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Research Article

PRAGELATINIZED CASSAVA STARCH PHTHALATE AS FILM-FORMING EXCIPIENT FOR TRANSDERMAL FILM OF KETOPROFEN

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ABSTRACT

This present study was intended to expand utilization of starch as transdermal film-forming excipient. In the previous study, starch have been physically and chemically modified through complete pregelatinization and phthalatization process in aqueous-alkaline medium (pH 8-10), resulting pragelatinized cassava starch phthalate (PCSPh). The obtained PCSPh possesed the degree of subtitution of 0.0541 ± 0.0019 and showed different physical, chemical, and functional properties compared to pragelatinized cassava starch (PCS). PCSPh showed higher gel strength value than PCS, a good characteristic to be used as film forming for transdermal dosage forms. In this study, transdermal film were produced using PCSPh as film-forming, glycerin and propylenglycol as plasticizer and ketoprofen as drug model. This transdermal film showed good mechanical properties, including folding endurance, elongation and tensile strength. The in-vitro drug release study showed that 71.78 – 107.07% of ketoprofen has been released from transdermal film in 4 hours by diffusion-controlled mechanism. In vitro penetration study using Franz diffusion cell showed that 72.77 – 108.04% of ketoprofen were able to penetrate the skin membran of Spague-Dawley rats with the flux of 1.499 – 2.311 mg/cm^2.hour in first three hours and 0.865 – 1.301 mg/cm^2.hour up to 8 hour. Therefore, it was concluded that PCSPh had good characteristics to be applied as film-forming excipient for transdermal dosage form.

Keywords: pragelatinized cassava starch phthalate, transdermal film, ketoprofen.

INTRODUCTION

Oral administration of drugs are preferred route of administration for the patients. Nevertheless, several disadvantages such as hepatic first pass metabolism, gastric irritation, and enzymatic degradation within the gastrointestinal tract have been identified in oral administration. Therefore, transdermal route has been suggested and developed as alternative route of administration for drugs to overcome disadvantages in oral administration [1].

Starch are polysaccharides which are widely used in pharmaceutical industry because of their biocompatibility and low toxicity. However, utilization of starch in pharmaceutical dosage forms are sometimes limited by its solubility (unsoluble in cold-water) and mechanical properties (low flexibility and tensile strength). Therefore some modification (physical, chemical and enzymatically) are required to improve characteristic of starch [2,3,4]. In the previous study, starch have been physically and chemically modified through complete pregelatinization and phthalatization process in aqueous-alkaline medium (pH 8-10), resulting pragelatinized cassava starch phthalate (PCSPh) [5,6]. The obtained PCSPh showed higher gel strength value than PCS, a good characteristic to be used as film forming for transdermal dosage forms.

Ketoprofen was used as drug model in this study due to its gastric-irritating side effect. Formulating ketoprofen in transdermal film dosage forms was intended to overcome its side effect and get immediate antiinflamation effect in pain location [7,8].

MATERIALS AND METHODS

Materials

Ketoprofen (handly-gifted from Sanofi Aventis, France), pragelatinized cassava starch phthalate (Universitas Indonesia, Indonesia), glycerin (Brataco, Indonesia), propylenglycol (Brataco, Indonesia), skin membrane of Sprague-Dawley rats, aquadest (Brataco, Indonesia).

Methods

Preparation of Ketoprofen Transdermal Film

Formulation of ketoprofen transdermal film is described in Table 1. All of these transdermal films were prepared by solvent casting method [9,10]. Dispersion of PCSPh in aquadest, solution of ketoprofen in NH_4OH, and plasticizer (propylenglycol and glycerin) were stirred homogenously. Fifteen mililiters of the mixture was poured into 7 x 7 cm^2 container and dried at 50^{o}C in an oven until a flexible film was formed. The dried film was carefully removed from container, cut into 1 x 1 cm^2 size and attached to the backing layer.

Table 1. Formulation of Ketoprofen Transdermal Film

FORMULA	F1	F2	F3
Ketoprofen (g)	5	5	5
PCSPh (g)	5	10	15
NH_4OH 21% (mL)	5	5	5
Glycerin (g)	2	4	6
PEG 400 (g)	0.5	1	1.5
Aquadest ad (mL)	150	150	150

Physical and Morphological Properties

Weight uniformity of film was measured using digital balance (Mettler Toledo AL204, USA). Film thickness was measured using a micrometer screw gauge (Din – 863/11, England) on five different locations. Morphology of transdermal films (upside, bottomside, and cross-section) were observed by using Scanning Electron Microscope (SEM).

Surface pH

The films were allowed to swell by placing it in 5 ml of distilled water for 2 hours at room temperature. The pH was measured by contacting the film surface with electrode of pH meter (Eutech pH 510, Singapore) and allowing it to equilibrate for 1 minute.

Moisture content

Moisture content of films were analyzed with moisture content analyzer (Adam AMB50, UK) at 105°C.

Assay

Drug content of the film was measured by dissolving 1x1 cm^2 of film in phosphate buffer solution (pH 7.4). The amount of ketoprofen was determined spectrophotometrically at λ 260 nm. Drug content measurement was performed triplicate [11].

Mechanical properties [9,10]

Folding endurance of the transdermal films were determined by repeatedly folding the film more than 300 times at the same place without breaking it. Tensile strength and elongation were analyzed using texture analyzer (TA.XT2 Rheoner 3305, Germany) and XTRA Dimension software. Films were placed between two nippers and were pulled at speed 100mm/min. The force needed to break the film was determined by measuring total weight loaded on the string. The weight required to break the film has been reported as the tensile strength. Elongation percentage was calculated by the following equation:

$$\textbf{Tensile strength} = \frac{\textbf{force when films fractured (N)}}{\textbf{area of film (mm}^2\textbf{)}}$$

$$\textbf{\% Elongation} = \frac{\textbf{final long} - \textbf{initial long}}{\textbf{initial long}} \textbf{ x 100\%}$$

In Vitro Drug Release Study

In vitro drug release study was performed using modified dissolution apparatus (beaker glass and magnetic stirrer) at rotation speed of 50 rpm. One centimetersquare of film which has been attached to a backing layer were attached to a glass object, and then placed in a beaker glass containing 250 mL phosphate buffer pH 7.4 at 37 ± 0.5°C. Samples of 5 ml were withdrawn at pre-determined time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180 and 240) and replaced with fresh medium phosphate buffer pH 7.4. Samples were analyzed, after appropriate dilution, using UV spectrophotometer (Shimadzu, Japan) at λ 260 nm [9,10,12].

In Vitro Mucoadhesion Study

The mucoadhesion strength was determined using texture analyzer. Abdominal skin membrane of Sprague-Dawley female rats aged 8-10 weeks with weight of ± 200 grams were used in this study. All experiments which involving animal (rat) were conducted based on local ethic requirement.

A piece of film (1x1 cm^2) were attached on the skin membrane and were soaked with distilled water and remained to contact for 50 seconds. The film attached skin membrane was put on texture analyzer plate and and the probe was managed to give force 150 gF with speed 0.5 mm/sec. The probe was then lift with speed 1 mm/s. The force and time required to remove the film from the rat skin membrane was recorded [9,10,12].

In Vitro Penetration Study

In vitro penetration study was performed using Franz diffusion cells. Receptor compartment was filled with phosphate buffer pH 7.4, the temperature was maintained around 37 ± 0.5 ° C and stirred with a magnetic stirrer at 300 rpm.

Abdominal skin membrane of Sprague-Dawley female rats aged 8-10 weeks with weight ± 200 grams were used in this study. Skin membrane of rats were placed in between donor and receptor compartment. Ketoprofen transdermal films (without backing layer) was placed on the skin at donor compartment of Franz diffusion cells.

Samples of 0.5 ml were withdrawn from receptor compartment at pre-determined time intervals (15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480) and replaced with fresh medium phosphate buffer pH 7.4. Samples were analyzed, after appropriate dilution, using UV spectrophotometer (Shimadzu, Japan) at λ 260 nm [9, 10,12].

Flux of penetration were calculated refered to Ficks Law I:

$$\mathbf{J} = \frac{\mathbf{W_t}}{\mathbf{A \times t}}$$

J = Flux (mg cm^{-2} $hour^{-1}$)

Wt = Cumulative amount of penetrated ketoprofen (mg)

A = Diffusion area (cm^2)

t = Time (hour)

RESULTS AND DISCUSSION

Physical Appearance and Properties

Transdermal films were prepared using ketoprofen as a model drug and a PCSPh as film-forming polymer. Glycerin-PEG 400 (4:1) were used as plasticizer in formula, 50% of the weight of PCSPh. This was the optimal combination which obtained from preliminary trials. The obtained film was a yellowish-transparant film. Addition of plasticizer into formula contribute in flexibility and good physical characteristics of the film. Utilization of PEG 400 as single plasticizer produced brittle films [13]. When PEG 400 were used in combination with glycerin, the obtained film possessed elastic characteristic, good mechanical properties (folding endurance up to 300 times of folding without breaking) and good adhesivity to skin membrane.

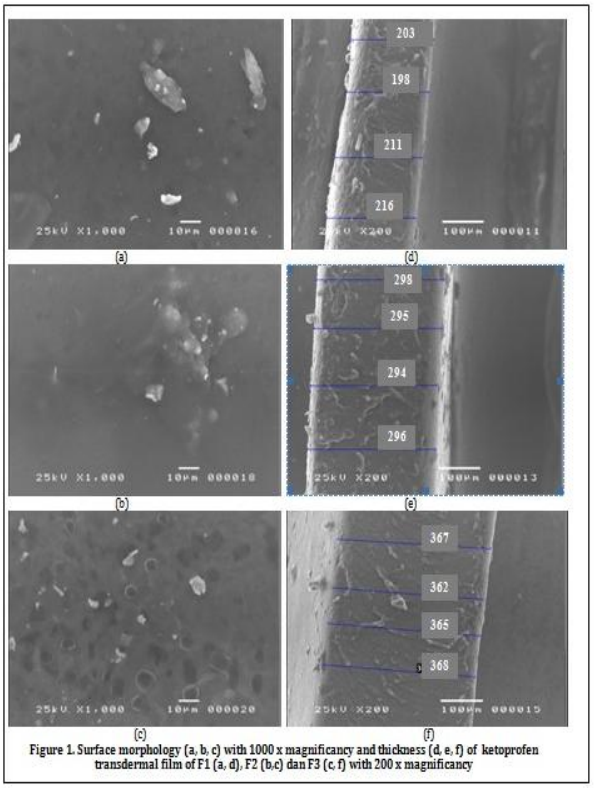

Figure 1. Surface morphology (a, b, c) with 1000 x magnificancy and thickness (d, e, f) of ketoprofen transdermal film of F1 (a, d), F2 (b,c) dan F3 (c, f) with 200 x magnificancy

Physical and functional characteristics of the film are described in Table 2. The results show that the weight and thickness of the film increased as concentration of PCSPh increase. The crosssectional SEM micrographs of the films shows that film thickness increase as concentrations of PCSPh increase. On the other hand, the watercontent decreased by increasing of PCSPh amount in films

formula. It was influenced by less water content in formula with increasing concentrations of PCSPh.

Surface morphology and film thickness were measured using SEM. Figure 1 (a, b, c) shows that formula F1 has smoother surface than F2 and F3. This phenomena due to uncomplete-dissolve ketoprofen in F2 and F3 film. The more concentration of PCSPh in a film caused less of ketoprofen dissolved. Ketoprofen was only dispersed in film, not dissolved in. The crosssectional SEM micrographs of the films (Figure 2 d, e, f) showed that the film thickness is homogeneous at all parts of the film.

Measurements of the surface pH of the film shows that there was no significant difference between the all film formulas. All films possessed a pH of approximately 6, compatible to pH of human skin (pH 4.5 to 6.5), thus it did not irritate the skin. The results also show that there was no significant difference between surface pH of the PCSPh film and pH of native PCSPh altough NH_4OH was added into formula to dissolve ketoprofen. This result proves that NH_4OH was decomposed into NH_3 and was evaporated when the films were dried at 50°C. It indicates that there were no NH_4OH residue within the obtained film.

All films from three formulas (F1, F2 and F3) possessed good mechanical properties which indicated by its endurance after 300 times folding. The results reveal that increasing PCSPh concentration in formula resulted the high value of tensile strength and elongation percentage, which indicated the good elasticity properties and film ability to be streched. There were no significant difference of mucoadhesion strength from all of three formulas. Increasing of PCSPh concentration in formula give no effect on mucoadhesion property of film.

Tabel 2:Evaluation of ketoprofen transdermal film

PARAMETER	F1	F2	F3
Weight (mg)	31.00 ± 2.40	41.30 ± 3.60	51.50 ± 4.01
Thickness (µm)	178.80 ± 2.40	272.00 ± 2.83	352.80 ± 4.83
Assay (mg/film)	12.14 ± 0.76	11.77 ± 0.74	11.46 ± 0.30
Moisture Content (%)	32.19 ± 3.64	23.95 ± 3.60	9.98 ± 1.46
Surface pH	6.05 ± 0.14	5.97 ± 0.09	5.90 ± 0.17
Tensile Strength (N/mm^2)	0.261± 0.0	0.392 ± 0.046	0.621 ± 0.092
Elongation (%)	109.83 ± 0.71	155.17 ± 33.71	200.65 ± 3.77
Mucoadhesivity (gF)	6.10 ± 0.46	6.60 ± 0.53	6.47 ± 0.98
Folding Endurance	Not break after 300 times folding	Not break after 300 times folding	Not break after 300 times folding
Penetration Flux (mg/cm^2.hour)			
Hour 0 – 3	2.291 ± 0.197	2.311 ± 0,227	1.499 ± 0.013
Hour 3 – 8	1.301 ± 0.175	0.913 ± 0,069	0.865 ± 0.068

In Vitro Drug Release

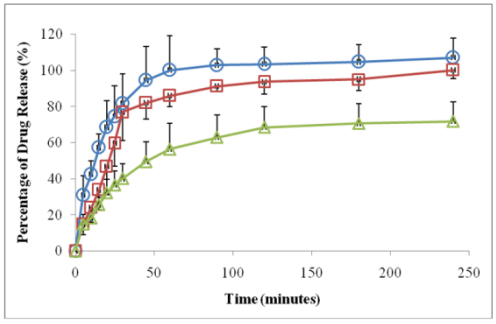

Figure 2: Drug release profile of ketoprofen from transdermal film of F1 (○), F2 (□), dan F3 (△) in phosphate buffer medium pH 7,4

Release profile of ketoprofen transdermal preparations films were evaluated using a modified dissolution test equipment. Figure 2 shows the release profiles of ketoprofen from transdermal films. It shows that the release of ketoprofen from formula F1 is faster than formula F2 and F3. The higher concentrations of PCSPh in formula, the slower rate of drug release the film. In the first hour, 100% ketoprofen was dissolved from film F1, though 84% and 52% from film F2 and F3, respectively. Furthermore, ketoprofen released from film F2 and F3 were 100% and 72%, respectively, during 4 hours. The phenomena was caused by the thickness of matrix.

Drug release profile from all formulas were calculated and analyzed against several kinetics equation (zero order, first order, Higuchi and Korsmeyer-Peppas) to determine the mechanism of drug release from the film dosage forms [14]. Analysis of the release kinetics mechanism of ketoprofen from transdermal films were performed on drug release profile for 4 hours. However, the analysis can not be performed for 4 hours on formula F1 since all the drug contained had been dissolved in 1 hour. Therefore, the analysis of drug release in formula F1 was performed only on release profile up to 1 hour.

Calculation on kinetics equation show that the release profile of all formulas fit into Korsmeyer-Peppas equation with n value ± 0.5, indicating that the release of ketoprofen from film were controlled by diffusion mechanism. Dissolution medium were absorbed into the film and dissolving-out ketoprofen which were homogeneously dispersed in film without causing erosion of film-forming polymer. Release rate constant of film formula F1, F2 and F3 were 0.1476, 0.1003 and 0.0806, respectively. Peppas exponent value of F1, F2 and F3 were 0.5133, 0.4979 and 0.4453, respectively. Peppas exponent value of all formulas which is close to 0.5 indicated that the release profile follow Higuchi kinetics ($Qt/Qo = k_h\ t^{½}$). Higuchi equation is applied to describe the drug release from a matrix system in diffusion controlled mechanism, that the drug release rate constant to squareroot of time and slower over the time [14]. This is caused by the diffusion distance between the position of the drug in the matrix from the surface of the dissolution medium so it takes longer time for the drug to be dissolved.

The k value (release rate constant) of film decreases as the concentration of polymer increase. The smaller the k value indicates the slower release of the drug from the film. The concentration of polymer in the film increased so the ability of the film to retain the drug release increased, thus the drug release rate decreased.

In Vitro Penetration Study

In vitro penetration study was performed on all film formulas to describe the penetration of drugs into the skin. Skin is a barrier that often becomes an obstacle for many substances to penetrate through it [15]. However, Figure 3 shows that there were more than 70% of the drug from all film formulas had successfully penetrated through the skin membrane. The high penetration rate might be caused by high levels of drug in the films (30-50%), resulting in high concentration gradient between the drug levels in the film with the drug levels in the receptor compartment. This gradient concentration act as driving force for the penetration of ketoprofen

through the skin membrane. Additionally, using of high concentration of plasticizers also gave high penetration rate. In the film formulas were used glycerin and propylenglycol as plasticizers, which had function to improve the film elasticity and also enhance penetration.

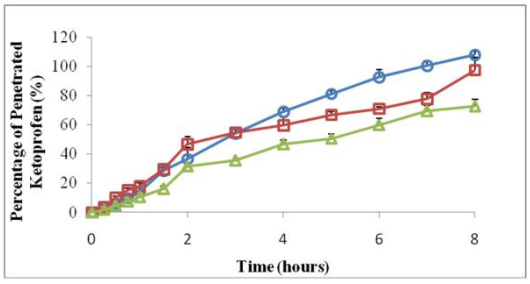

Figure 3:Penetration profile of ketoprofen from transdermal film F1(○), F2 (□), dan F3 (△) through skin membrane of Sprague-Dawley female rats

Average flux of each formula was calculated by plotting the amount of ketoprofen that penetrated per unit area versus time. The average flux value of each formula is obtained from the slope of the linear curve which was calculated in 2 phase (hour 0 – 3 and hour 3 - 8). Intercept values were positive on all formula films indicates that there were no lag time required by ketoprofen to diffuse through the membrane. Positive intercept value also indicates burst release phenomena, there are very fast release of the drug at the initial time. Burst release can be caused by several factors such as the ratio of the concentration of the drug and polymer [16]. In all three films transdermal formula, the drug concentration ranged from 30-100% film-forming polymer. These high concentration of the drug causes the polymer is not strong enough to fight the driving force due to the concentration gradient between the film and the membrane so that a large number of drugs can be quickly penetrated at the initial time.

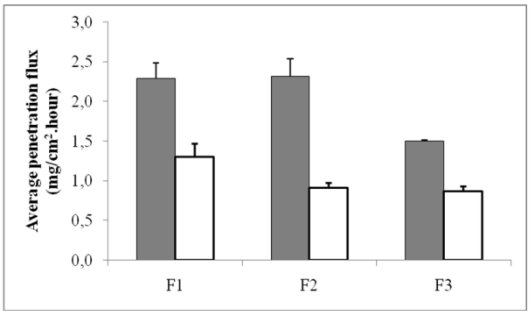

Figure 4: Average penetration flux of ketoprofen from transdermal film at hour 0-3 (■) and hour 3-8 (□)

Swelling index of the film-forming polymer (PCSPh) were other factor that caused the burst release. In previous study, swelling index of PCSPh had been evaluated. The characterization result showed that PCSPh swelled rapidly in the first ten minutes. As the film was attached to the skin membrane, it immediately absorbed water from the hydrated-membrane skin, swelled fast and allowed the medium to diffuse into the film easier, dissolved ketoprofen and take it out of the film and penetrated it through the skin [16].

Burst release effect is unwanted phenomenon effect. In this study, this burst release phenomena could be considered as beneficial so the ketoprofen could penetrate the skin rapidly and give antiinflammatory effects in pain location immediately [1].

Eventhough the steady-state condition was reached after third hour, but the flux penetration of ketoprofen within the first three hours could not be ignored because of a burst release phenomena which penetrated drug up to 30-60%. Figure 4 shows that at the first three hours, film F1 and F2 show the same flux. However, increasing in some controlled dosage forms, but for some dosage forms burst release phenomena is beneficial to rapidly achieve the minimum effective concentration (MEC) and get immediate pharmacological

polymer concentration (PCSPh) resulted penetration flux of drug from F3 decreased. After 3 hours, the film formula F1 showed the greatest flux penetration. The higher PCSPh concentration in the formula, the slower flux penetration of ketoprofen from the film. This is because the film forming polymer matrix (PCSPh) retained the release of the drug from the dosage. This penetration flux result show correlation to in vitro drug release result. The thicker the film, the more difficult for ketoprofen to diffuse out of the film and penetrate through the skin membrane.

Based on the above evaluations, it was concluded that transdermal films F1 formula is the best formula as drug carriers for transdermal film dosage forms which drug can immediately penetrate through the skin thus results anti-inflammatory therapeutic effect. Remarkably, the formula F3 which drug slowly penetrate through the skin, showed that PCSPh can also be utilized as film-forming for transdermal sustained-release dosage forms.

CONCLUSION

Pragelatinized cassava starch phtalate (PCSPh) have good characteristic as film-forming excipient and can be utilized as matrix for transdermal film dosage forms, either as immediate-release or controlled-release dosage forms.

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REFERENCES

1. Langer, R. Transdermal drug delivery: past progress, current status, and future prospects. Adv. Drug Dev. Rev ; 2004 : 56 , 557–558.
2. Cui, S.W., Xie, S.X., & Liu, Q. Starch Modifications and Applications. In Food Carbohydrates: Chemistry, Physical Properties,and Applications. Florida: CRC Press Taylor & Francis Group, LLC. 2005.
3. BeMiller, J., & Whistler, R. Starch: Chemistry and Technology, 3rd ed. New York: Academic Press, Elsevier Inc; 2009. p. 629-657.
4. Jarowenko., W. Acetylated Starch and Miscellaneous Organic Esters. In: Wuzburg O.B Modified Starces : Properties and Uses. CRC Press Inc Florida; 1989. p.51-73.
5. Billmers, R.L., & Tessler, M.M. Method of Preparing Intermediate DS Starch Esthers in Aquoeus Solution. US Patent; 1994 : 5,321,123.
6. Jerachaimongkol, S., Chonhenchob, V., Naivikul, O., & Poovarodom, N. Modification of Cassava Starch by Esterification and Properties of Cassava Starch Ester Films. Kasetsart J. (Nat. Sci.); 2006 : 40, 148 – 151.
7. Shohin, I.E., Kulinich, J.I., Ramenskaya, G.V., & Vasilenko, G.F. Evaluation of In Vitro Equivalence for Drugs Containing BCS Class II Compound Ketoprofen. Dissolution Technologies; 2009: 26 – 29.
8. Tettey-Amlalo, R.N.O. In Vitro Release of Ketoprofen from Propietary and Extemporaneously Manufactured Gels. A Thesis of Master Degree of Pharmacy, Rhodes University, Grahamstown; 2005.
9. Nesseem, D.I., Eid, S.F., & El-Houseny, S.S. Development of novel transdermal self-adhesive films for tenoxicam, an anti-inflammatory drug. Life Sciences; 2011: 89, 430 – 438.
10. Guyot, M & Fawaz, F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol. International Journal of Pharmaceutics; 2000: 204, 171 – 182.
11. United States Pharmacopoeia 30th edition. USA: The Official Compendia of Standards; 2007.
12. Krista, W., & Bucks, D. Studying in vitro skin penetration and drug release to optimize dermatological formulation. In: Pharmaceutical Technology. New York: Advanstar Commucination Inc. 2003.
13. Rowe, R. C., Sheskey, P. J., & Owen, S. C. Handbook of pharmaceutical excipients, 6th ed. London: Pharmaceutical Press; 2009. p. 124-127, 691-694, 725-733.

14. Siepmann. J & Peppas, N.A.. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews, 2001: 48, 139–157.
15. Touitou, E., & Barry, B.W. Enhancement in Drug Delivery. CRC Press: Taylor & Francis Group; 2007. p. 215-278.
16. Huang, X., & Brazel, C.S. Review on the importance and mechanism of burst release in matrix controlled drug delivery system. Journal of Controlled Release; 2001: 73, 121 – 136.