

# Effect of $\text{Ca}^{2+}$ to Salicylic Acid Release in Pectin Based Controlled Drug Delivery System

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## Abstract

Wastes from orange peel are potentially be utilized to produce pectin, which is currently an import commodity. Pectin can be used in making edible film. Edible films are potentially used as a drug delivery system membrane after a tooth extraction. Drug that used in the drug delivery system is salicylic acid. It is an antiseptic. In order to control the drug release rate, crosslinking process is added in the manufacturing of membrane with  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  as crosslinker. Pectin was diluted in water and mixed with a plasticizer and  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  solution at  $66^\circ\text{C}$  to make edible film. Then the mixture was dried in an oven at  $50^\circ\text{C}$ . After edible film was formed, it was coated using plasticizer and  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  solution with various concentration 0, 0.015, 0.03 and 0.05 g/mL. This study show that the more concentration of crosslinker added, the slower release of salicylic acid would be. This was indicated by the value of diffusivities were getting smaller respectively. The addition of crosslinker also caused smaller gels swelling value, which makes the membrane mechanically stronger.

**Keywords:** Pectin, membrane, tooth extraction, controlled release, drug delivery system

## I. INTRODUCTION

Orange is a fruit that is commonly found and widely cultivated in Indonesia. These plants can be grown in lowland areas up to 770 meters above surface area of the sea [1]. The production of orange in Indonesia is very abundant, since the 2004 – 2012 average yield of citrus productions as much as 2 million tons every year [2]. Production with raw materials from oranges such as orange juice will have the wastes from skin, pulp and seed. Citrus processing wastes, especially the skin is one of the raw material for production of pectin that is widely used in the food industry [3]. Indonesia has a good potential as a producer of citrus fruits, but

the utilization of citrus wastes as a source of pectin in the industry has not been done. Pectin is a polysaccharide compound anions contained in the primary cell wall and intercellular wall plants. The constituent molecules consist of galacturonic acid molecules that bind to the  $\alpha$ -(1-4)-glycosidic bond thus forming polygalacturonic acid [4]. Figure 1 shows the compound of pectin in the cell walls of plants [5].

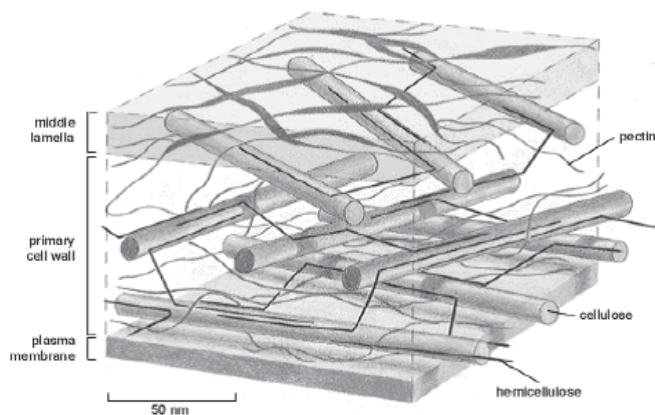


Fig. 1. Plants Cell Wall Structure

The molecular chain of pectin that is a combination from galacturonic acid molecules is shown in Figure 2.

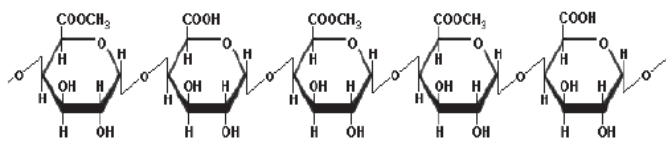


Fig. 2. The Molecular Chain of Pectin

Pectin is an important additional component in the food industry, cosmetics, and pharmaceuticals, because of its ability to change the functional properties of food products such as viscosity, emulsions, and gels. Based on its advantages, the uses of pectin are increasing, both as a food industries or non-food industries raw materials. In addition, pectin has the property that can deliver different types of drugs, proteins and cells. Because of these properties, pectin has the potential to be applied in drug delivery systems.

Drug Delivery System (DDS) is a term which closely associated with delivery of pharmaceutical compounds (drugs) in humans or animals [6]. DDS is usually made in a patch form which should be a thin, elastic, and transparent to be attached at the skin surface. DDS is widely used to replace conventional drug delivery, because :

1. DDS can give a controlled drug dose that can reduce the need for repetition of drug consumption.
2. DDS can reach the right target object.
3. DDS does not cause pain and discomfort as we usually get in conventional drug delivery.
4. If there are side effect, it can be stopped easily
5. It can be given in a longtime without being replaced as long as the patch still adhere on the object.
6. There is no risk of interaction with the gastric fluid [7].

The drug used in the DDS for example salicylic acid (acid ortohidroksibenzoat). Salicylic acid is a drug that used to treat a number of skin problems such as acne, warts, dandruff, psoriasis, and other skin problems. Salicylic acid can also be used to preserve food, antiseptic, and mix it in

tooth paste. At this time, salicylic acid is widely applied in the manufacture of aspirin in industrial scale.

Release of a drug in DDS is controlled by diffusion. This phenomenon can be modeled mathematically that would provide many advantages, there are several of them :

1. It can allow getting deeper insight into the mechanism, which control drug release from a particular type of dosage forms.
2. It can allow for the quantitative prediction of the effects of formulation and processing parameters on the resulting drug release rate.
3. Drug product development can be accelerated and time and cost intensive series of trial and error experiments can be replaced [8].

Drug release analysis was done by dipping edible film containing drugs in a particular solvent. Mass transfer of the drug from solid to liquid is shown in the following figure:

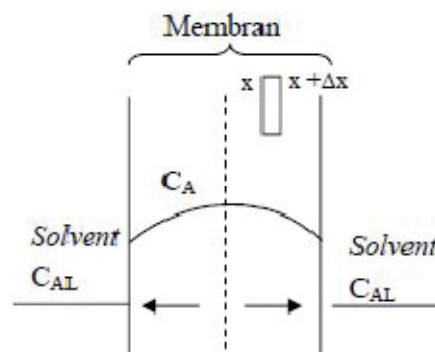


Fig.3. Mass Transfer of Salicylic Acid

In the experiment, mass transfer occurs in two both sides. However, in the real situation, mass transfer occurs in one side. The value of diffusivity will be the same because it is a microscopic property. Release of the drug into the solvent is approximated by a mathematical models with several assumptions to develop the equation as follows:

1. Diffusion through the membrane side is one dimensional (z direction).
2. Volume of the system is constant.
3. The process is isothermal.
4. Initial concentration of the drug in the membrane are uniform.
5. The mass transfer rate from the surface of The membrane to the solution is fast.
6. Membrane does not swell or eroded significantly as long as the release of drugs.

Release of drugs that was delivered in a dominant drug delivery system was controlled by mass transfer. The differential equation obtained by setting up mass balance in the volume element is :

$$\frac{\partial^2 C_A}{\partial z^2} = \frac{1}{De} \cdot \frac{\partial C_A}{\partial t} \dots\dots\dots(1)$$

where,

- $C_A$  = Concentration of drug measured (g/mL),
- $De$  = Drug diffusivity (cm<sup>2</sup>/s),
- $z$  = Distance from the center of the membrane (cm)
- $t$  = The release time (minutes).

Boundary conditions :

$$C_A(z,0) = C_{A0} \dots\dots\dots(2)$$

$$C_A(L,t) = H_A \cdot C_{AL} \dots\dots\dots(3)$$

$$\frac{\partial C_A}{\partial z}(0,t) = 0 \dots\dots\dots(4)$$

$C_{AL}$  value can be found by equation (5) as follows:

$$C_{AL} = C_{AL0} + \frac{n \cdot S}{V} \left( L \cdot C_{A0} - \int_{z=0}^{z=L} C_A(z,t) \partial z \right) \dots\dots\dots(5)$$

where,

- $C_{AL}$  = Concentration of drug in solution (g/mL)
- $S$  = Total area of the membrane (cm<sup>2</sup>)
- $L$  = Thickness of membrane (cm)

The boundary condition (3) is derived from the assumptions that mass transfer from the surface of the membrane is relatively fast, so the solute

concentrations on the surface of the membrane are balance with the solute concentrations in liquid. The correlation of balance can be approached with the equation that resemble with Henry's Law. The boundary condition (4) represents the maximum concentration of salicylic acid in time t is zero. It is described in maximum condition because we can not predict the definite concentration directly.

The finite different method is chosen as solution method of the differential equation. DDS membrane made in this research are pectin-based edible film and will degrade after a long time. In Indonesia, the edible film is still made from gelatin, PLA (Poly Lactic Acid), PVA (Poly Vinyl Alcohol), and hydrogels. All of these components are imported from overseas [9].

After tooth extraction, a blood clot will be formed in the tooth hole. The surface of the opened gums also allows bacteria or food residue entering easily [10]. The membrane containing salicylic acid drugs is used as antibiotics after tooth extraction. To improve the effectiveness of drug delivery system, it is necessary to control rate of drug release. The release rate is controlled by diffusivity, but the diffusivity is controlled by crosslinking of the membrane polimer.

The aims of this research are to observe the impact of crosslinker (Ca<sup>2+</sup>) to the edible film characteristic especially the diffusivity and estimate the salicylic acid mass transfer parameters by proposing a mathematical model.

## II. MATERIALS AND METHOD

### A. Materials

The materials used are pectin, glycerol, CaCl<sub>2</sub>.2H<sub>2</sub>O, salicylic acid, a solution of 37% HCl, KCl, KH<sub>2</sub>PO<sub>4</sub>, NaOH and distilled water.

### B. Instruments

The main instruments used to analyze the parameters are magnetic stirrer, oven and UV-vis spectrophotometer.

### C. *Manufacture of Edible Film from Pectin and Crosslinking Process*

The edible film was made by the two following steps. First, 0.015 g/mL pectin were diluted in 200 mL of solution containing 0.6 g plasticizer/g pectin while stirring for 1.5 hours for a homogeneous solution. The solution was heated to 66°C, then CaCl<sub>2</sub>.2H<sub>2</sub>O solution with proportion 0.04g/g pectin was added little by little for 30 minutes. The solution was scored on a teflon mold and dried in an oven at 50 °C for 15 hours. Second, the film was dipped in a solution with many various concentrations of CaCl<sub>2</sub>.2H<sub>2</sub>O that already contains plasticizer for 30 minutes. The film was separated from the solution and allowed to dry at ambient temperature and stored at the desiccator.

### D. *Analysis of Drug Loading*

Salicylic acid was added into edible films by diffusion method. Edible films were dipped in a solution of salicylic acid (1 gram of salicylic acid in 10 ml acetone) for 2 hours. The edible film that already contains drug was placed on the open space until it dries. The remaining of the concentration of salicylic acid in solution was measured by UV-vis spectrophotometer with a wavelength of 542 nm.

### E. *Preparation of Buffer Solution*

Buffer solution with pH 7.4 was prepared by mixing 1 L of distilled water with 8 grams of NaCl until homogeneous continued by adding 0.2 grams KCl, 1.44 grams Na<sub>2</sub>HPO<sub>4</sub> and 0.24 grams KH<sub>2</sub>PO<sub>4</sub>. The mixture was stirred until homogenous. To ensure the pH closed to 7.4, 37% HCl solution was added using a pipette.

### F. *Analysis of Drug Release*

Edible film that containing drugs was put into a beaker glass containing 25mL of buffer solution with pH 7.4. One mililitre samples were taken periodically from the beaker glass. Then the samples were analyzed using UV-vis spectrophotometer with a wavelength 296 nm.

Each volume of the sample which was taken and completely analyzed will be returned to the glass beaker to keep the volume steady.

### G. *Analysis of Gels Swelling*

Edible films were immersed in a buffer solution with pH 7.4 at room temperature for 72 hours. Then the already swollen edible films were dried in a vacuum oven at 37 °C until the weight was constant. Percentage of swelling was measured by the following formula :

$$\% \text{ Swelling} = \frac{W_s - W_D}{W_D} \times 100$$

where,

W<sub>s</sub> = weight of edible film after hydration for 72 hours

W<sub>D</sub> = weight of dry sample test

## III. RESULT AND DISCUSSION

### A. *Effect of Concentration Crosslinker (CaCl<sub>2</sub>) to Diffusivity Coefficient (De)*

The effect of crosslinker concentration was studied by varying the CaCl<sub>2</sub> concentration added in the second stage of the manufacture of edible film. The concentration were 0, 0.015, 0.03 and 0.05 g/mL.

The release of salicylic acid from edible film to the buffer solution can be presented by the plotting the measuring concentration of salicylic acid in the buffer solution as function of times.

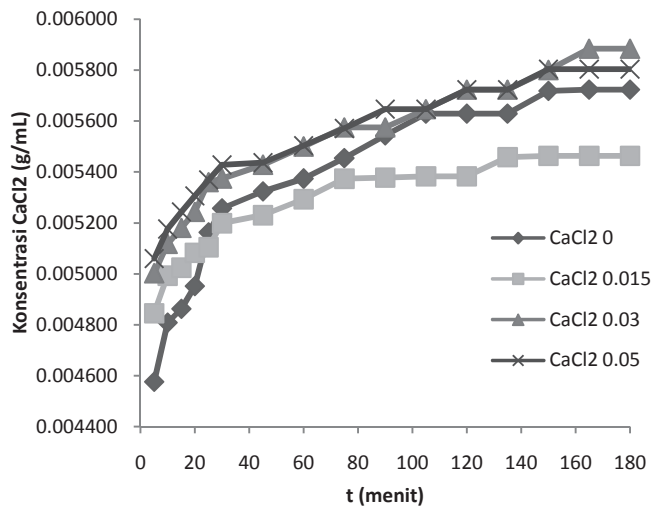


Fig.4. Drug Release Profile in Various Concentration of Crosslinker

Figure 4 show that for different  $\text{CaCl}_2$  concentration, the profiles at salicylic acid release are similar. The value vary from 0.0046 to 0.0059 g/mL. It can be seen also at  $\text{CaCl}_2$  concentration at 0.05 g/mL, the release of salicylic acid slightly maximum. In the beginning (0 to 20) minutes, the salicylic acid concentration increased significantly due to high driving force for mass transport.

The model that has been proposed in equation 1 and 5 was used to predict the trend of salicylic acid concentration profile and to estimate the parameters  $D_e$  and  $H_A$  with trial and error. The experimental and modeling result are presented in table 1, figure 5, 6, 7 and 8.

TABLE I  
DIFUSIVITIES AND DISTRIBUTION COEFFICIENT AT VARIOUS  
CONCENTRATION OF CROSSLINKER

$\text{CaCl}_2$ (g/mL)	$D_e$ ( $\text{cm}^2/\text{s}$ )	H
0	$3.4688 \times 10^{-7}$	0.7084
0.015	$7.5382 \times 10^{-8}$	1.8542
0.03	$7.464 \times 10^{-8}$	2.7734
0.05	$5.8838 \times 10^{-8}$	5.5445

Then, curve fitting had been done based on laboratory experimental in fig.4 and simulation of equation (1) and (2). The results are :

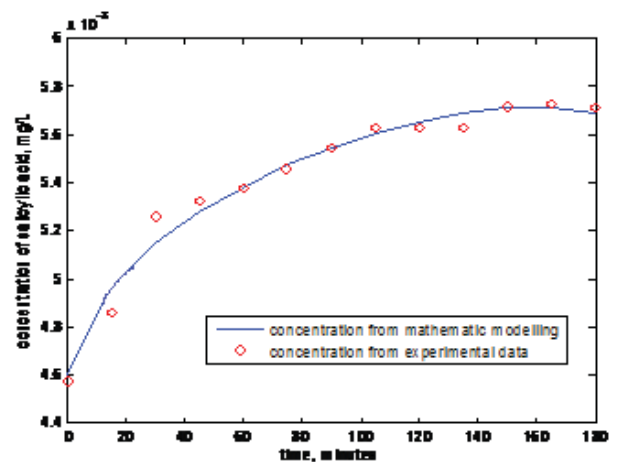


Fig.5. Drug Release Profile in Concentration of Crosslinker 0 g/mL

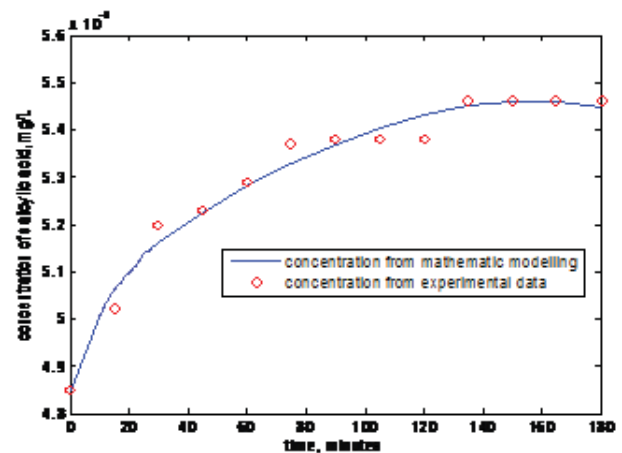


Fig.6. Drug Release Profile in Concentration of Crosslinker 0.015 g/mL



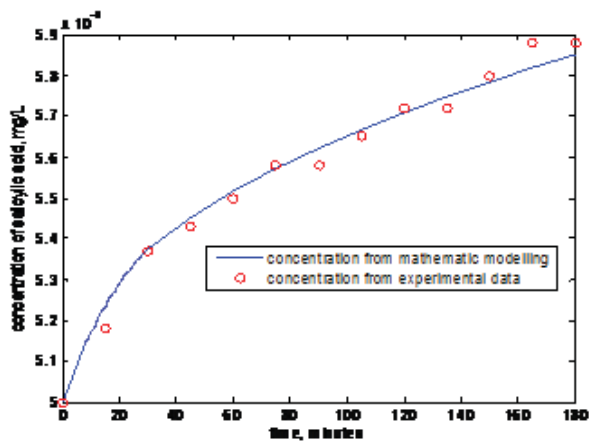


Fig.7. Drug Release Profile in Concentration of Crosslinker 0.03 g/mL

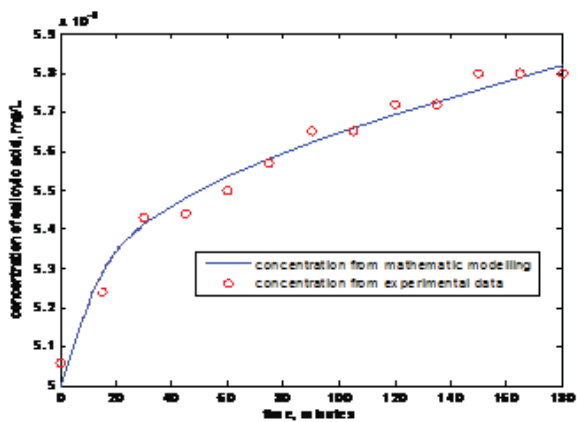


Fig.8. Drug Release Profile in Concentration of Crosslinker 0.05 g/mL

Figure 5,6,7 and 8 show the rate of salicylic acid release in a variety of time and concentration of crosslinker. Overall, the model proposed can quantitatively describe the release of salicylic acid from the membrane because the relative error is 11.5891 %. From table 1, the correlation between CaCl<sub>2</sub> concentration and diffusivity coefficient (De) can be represented in figure 9.

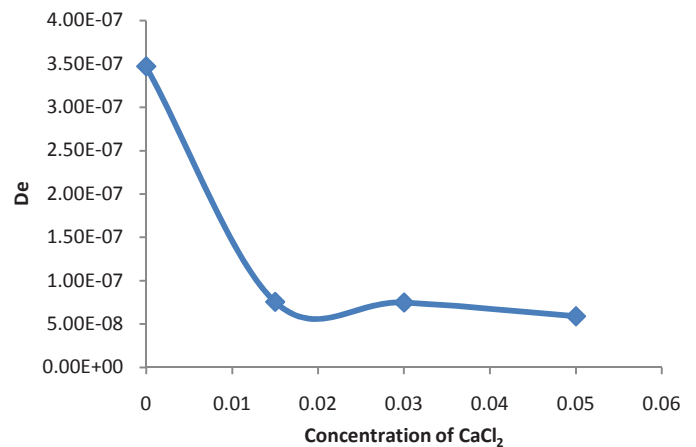


Fig.9. The Diffusivity Profile in Various Concentration of Crosslinker

Figure 9 shows the diffusivity coefficient in many concentrations of crosslinker. It is proposed to help us in predicting the diffusivity coefficient in the concentration of crosslinker that we need.

Salicylic acid concentrations were increased in line with increasing time of release. In the range from 150 to 180 minutes, release of salicylic acid was approximately constant. This indicates that the concentration of salicylic acid in liquid has reached a saturation condition. Table 1 shows that the value of diffusivity (De) tends to decrease with increasing concentrations of CaCl<sub>2</sub>. It is because of Ca<sup>2+</sup> ions contained in the CaCl<sub>2</sub> has the ability to form complex compounds that are not soluble in water by binding the free carboxyl groups contained in the pectin. Hydrophilic properties of pectin before it is crosslinked comes from the presence of the carboxyl group [11]. It causes the pectin carboxyl groups are negatively charged, so it is easy to react with positively charged molecules. If concentration of CaCl<sub>2</sub> is added more, many of Ca<sup>2+</sup> ions will bind the free carboxyl groups in the pectin. The amount of crosslinking bonds formed make the distance between the molecules in the membrane become smaller, so it makes the release of salicylic acid slower.

Moreover, the value of distribution coefficient (H) tends to rise in line with increasing

concentrations of  $\text{CaCl}_2$ . The distribution coefficient is the ratio between the concentration of salicylic acid in the membrane with the concentration of salicylic acid in the liquid.  $\text{Ca}^{2+}$  ions with carboxyl groups on the pectin form a strong bond with a structure that is often called "egg box" structure (Figure 9) [12]. This causes the molecules of salicylic acid is difficult to release from the membrane, so the concentration of salicylic acid in the membrane is greater than the concentration of salicylic acid in the liquid. It means the value of the distribution coefficient is greater too.

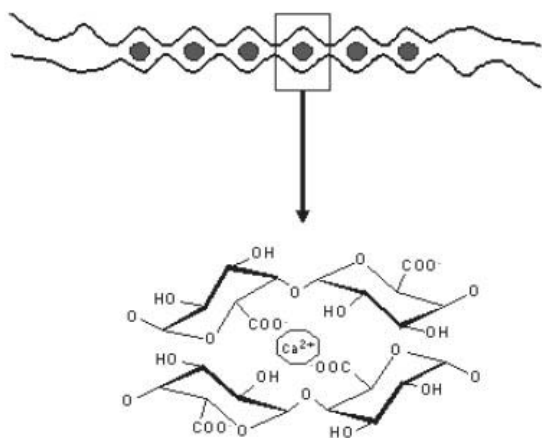


Fig.10. Schematic representation of calcium binding to polygalacturonate sequences: 'egg box' dimer and 'egg-box' cavity

### B. Effect of Crosslinker ( $\text{CaCl}_2$ ) Concentration on Gels Swelling

Beside affecting drug release rate, the strength of  $\text{CaCl}_2$  also affect the ability of the liquid to penetrate into the membrane[12]. This is relate to the gels swelling of the membrane. Analysis of membrane swelling percentage was done in PBS solution with pH 7.4. The changes of swelling percentage are measured until a constant weight. The results from the analysis of swelling percentage are shown in Figure 10 below:

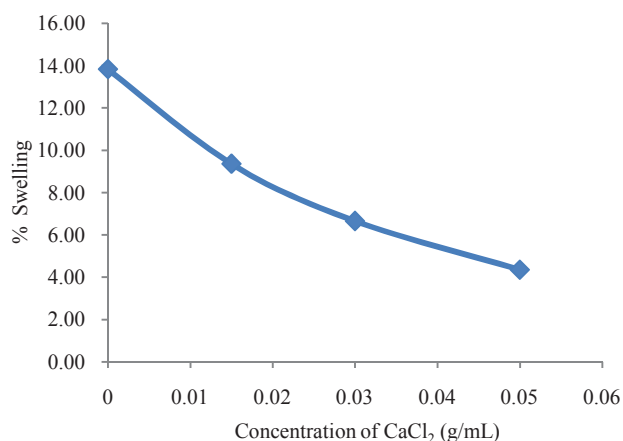


Fig.11. Swelling Profiles in Various Concentration of Crosslinker

PBS solution which has a pH 7.4 indicates an excess of  $\text{OH}^-$  ions. The presence of  $\text{OH}^-$  ions can improve the electrostatic repulsion between the carboxyl group, thus increasing the gels swelling and make the release of salicylic acid is increase too [13]. Therefore we need the addition of crosslinker to make the release of salicylic acid slower. Based on figure 10, the percentage of swelling tends to decline with increasing concentrations of  $\text{CaCl}_2$ . It is because after the crosslinking process, intermolecular bond in the membrane is stronger than before. So, the liquid is difficult to be permeated into the membrane and salicylic acid is difficult to be released from the membrane into the liquid. It also make the membrane can not be degraded and broken easily.

### IV. CONCLUSION

Membrane drug delivery system can be made from pectin that derived from citrus peels. Addition of  $\text{Ca}^{2+}$  on drug delivery system membrane decreases the diffusivity values, so the drug release rate can be controlled more. The mathematic model proposed can quantitatively describe the release of the drug from the membrane with relative error 11.5891 %. Moreover, the addition of crosslinker also makes the membrane swelling percentage decrease, so the membrane

mechanically stronger. Further studies on drug delivery system membrane is very potential to be developed as an innovation in the biomedical engineering field.

#### REFERENCES

- [1] Sarwono, B. 1994. *Jeruk dan Kerabatnya*. Penebar Swadaya. Jakarta.
- [2] Anonim, 2013, *Jumlah Produksi Jeruk Indonesia*. Badan Pusat Statistik. accessed on December 8<sup>th</sup>, 2013.
- [3] Herbstreith, K., dan G. Fox. 2005. *Pectin*. [http://www.herbstreithfox.de/pektin/forschung\\_und\\_entwicklung /forschung\\_entwicklung04a.htm](http://www.herbstreithfox.de/pektin/forschung_und_entwicklung/forschung_entwicklung04a.htm). accessed on March 11<sup>th</sup>, 2014.
- [4] Herbstreith, K and G. Fox. 2005. *Pectin*.<http://www.herbstreithfox.de/pektin/>, accessed on February 12<sup>th</sup>, 2014.
- [5] IPPA (*International Pectins Procedures Association*). 2002. *What is Pectin*.[http://www.ippa.info/history\\_of\\_pektin.htm](http://www.ippa.info/history_of_pektin.htm). access on April 7<sup>th</sup>, 2014.
- [6] Gaurav Upadhyay, Shubham Verma, Nayyar Parvez and Pramod Kumar Sharma. 2014. *Recent Trends in Transdermal Drug Delivery System - A Review*. Advances in Biological Research. vol. 3. pp. 131–138.
- [7] Kurniasih, Nia, 2004. *Jeruk Kurangi Resiko Kanker*. <http://pikiranrakyat.com/cetak/0904/02/cakrawala/lainnya03.htm>. access on May 4<sup>th</sup>, 2014.
- [8] Siepmaan, Juerge and Siepmaan, Florence. 2012. *Modeling of Diffusion Controlled Drug Delivery*. Jurnal of Controlled Release.
- [9] Sadeghi, Mohammad. 2011. *Pectin-Based Biodegradable Hydrogels with Potential Biomedical Application as Drug Delivery System*. Journal of Biomaterials and Nanobiotechnology.
- [10] Anonim. 2013. *Hal-hal Yang Perlu Diperhatikan Setelah Pencabutan Gigi*,[http://johorindahdentalclinic.blogspot.com/2013/02/hal2-yang-perlu-di-perhatikan-setelah\\_26.html](http://johorindahdentalclinic.blogspot.com/2013/02/hal2-yang-perlu-di-perhatikan-setelah_26.html), accessed on August 22<sup>th</sup>, 2014
- [11] Deuel, H., Huber, G., and Anyas Weisz, L. 1950. *Über 'Salzbrücken' zwischen Makromolekullen von Polyelektrolyten, besonders bei Calcium pektinaten*. Helv.Chim.Acta 33, pp.563-567.
- [12] Maestrelli, F., Cirri, M., Corti, G., Mennini, N., Mura, P. 2008. *Development of enteric-coated calcium pectinate microspheres intended for colonic drug delivery*. European Journal of Pharmaceutics and Biopharmaceutics. 69, pp. 508–518.
- [13] M. Mahkam and M. Allahverdipoor, *Drug Targeting*, Vol.12, 2004, pp. 151-156.