from acetate. This material then called Na-MMT clay intercalated chitosan. For characterization, composite were dried at 50^0C and finely crushed.

Characterization of Na-montmorillonite intercalated MMW chitosan

Characterization with X-Ray Diffraction (XRD) Shimadzu Type 6000 tested the crystallinity of clay. XRD reflection intensity indicates about the perfection of the crystal and the density of the atoms arrangement in a crystal. An intensity reflection peaks that were increasingly sharp indicates better clay crystallinity with close atoms arrangement. XRD data were compared to initial diffractogram basal spacing and intercalated to find out the optimum MMT intercalation. Functional group which contained in clay from Wonosegoro was analyzed using Fourier Transform Infrared (FT-IR) Spectrophotometer Shimadzu type 8201 PC. MMT Clay has an absorbance at certain area. To prove that chitosan had been entered into MMT basal spacing, analysis was done using a Philips XL30 CP scanning electronic microscopy (SEM) to study surface morphology from composite after intercalation process conducted with chitosan. With this analysis, differences will be seen between montmorillonite before involving intercalation and montmorillonite after intercalation with chitosan.

Table 1: Matrix Composition Formula

Composition	Content per tablet (mg)			
	F I	F II	F III	FIV
Theophylline	200	200	200	200
Montmorillonite (MMT)	-	-	85	-
Na-montmorillonit(Na-MMT) Intercalated MMW chitosan	-	-	-	85
HPMC	-	85	-	-
Lactose	137.5	95	95	95
Starch	137.5	95	95	95
Magnesium stearate	1	1	1	1
Talc	9	9	9	9
Starch mucilage10%	15	15	15	15

Formula Composition

Preparation of Theophylline Tablet

Theophylline granules were prepared using wet granulation. Theophylline, matrix material (for Na-MMT intercalated MMW chitosan ratio 1.500:2.415), starch, and also lactose were mixed until homogeneous with cube mixer for 10 minutes at agitation speed of 90 rpm. Few binding agents starch mucilage10% were added into the mixture so wet mass granule was formed. Wet Mass granules were passed through 16 mesh sieve, then dried at 60^0C for 3 hours. Dried granules were passed through 18 mesh sieve, then mixed with magnesium stearate and talc in a tumbler for 10 minutes at agitation speed of 90 rpm. Physical properties of granule test were conducted to find out the feasibility of physical properties before compressed into tablets, includes: test of flow time, angle of repose and carr's index using volumenometer (Makita). Physical properties of granule that has been examined, then compressed into tablets using single punch tablet machine (korsch, Germany) with 500 mg weight per tablet. Compression pressure in the manufacture of the tablets was maintained at 60-70 N so that the weight of the tablet in every formula is all the same. Physical properties of tablets conducted including: weight variation test, hardness test using hardness tester (Gouming YD-1), and friability test using friability tester (Roche).

In Vitro drug release

Dissolution test of theophylline sustained release preparation using dissolution paddle type apparatus (Electrolab TD-08) USP XXIII model with paddle stirrer was done in the following way: medium phosphate buffer pH 7.2 500 ml was added to dissolution flask, paddle stirrer maintained at an agitation speed of 100 rpm with 2.5 cm distance of paddle stirrer from the bottom. Tablets then weighed and added into dissolution flask. The experimental temperature was maintained at a rate of 37 ± 0.5 °C. A sample was taken 5 ml at every 15, 30, 45, 60, 90, 120, 240, 300, 360 minutes. These samples were exchanged with new dissolution medium with the same amount so the volume of dissolution medium was fixed. Absorbance of the samples was measured using a spectrophotometer UV (Genesys 10, Thermo) at a theophylline maximum wavelength (λ_{max} = 272 nm) based on maximum wavelength that has been tested. Furthermore, theophylline levels were determined using the standard curve that has been made.

RESULTS AND DISCUSSION

Preparation of montmorillonite

The montmorillonite (MMT) that have been used in this study was natural MMT which was purged from impurity by taking the colloid

phase. MMT was analyzed by XRD to find out the character of MMT as shown in figure 1.

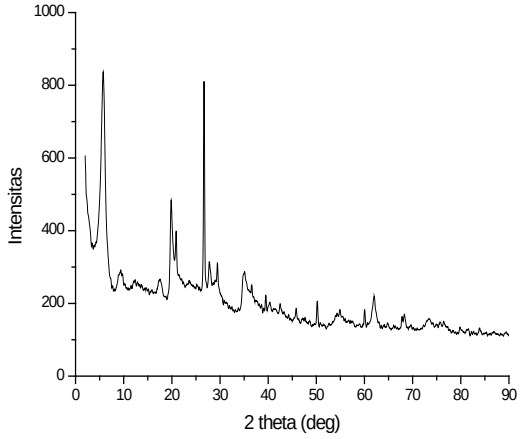


Fig. 1: Diffractogram of natural MMT

Figure 1 shows MMT diffractogram results with 3 strongest peaks at 2θ that were 5.720^{o}; 6.000^{o}; 26.674^{o}with d value of 15.438 Å; 14.718 Å and 3.339 Å. The strongest peak with highest intensity peak was used as an identifier of mineral. Diffractogram data in figure 1 shows diffraction peaks with the highest intensity at 2θ was 5.720^{o}. Joint Committee on Powder Diffraction Standards (JCPDS) data main diffraction peak MMT intensity at 2θ was 5^{o}-6^{o}with a diameter of 12.3Å-17.7Å. So, this diffractogram data showed that the main mineral constituent in clays was MMT.

Preparation of Na-Montmorillonite

MMT were modified into Na-MMT prior to intercalation. Na^{+} cation was used to extrude metal impurities in MMT. Other than that, Na^{+} also used as exchanged agent and replaced by Ammonium ion in chitosan. Diffractogram of Na-MMT as shown in figure 2, there was a slight shift of the 2θ peak to the right. It showed that decreasing basal spacing (d_{001}) was occurred. It was caused by the smaller Na^{+} cation size than dopants cation size. Distance between layers of Na-MMT in figure 3 became 15.20 Å which was decreasing in size. The effect from this decrease was Na-MMT in water became smaller size colloid phase It was harder to precipitate than MMT.

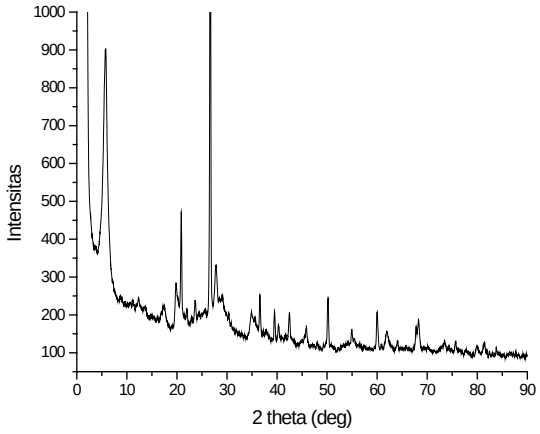


Fig. 2: Diffractogram of Na-MMT

Decreasing of basal spacing (d001) from MMT showed that MMT modification into Na-MMT had been successfully done. The effects of this modification increased the swelling ability from MMT when being dispersed in aquadest, so the MMT pores would open wider and chitosan would be easier to enter between MMT layers. Furthermore, intercalation would be done to the Na-MMT by using chitosan.

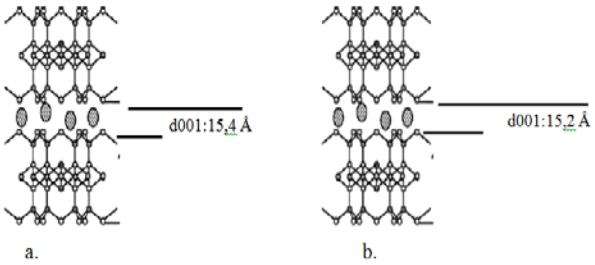


Fig. 3: Distance between layers: a). initial MMT b). Na-MMT

Characterization of MMW chitosan

The FTIR spectrum absorbance of a polycation has a typical pattern that allows to identify polycation and also to unveil the presence of main functional groups within the structure of identified compound. The Analysis result by spectrophotometer FTIR was given in figure 4. The result showed that chitosan have a ring group stretching (C-H cyclo or ring), C-O $_{asym}$ & C-O_{sym} stretching, bridge-O-stretching (C-O-C), N-H bending (-NH_2), and C=O stretching ($NHCOCH_3$) amida I.

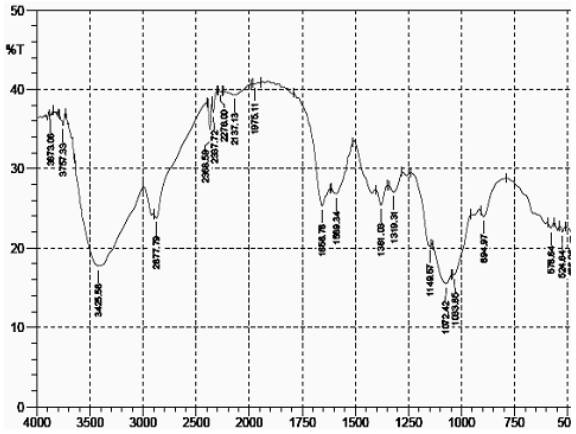


Fig. 4: FTIR spectrum of MMW chitosan

Pillarization Na-montmorillonit nanocomposite with MMW chitosan

Pillarization or intercalation is an inclusion of pillar agent into the interlayer of clay silicate so intercalated clay compound was obtained. Pillarization will increase chemical and physical properties including basal spacing (d001), specific surface area, porosity and acidity of MMT. This study used medium molecular weight chitosan to intercalate Na-MMT. Intercalation with polihydroxycation followed by heating will form intercalated clay with high thermal stability. The intercalated Na-MMT mineral was detected by analysis using XRD, FT-IR spectrophotometer and SEM. X-ray diffraction used for analyzing mineral in the qualitative and quantitative way. Qualitative analysis was conducted by matching the sample of diffractogram with JCPDS standard data of MMT. While the quantitative analysis was conducted by focusing diffractogram review at angle of 2θ under 6^{0}, because this area showed chitosan was in the space between the layers. If a new peak appeared under initial peak, the basal spacing (d001) was increased, marked by 2θ shift to the left or 2θ peak appeared which dominantly had a smaller value from the initial peak.

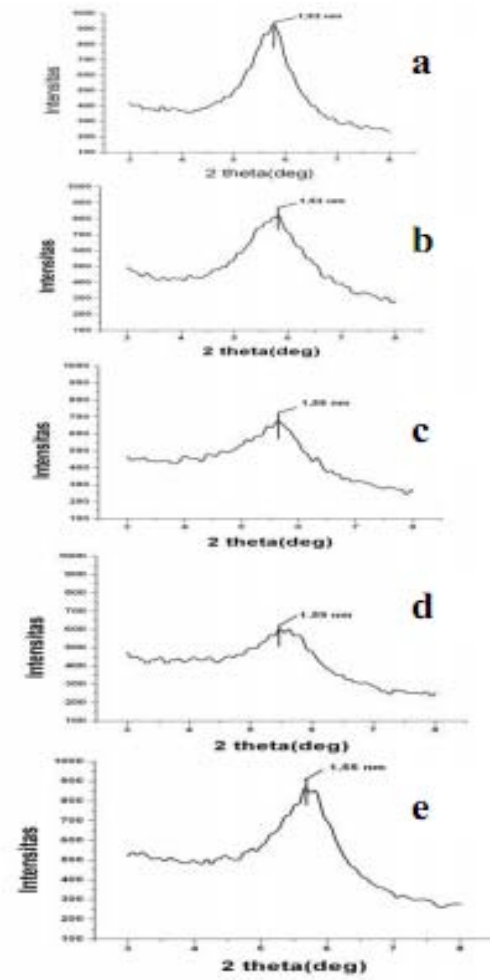


Fig. 5: Diffractogram: a). Na-MMT b). Chitosan-Na MMT 0.603:1.500 c). Chitosan-Na MMT 1.206:1.500 d). Chitosan-Na MMT 2.415:1.500 e). Chitosan-Na MMT 4.830:1.500

In figure 5a) demonstrates Na-MMT diffractogram before intercalation process. MMT before intercalation characterized by the presence of peak at 5.800^0 which was basal spacing from Na-MMT with d value of 15.225 Å. Figure 5b) to 5e) displayed the result from diffractogram of intercalated Na-MMT by chitosan with different ratio. For example in figure 5d) disappearance of 5.800^0 peaks characterized by appearance of new peak which dominant at $2\theta=5.541^0$ indicated that basal spacing was increasing, this was reinforced by the increasing of d value to 15.937 Å, which was the highest d value compared to other ratio composition, so the material was conducted for dissolution evaluation.

Every mineral has a typical vibration absorbance pattern that allows to identify the mineral and also to find out the presence of main functional groups in the identified structure compound. Shifting of wave numbers toward a smaller one was the proof of chitosan entering MMT. Change of wave numbers from chitosan, Na-MMT and each composite were shown in figure 6.

Figure 6 shows that the initial MMT sample had Si-O/Al-O groups, -O-Al-O- groups, -O-Si-O- groups, O-H groups at H_2O and O-H groups from Si-OH groups and Al-OH groups. The presence of functional groups showed that on the initial MMT clay sample had aluminosilicate structure and Si-O-Si ring. Spectra IR of intercalated Na-MMT by MMW chitosan showed that intercalation with chitosan did not damage the MMT aluminosilicate structure. Vibration frequency was at 1597.06 cm^{-1} on the first chitosan which was the vibration absorbance of NH_3 (δ_{NH3}), protonated amino groups also appeared on intercalated chitosan composite of which frequency was decreased with the increasing of total chitosan needed. A chitosan intercalation on Na-MMT was already occurred at this wavelength because of hydrogen bond between amino with Na-MMT. The larger the amino groups means the greater of possibility to form hydrogen bonds. This was the reason for wavelength decreased significantly. Another chitosan group absorbance like C-O $_{sym}$ stretching at wave length of 1033.85 cm^{-1} was not seen, because overlapping the vibration absorbance strain –O-Al-O and –O-Si-O- found in Na-MMT. Besides, amino groups absorbance at 3425.58 cm^{-1} found in chitosan also overlapping the absorbance of O-H group from Si-OH/Al-OH group appeared as a broadening absorbance peak.

The analysis result of surface morphology from composite using SEM are given in figure 7.

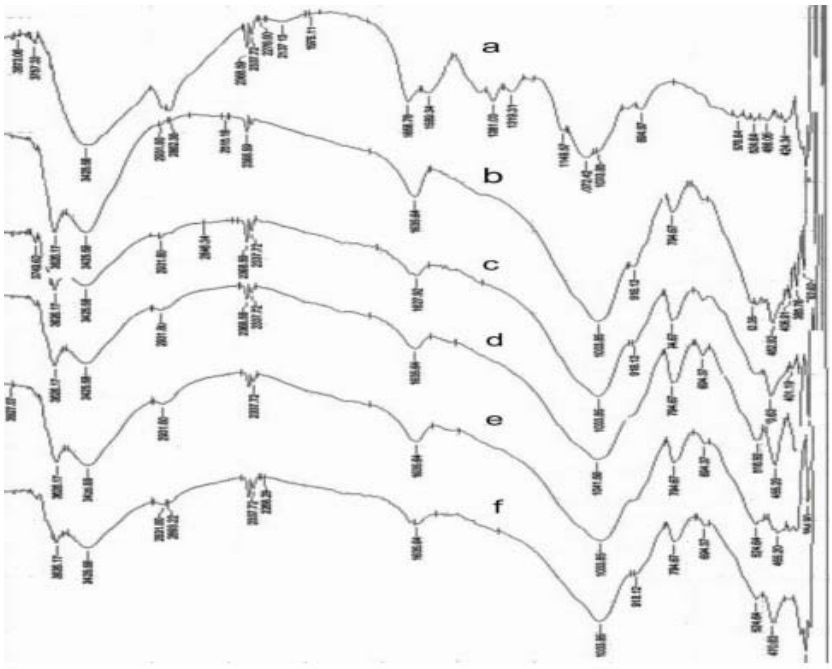
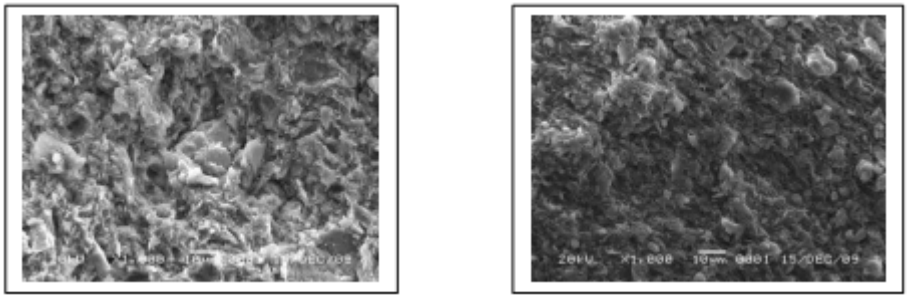


Fig. 6: FTIR spectra of MMT Intercalated chitosan: a). MMW chitosan; b). Na MMT; c). Chitosan-Na MMT 0.603:1.500; d). Chitosan-Na MMT 1.206:1.500; e). Chitosan-Na MMT 2.415:1.500; f). Chitosan-Na MMT 4.830:1.500



a b

Fig. 7: a). SEM photograph of MMT b). SEM photograph of chitosan-Na MMT with a magnification of 1000x.

Characterization of surface morphology with SEM shown different surface structure between MMT and composite of chitosan-Na MMT. The analysis result shown that chitosan formation inside interlayer surface or MMT surface result in changes of morphology with silica layers stacked with one another (intercalated composite) and silica layer which were layered by MMT. This SEM analysis result matched the XRD analysis result that produced increase in basal spacing value which was relatively small. This small increase indicated that most of chitosan were on MMT surface.

Evaluation properties of granules

The aim of this evaluation was to find out whether the used granules met the requirements based on the reference. The results of granules physical properties were demonstrated in table 2.

Good flow time for granules is less than 10 seconds for 100 grams of granules [29]. Angle of repose is a series examination of granules flow time, granules have a good fluidity at the angle of repose of 25^0-45^0 and the smaller value of angle of repose shows a better characteristic [30]. A good granules have carr's index value for less than 20% [31]. Based on the data from the table, everything met the requirements based on the reference. It indicated that the granules in this study were feasible and relatively fine. The results were analyzed statistically by using ANOVA with level confidence interval of 95% showed sig value > 0.05 for all evaluations of physical properties of granule, which means there was no significant difference between formula compositions against physical properties of granule.

Evaluation properties of tablet

This evaluation aims to find out the quality of tablets produced, whether it meets the standard that has been set or not. The results of the tablets physical properties evaluation were demonstrated in table 3.

Table 2: Granules physical properties

Formula	FI	FII	FIII	FIV
Flow time (second)	10.749 ± 1.654	9.887 ± 0.532	7.048 ± 1.373	9.342 ± 2.631
Angle of repose (^{0})	29.750 ± 1.081	28.026 ± 1.159	28.778 ± 2.400	28.831 ± 2.137
Carr's index (%)	12.031 ± 3.517	13.411 ± 6.221	11.469 ± 2.937	11.469 ± 2.856

Table 3: Physical properties and release rate of tablets

Test	FI	FII	FIII	FIV
Weight variation (mg)	478.7 ± 2.003 (CV=0.325)	495.65 ± 2.834 (CV=0.386)	494.05 ± 3.41 (CV=0.424)	489.60 ± 3.648 (CV=0.745)
Hardness (N)	66.98 ± 0.495	66.29 ± 1.841	72.54 ± 0.673	66.78±2.100
Friability (%)	2.620 ± 2.674	0.733 ± 0.348	0.875 ± 0.145	1.159 ± 0.359
DE_{360} (%)	59.995	31.573	43.971	48.779

The requirement of weight variation for non-coating tablets with average tablet weight more than 300 mg was weighted one by one, it cannot be more than 2 tablets stray more than 5% and not even one tablet stray more than 10% from the average weight [32]. The calculation results of tablets weight variation on four of the formulas showed that there were no tablet strayed for more than 5% and not even one tablet strayed more than 10% from the average weight. Friability stated in percent which referring to the initial tablet mass before evaluation. Good tablet has friability value not more than 0.5-1% [31]. Friability data on FI and FIV did not meet the requirements. So FI (without matrix) was relatively more friable compared to other formulas. In this study, tablet hardness from four of the formulas was maintained between 60-70 N. The results of the statistical analysis with one way ANOVA showed that there was no significant difference between one formula and another, with significant value >0.05, so the physical properties of the tablets was the same. Statistical test results for four of the formulas were not significantly different, because formulation of tablet hardness was maintained the same, so that dissolution parameters were not affected by tablet hardness.

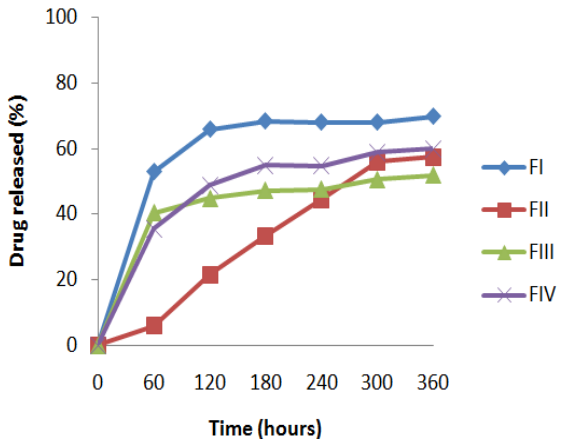


Fig. 8: Dissolution profile of theophylline tablet

***In Vitro* Drug Release**

Dissolution test aims to find out profile of theophylline release from tablet *In Vitro* way. This test was conducted using dissolution apparatus XXIII USP model with phosphate buffer pH 7.2 medium maintained at body temperature 37^0± 0.5° for 6 hours. Before testing, maximum wavelength was measured for theophylline solution and standard curve measurement. Scanning results obtained maximum wavelength of 272 nm. Standard curve linear regression equation obtained from plot between theophylline levels and absorbance was y = 0.0615 x + 0.0159, R^2 = 0.999. This equation could be used to set the levels of typical compounds from a sample in the same medium.

Dissolution results of theophylline sustained release tablet made in the curve, between theophylline levels released (%) and time presented in figure 8.

Release of theophylline active substances could be seen in four of the dissolution profiles shown in figure 8. FI was a conventional preparation so active substances released quickly, FII that contains HPMC matrix released gradually and active substances released slowly, while FIII and FIV which contains MMT matrix and intercalated Na-MMT by MMW chitosan slowly released with its profile between without MMT formula (FI) and HPMC matrix properties. The ability of poloxamer 188 modified MMT clay to prolong the release of the drug as compared to that of the pristine drug without MMT [33]. HPMC has a high viscosity so the formed gel layer was relatively difficult to be further eroded by solvent. It caused matrix difficult to experience erosion, so theophylline diffusion to exit from matrix occurred slowly. FIII that contains MMT matrix gave a good drug release profile, slowly and between profile range of FI and FII. The matrix would swell and formed gel layers around the properties with specific viscosity on contact with solvent medium and the drug would be diffused through pores between matrixes. FII as a comparison was releasing drug dose slowly at the initial therapy, it was concerned that therapeutic effect was not soon achieved. FIII was faster on releasing drug at first, and then followed by constant slow release. While the FIV contained intercalated Na-MMT by MMW chitosan with hydrophilic properties on contact with water, the matrix would swell then bind theophylline and made the drug release longer.

It was supported by MMT characteristics which potentially become the carrier material of a sustained release properties. MMT had pores or basal spacing which able to insert theophylline inside, so MMT could release theophylline in sustained release and could be controlled. It was reported that MMT is a mineral group that's able to be intercalated by other compound to form a new nanocomposite material, with method of cation exchange so d-spacing would became larger and more active substances could enter into matrix [34].

Based on Dissolution Efficiency (DE) value for every formula was shown in table 3 including FI 59.995; FII 31.573; FIII 43.971, and FIV 48.779. DE Statistic test results using Kolmogorov-Smirnov showed that the obtained data normally distributed with p>0.05, then continued to one way ANOVA test that showed a significant difference between added matrix to tablet dissolution with signification value <0.05, test was continued to t-LSD test which obtained a significant difference between FI and FII, FIII and FIV. But there was no significant difference between FII and FIII nor FIV. So, statistically between FII, FIII and FIV there were no significant difference of matrix type variation.

CONFLICT OF INTERESTS

Declared none

CONCLUSION

Characteristics of the MMT, Na-MMT, Na-MMT intercalated MMW chitosan did not change much. Sustained release tablet of theophylline with intercalated Na-montmorillonite matrix by MMW chitosan, was faster in drug release than with natural montmorillonite matrix, although statistically not significant and exhibited a prolonged release as compared to the pure drug without MMT.

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