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Original Article

FORMULATION OF DICLOFENAC SODIUM SUSTAINED RELEASE TABLET USING COPROCESSED EXCIPIENTS OF CROSSLINKED AMYLOSE–XANTHAN GUM AS MATRIX

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ABSTRACT

Objective: This present study was intended to design sustained release tablet containing diclofenac sodium using a matrix of excipient co-processed xanthan gum-crosslinked amylose.

Methods: In the previous study, xanthan gum and amylose have been physically and chemically modified by the co-processed and crosslinking method, resulting co-processed excipient xanthan gum-crosslinked amylose are Co-CLA6-XG and Co-CLA12-XG (method A); CL6-Co-A-XG and CL12-Co-A-XG (method B) with each ratio 1:1, 1:2 and 2:1. All excipients had a good swelling index, high viscosity and good gel strength, good characteristics to be used as a matrix for sustained release tablet dosage form. In this study, a tablet with excipient Co-CLA6-XG, Co-CLA12-XG, CL6-Co-A-XG and CL12-Co-A-XG were formulated by direct compression method. The prepared formulations were evaluated for weight variation, thickness, and diameter, hardness, friability, drug content estimation, swelling index, *in vitro* drug release are within the acceptable standard.

Results: The release profile of diclofenac sodium which contained matrix from Co-CLA6-XG (F1–F3), Co-CLA12-XG (F4–F6), CL6-Co-A-XG (F7–F9) and CL12-Co-A-XG (F10–F12) in phospate buffer medium for 8 h, showed that the sustained release profile followed zero order kinetics (F1–F6, F9, F11) and Korsmeyer-Peppas (F7, F8, F10, F12). Formula F1 to F6 tablet formulations could be applied as sustained release tablet formula and could retard drug release up to 16 h. Then, formula F7 to F12 could be applied as sustained release tablet formula and could retard drug release up to 32 h.

Conclusion: It may be concluded that coprocessed excipients of crosslinked amylose–xanthan gum can be used for the preparation of sustained release tablets of diclofenac sodium and can retard the drug release for 16 h and 32 h.

Keywords: Excipient coprocessed xanthan gum-crosslinked amylose, Matrix, Diclofenac sodium, Sustained release tablet

INTRODUCTION

In recent years, designing of drug products with modified release has been done to reduce the frequency of drug administration in order to improve patient compliance, reduce fluctuations of drug levels in the blood and minimize the side effects of drugs [1, 2]. The use of natural polymers for pharmaceutical applications is more attractive because of economical, biocompatible, non-toxic, easy to chemically modified and potentially biodegradable. Natural polysaccharides such as pectin, chitosan, starch (amylose and amylopectin), guar gum, xanthan gum and gum karaya commonly used in controlled release dosage forms [3]. Nevertheless, based on high-amylose starch and xanthan gum chemical structure [4] has many hydroxyl groups (-OH) so that the swelling index become fast which caused the rapid release of the drug. Therefore, some modification (physical, chemical and enzymatically) are required to improve the characteristic of starch [5, 6]. Based on the previous study, co-processed method (physical modification) and crosslinking method (chemical modification) had a good swelling index, high viscosity, and good gel strength [7–10].

Diclofenac sodium was used as a model drug for patients who have osteoarthritis. The main side effects of this drug are nausea, gastritis, skin erythema and headache. In addition, this drug has a short half-life (1-2 h) and oral drug bioavailability approximately 50% due to the first-pass metabolism by the liver [11]. It was the basic aim to be made into sustained release dosage form that can be sustained levels of drug therapy, minimize the frequency of drug administration and overcome its side effect.

MATERIALS AND METHODS

Materials

Diclofenac sodium (Yung Zip Chemical, Taiwan), excipient coprocessed xanthan gum-crosslinked amylose (Universitas Indonesia, Indonesia), Avicel pH 102 (Merck, Germany), aqua dest (Brataco, Indonesia).

Methods

Preparations of sustained release matrix tablet of diclofenac sodium

Formulation of sustained release tablet of diclofenac sodium was described in table 1. All of these sustained release tablets were prepared by direct compression method. Diclofenac sodium, excipient co-processed xanthan gum-crosslinked amylose (Co-CLA6-XG, Co-CLA12-XG, CL6-Co-A-XG and CL12-Co-A-XG) each ratio 1:1, 1:2 and 2:1 and Avicel pH 102 mixed well for 15 min in a mortar and pestle until homogenous. Then compressed into tablets using a rotary tablet machine (Korsch, Germany). Furthermore, all tablet formulations were evaluated.

Weight variation

Twenty tablets from each batch were weighed using an electronic balance (Adam AFA–210 LC, USA) together and individually. If weighed individually, no more than 2 tablets, which weight deviate from the average weight more than a set price column A, and none of the weight deviates from the average weight was more than the price set column B (table 2) [12].

Thickness and diameter

Randomly drawn 20 tablets individually, diameter and thickness was measured using calipers.

Terms: Unless otherwise stated, the diameter no more than 3 times and not less than 1 ⅓ thick tablet [12].

Tablet hardness

This measurement was used to know tablet's resistance under the condition of storage, transportations and handling before usage. The hardness of twenty tablets from each batch was checked using hardness tester. The hardness was measured in terms of kP.

Table 1: Formulation of diclofenac sodium sustained release tablet

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Diclofenac sodium	75	75	75	75	75	75	75	75	75	75	75	75	75
Co-CLA6-XG (1:1)	300	-	-	-	-	-	-	-	-	-	-	-	-
Co-CLA6-XG (1:2)	-	300	-	-	-	-	-	-	-	-	-	-	-
Co-CLA6-XG (2:1)	-	-	300	-	-	-	-	-	-	-	-	-	-
Co-CLA12-XG (1:1)	-	-	-	300	-	-	-	-	-	-	-	-	-
Co-CLA12-XG (1:2)	-	-	-	-	300	-	-	-	-	-	-	-	-
Co-CLA12-XG (2:1)	-	-	-	-	-	300	-	-	-	-	-	-	-
CL6-Co-A-XG (1:1)	-	-	-	-	-	-	300	-	-	-	-	-	-
CL6-Co-A-XG (1:2)	-	-	-	-	-	-	-	300	-	-	-	-	-
CL6-Co-A-XG (2:1)	-	-	-	-	-	-	-	-	300	-	-	-	-
CL12-Co-A-XG (1:1)	-	-	-	-	-	-	-	-	-	300	-	-	-
CL12-Co-A-XG (1:2)	-	-	-	-	-	-	-	-	-	-	300	-	-
CL12-Co-A-XG (2:1)	-	-	-	-	-	-	-	-	-	-	-	300	-
Avicel pH 102	125	125	125	125	125	125	125	125	125	125	125	125	425
Total (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500

Co-CLA-XG: excipient co-processed amylose crosslinked-xanthan gum (method A), CL-Co-A-XG: excipient co-processed xanthan gum-amylose crosslinked (method B), Each batch contains 80 tablets.

Table 2: Weight uniformity limits

Average weight	Average weight Uniformity (%)	
	A	B
25 mg or less	15	30
26 mg–150 mg	10	20
150 mg–300 mg	7,5	15
More than 300 mg	5	10

Friability

Twenty tablets were weighed and the initial weight of these tablets was recorded and placed in friabilator tester and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{Friability (\%)} = \frac{W1-W2}{W1}\ x\ 100\% \quad \text{(Eq. 1)}$$

where:

W1= weight of the tablet before test

W2= weight of the tablet after test

Determination swelling index tablet

The extent of swelling was measured in terms of percent weight gain by the tablet. One tablet from each formulation was kept in a petri dish containing 20 ml of phosphate buffer pH 7.4. Swelling index was measured by measuring the increase of weight of the tablet for 8 h. Measured the weight of the tablet in time intervals (5, 15, 30, 60, 90, 120, 180, 240, 360, and 480).

Assay

Drug content of the sustained release tablet was calculated using UV-Vis Spectrophotometer. Weighing tablet powder equivalent to 50 mg of diclofenac sodium. Subsequently incorporated into 100.0 ml of volumetric flask and dissolved with 0.1 N NaOH. Then filtered and discarded the first 10 ml of filtrate. The filtrate pipetted 2.0 ml and then added to the 100.0 ml volumetric flask with 0.1 N NaOH. Measured the wavelength of maximum absorbance (λ 276 nm) [13]. The tablet was eligible if it contained diclofenac sodium from 95.0 to 105.0% of that stated on the label.

***In vitro* drug release study**

In vitro drug release study was performed using dissolution test apparatus.

Dissolution test apparatus

Medium: pH 7.4 phosphate buffer solution

RPM: 50

Time: 8 h

Temp: 37 °C±5 °C

Volume: 900 ml

Wavelength: 276 nm

Procedure: Tablet was introduced into test dissolution apparatus and the apparatus was set at 50 rpm. A sample of 10 ml was withdrawn at a predetermined time interval (5, 15, 30, 60, 90, 120, 180, 240, 360, and 600) and replace with fresh medium phosphate buffer pH 7.4. Samples were analyzed by UV Spectrophotometer (Shimadzu, Japan) at λ 276 nm [14].

Release Kinetics: Data obtained from *in vitro* release studied was evaluated using the model of release drug kinetics with different equations relating to the cumulative amount of drug dissolved (Q) against time. The equations use were zero-order kinetics, first-order kinetics, Higuchi and Korsmeyer-Peppas as shown in table 3 below [2,15]. The goodness of it was evaluated using the correlation coefficient values (R^2).

RESULTS AND DISCUSSION

Excipients Co-CLA-XG and CL-Co-A-XG have been employed to formulate sustained release tablets of diclofenac sodium in different batch (13 batch). The sustained release tablets were formulated by direct compression method based on the formula given in table 1. The direct compression method had been chosen because it available for any excipient and had a limited number of processing. This formulation used Avicel pH 102 as other excipients which have functioned as diluent, binder and lubricant.

The prepared tablets were subjected to all the quality control tests that they were within the official pharmacopoeial limits. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit. The thickness of the tablets was 1.22 mm and diameter of the tablets were range from 0.33–0.41 mm. Friability is less than 1%, indicated that tablets had a good mechanical resistance. The evaluation parameters were within acceptable range for all the formulations. The drug content of the tablets ranged from 97 % to 99%. The results of hardness, friability, weight variation, thickness & diameter and drug content were given in table 4.

Table 3: Drug release kinetics

Model	Equations
Zero-order	$Q_t/Q_0 = K_0 . T$
First-order	$L_n Q_t/Q_0 = K_1 . T$
Higuchi	$Q_t/Q_0 = K_H . t^{1/2}$
Korsmeyer–Peppas	$Q_t/Q_0 = k . t^n$

Qt/Q_0 = fraction of drug at t time, K0,K1,Kh and k= constant drug release for each equation, n = diffusion's Peppas exponent

Table 4: Evaluations of diclofenac sodium sustained release tablets*

Formula	% weight variation	Diameter (cm)	Thickness (cm)	Hardness (Kp)	Friability (%)	Drug content (%)
1	0.11 ± 0.06	1.22 ± 0.00	0.33 ± 0.01	19,.3 ± 0.31	0.68 ± 0.12	98.43 ± 1.39
2	0.14 ± 0.09	1.22 ± 0.00	0.34 ± 0.01	19.09 ± 0.23	0.70 ± 0.08	98.69 ± 1.72
3	0.13 ± 0.08	1.22 ± 0.00	0.33 ± 0.00	19.03 ± 0.24	0.62 ± 0.21	97.26 ± 1.78
4	0.12 ± 0.06	1.22 ± 0.00	0.34 ± 0.01	19.09 ± 0.26	0.70 ± 0.10	97.99 ± 0.89
5	0.11 ± 0.08	1.22 ± 0.00	0.33 ± 0.00	19.05 ± 0.21	0.68 ± 0.13	98.82 ± 1.61
6	0.13 ± 0.08	1.22 ± 0.00	0.34 ± 0.01	19.09 ± 0.25	0.64 ± 0.04	98.01 ± 1.63
7	0.12 ± 0.09	1.22 ± 0.00	0.33 ± 0.00	15.15 ± 0.31	0.78 ± 0.18	99.37 ± 1.23
8	0.13 ± 0.08	1.22 ± 0.00	0.34 ± 0.01	15.17 ± 0.28	0.82 ± 0.16	98.60 ± 1.54
9	0.12 ± 0.11	1.22 ± 0.00	0.34 ± 0.01	15.13 ± 0.26	0.86 ± 0.05	98.96 ± 1.40
10	0.13 ± 0.10	1.22 ± 0.00	0.33 ± 0.01	15.16 ± 0.26	0.84 ± 0.11	98.27 ± 1.76
11	0.11 ± 0.09	1.22 ± 0.00	0.33 ± 0.00	15.16 ± 0.31	0.82 ± 0.17	97.12 ± 1.69
12	0.13 ± 0.08	1.22 ± 0.00	0.34 ± 0.01	15.14 ± 0.29	0.84 ± 0.13	98.67 ± 1.97
13	0.11 ± 0.09	1.22 ± 0.00	0.41 ± 0.01	25.07 ± 0.26	0.42 ± 0.16	98.15 ± 1.98

*All values are expressed as mean ± SD, n=3

The swelling study of prepared formula tablets (F1–F13) was performed in phosphate buffer pH 7.4 and the results as shown in (fig. 1). This condition was made to determine the correlation between the swelling index formula tablet (F1 to F13) with drug release from formula F1 to F13. The swelling profile tablet in fig. 1 it is shown that F1 to F12 were able to swelling for 8 h. Formula F13, which did not contain excipient matrix swelling for 120 min, then it was disintegrated. Formula F12 with matrix CL12-Co-A-XG 2:1 showed the slowest swelling profile. Tablets with the excipient matrix, when contact with water, the tablets was swelling, then around the tablet has formed a gel. The gel which regulated the rate of drug release from tablets. Thus, the swelling index tablet affects the drug release rate. The greater swelling index tablet, the faster release of the drug or vice versa. But the drug release rate was also affected by the gel form; the best gel strength would give a slow in drug release. Drug released with excipient high amylose starch crosslinked were released the drug about 50%, while conventional starch could release the drug about 80% for 8 h [7, 8].

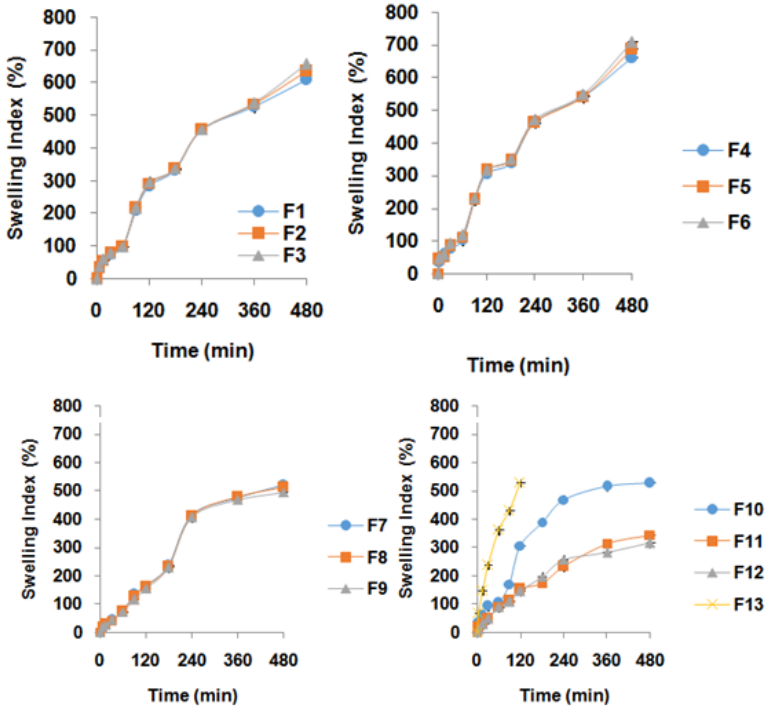

Fig. 1: Swelling index tablet with various concentrations of co-processed excipients matrix of crosslinked amylose-xanthan gum for 8 h (formula F1-F13). All values are expressed as mean±SD, n = 3

In vitro dissolution studies of all the formulations of sustained release tablets of diclofenac sodium were carried out in pH 7.4 phosphate buffers for 8 h respectively. Drug release profile of diclofenac sodium from the matrix as shown in (fig. 2).

Formula F1 to F6 was a formula using matrix Co-CLA6-XG with a ratio of 1:1, 1:2 and 2:1, and the matrix Co-CLA12-XG with a ratio of 1:1, 1:2 and 2:1. Formula F7 to F12 was a formula using matrix CL6-Co-A-XG with a ratio of 1:1, 1:2 and 2:1 and matrix CL12-Co-A-XG with a ratio of 1:1, 1:2 and 2:1. Formula F13 was a formulation that did not use a matrix comparison, only Avicel pH 102. All formulas that use matrix (F1 to F12) could released the drug for 8 h with a cumulative drug release was≤ 60%, while formula (F13) could release the drug for 2 h of almost 100%.

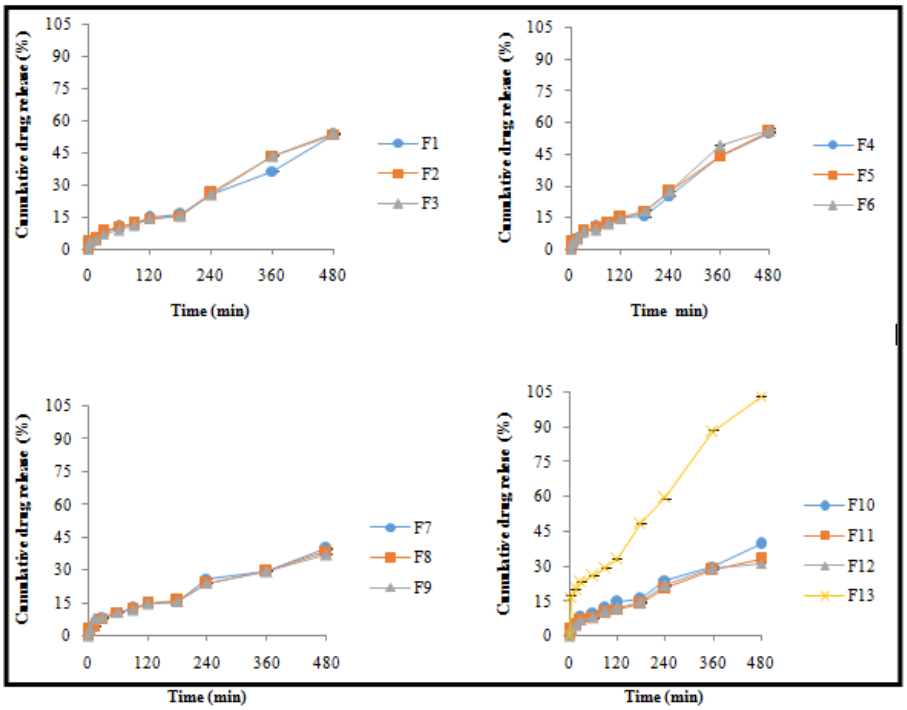

Fig. 2: *In vitro* release profile of diclofenac sodium with various concentrations of co-processed excipients matrix of crosslinked amylose-xanthan gum (formula F1-F13). All values are expressed as mean±SD, n = 3

Table 5: Kinetics release data of diclofenac sodium matrix tablets formula F1-F13

Formula	Parameter	Zero order			First order			Higuchi model			Korsmeyer-Peppas		
1	r	0.992	±	0.001	0.938	±	0.005	0.95	±	0.005	0.974	±	0.002
	n										0.593	±	0.02
2	r	0.989	±	0	0.937	±	0.004	0.946	±	0.002	0.969	±	0.001
	n										0.596	±	0.012
3	r	0.99	±	0.002	0.946	±	0.007	0.946	±	0.006	0.967	±	0.006
	n										0.606	±	0.012
4	r	0.988	±	0.001	0.941	±	0.002	0.942	±	0.002	0.967	±	0.006
	n										0.597	±	0.012
5	r	0.993	±	0.001	0.934	±	0.003	0.956	±	0.001	0.976	±	0.002
	n										0.599	±	0.002
6	r	0.987	±	0.001	0.943	±	0.004	0.948	±	0.002	0.968	±	0.002
	n										0.614	±	0.003
7	r	0.984	±	0.002	0.875	±	0.007	0.977	±	0.001	0.989	±	0.001
	n										0.569	±	0.014
8	r	0.991	±	0.001	0.881	±	0.004	0.981	±	0.002	0.993	±	0.001
	n										0.572	±	0.01
9	r	0.987	±	0.001	0.865	±	0.003	0.977	±	0.003	0.974	±	0.001
	n										0.516	±	0.011
10	r	0.991	±	0.002	0.884	±	0.011	0.979	±	0.002	0.992	±	0.001
	n										0.58	±	0.013
11	r	0.993	±	0	0.906	±	0.007	0.979	±	0.004	0.988	±	0.002
	n										0.554	±	0.014
12	r	0.983	±	0.003	0.898	±	0.008	0.981	±	0.002	0.988	±	0
	n										0.55	±	0.011
13	r	0.995	±	0	0.978	±	0.001	0.958	±	0	0.925	±	0.001
	n										0.398	±	0.007

n = exponent Peppas's difusion

Banakar's rules are used to explained amount of drug dissolved associated with the frequency of drug administration. If the dissolved drug percentage ranged 20-45%, the sustained release tablet could be used for 32 h, if the percentage of dissolved drug ranged 45-75%, it could be used for 16 h and the percentage of drug dissolved ranges over 75%, the sustained release preparations could used only for 8 h [16]. The results of the percentage of drug released for 8 h using Banakar's rules, the formulas F1 to F6 in the range of 45-75%. Formulas F7 to F12 in the range of 20-45%. So, formula F1 to F6 showed the controlled release of diclofenac sodium for 16 h and formula F7 to F12 used for 32 h. Drug released profile from all formulas was calculated and analyzed against several kinetics equation (zero order, first order, Higuchi, and Korsmeyer-Peppas) to determine the mechanism of drug release from the sustained release tablet dosage forms. The values of release parameters, n and r (coefficient correlation) are inversely related. The results of the calculation of diclofenac sodium release kinetics shown in table 5.

On Korsmeyer-Peppas equation, if n = 0.89, drug release mechanism was an erosion of the polymer matrix and the mechanism is named as Case II transport. If the value of n is in the range $0.45<n<0.89$, the release was diffusion-erosion matrix named as an anomalies or non-Fickian diffusion. However, if the value of $n<0.45$, the drug release occurs by diffusion and named as Fickian diffusion. If $n>0.89$, the drug release mechanism called super case II transport which the release occured by the swelling of the polymer. Drug release mechanism of formula F1 to F6, F9, F11 and F13 followed zero order kinetics. Then, formula F7, F8, F10 and F12 followed Korsmeyer-Peppas mechanism.

The drug release mechanism of formula F1 to F12 followed Korsmeyer-Peppas kinetics with n values are between 0.45 and 0.89. It means followed non-Fickian diffusion or anomalous, which describes the drug release mechanism was controlled by a combination of diffusion and erosion. Then, formula F13 has $n<0.45$ so that the drug release followed by Fickian diffusion.

CONCLUSION

Diclofenac sodium sustained release tablet could be prepared by direct compression method. The swelling index of matrix tablet containing Co-CLA6-XG (F1, F2 and F3) and Co-CLA12-XG (F4, F5 and F6) showed that slower swelling profile than matrix tablet of CL6-Co-A-XG (F7, F8 and F9) and CL12-Co-A-XG (F10, F11 and F12). Due to the swelling index, then the matrix tablets of formula F1-F6 could control the diclofenac sodium release effectively 16 h, while the matrix tables of formula F7-F12 significantly effective in sustaining the drug release for 32 h. The drug release mechanism was controlled by diffusion and erosion. It was concluded that excipients of Co-CLA-XG and CL-Co-A-XG could be used in the formulation of sustained release tablet.

CONFLICT OF INTERESTS

All authors have none to declare

REFERENCES

1. Krowcynsk L. Extended-release dosage forms. CRC Press, Inc; 1987.
2. Beringer P. Remington: The science and practice of pharmacy. 21st ed. Philadelphia Collage of Pharmacy and Science; 2005.
3. Ogaji IJ, Nep EI, Audu-Peter JD. Advances in natural polymers as pharmaceutical excipients: review article. Pharm Anal Acta 2011;3:1-16.
4. Cury BSF, Klein ST, Evangelista RC. Modeling a system of phosphate cross-linked high amylose for controlled drug release part 1: Synthesis and polymer characterization. React Funct Polym 2008;68:1200–6.
5. Cui SW, Xie SX, Liu Q. Starch modifications and applications in food carbohydrates: chemistry, physical properties, and applications. CRC Press: Taylor and Francis Group, LLC., Florida; 2005.
6. BeMiller J, Whistler R. Starch: chemistry and technology. 3rd ed. Academic Press: Elsevier Inc., New York; 2009. p. 629-57.
7. Carbinatto FM, Doris CA, Cury BSF, Magalhaes A, Evangelista RC. Physical properties of pectin–high amylose starch mixtures cross-linked with sodium tri metaphosphate. Int J Pharm 2012;423:281–8.
8. Onofre F, Wang YJ, Mauromoustakos A. Effects of structure and modification on sustained release properties of starches. Carbohydr Polym 2009;76:541-7.
9. Bejenariu A, Popa M, Dulong V, Picton L, Cerf DL. Trisodium tri metaphosphate crosslinked xanthan networks: synthesis, swelling, loading, and releasing behavior. Polym Bull 2009;62:525-38.
10. Nachaegari KS, Bansal AK. Coprocessed excipients for solid dosage form. Pharm Technol 2004;42:54-8.
11. Brunton L, Parker K, Blumenthal D, Buxton I. Goodman and Gilman's manual of pharmacology and therapeutics. Mc Graw Hill, New York; 2008.
12. Anonymous, Phamacopeia of Indonesia. 3rd ed. Ministry of Health Republic of Indonesia, Jakarta; 1979.
13. Pasaribu IS. Assay of diclofenac sodium in tablet dosage form using spectrophotometer ultaviolet essay of Bachelor's Degree. Faculty of Pharmacy University-Northern Sumatra, Medan; 2011.
14. The United States Pharmacopoeial Convention. United States Pharmacopoeia 32nd and National Formulary 27th. The USP Convention, Rockville; 2009.
15. Siepmann J, dan Peppas NA. Modelling of drug release from delivery systems based HPMC. Adv Drug Delivery Rev 2001;48:139-57.
16. Banakar UV. Pharmaceutical dissolution testing. Marcel Dekker Inc., New York; 1992.