First Order Kinetics of Salicylamide Release from κ-Carrageenan Hard Shell Capsules in Comparison with Gelatin

P Pudjiastuti1*, E Hendradi2, S Wafiroh1, H Darmokoesoemo1, M A R D Fauzi1, L Nahar3, and S D Sarker3
1Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia
2Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
3Medicinal Chemistry and Natural Product Research Group, School of Pharmacy and Biomolecular Science, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom.

*correspondent author : pratiwi-p@fst.unair.ac.id

Abstract. Drug delivery material is one of popular topics of research in this era because the development of medicines require a good carrier of the drugs produced and synthesized. However, recent produced capsules were made from animal’s extract such as bone or skin that could not be suitable for everyone, especially the ones with animal’s meat intolerant. Hard shell capsules were produced from κ-carrageenan-alginate (CA) and κ-carrageenan-starch (CS) of cassava. First order kinetics of salicylamide released from hard shell capsules of CA and CS were determined using the Noyes-Whitney modification equations. The optimum k1 of gelatin capsules calculated was 0.0108 ppm/min at pH 6.8, CA was 0.0493 ppm/min, and CS was 0.0237 ppm/min. This means that CA and CS could be recommended. Further development is needed to produce the best CA and CS capsules as drug delivery material.

Keywords: Drug Release Kinetics, Salicylamide, Hard Shell Capsules, Carrageenan

1. Introduction
Commercial hard shell capsules are commonly made from gelatin where it is produced by hydrolysis of collagen from pork, cow, or buffalo. On the other hand, carrageenan is a sulfated polysaccharide, mostly isolated from Eucheuma genus of red seaweed of Rhodophyceae class [1,2]. Currently, carrageenan had been expanded for hard-shell capsules as alternative gelatin capsules such as gellan gum [3], carbomer, hypromelose (HPMC), and xanthan gum [4]. Many hydrophilic polymers are used as drug delivery system (DDS) because of their biodegradability, biocompatibility and polyelectrolyte potential [5], immunogenicity, and cytotoxicity [6].

Drug release is a process where a drug migrates from initial position inside a drug delivery system out to the polymer’s outer surface and then to the release medium [7]. Intermediate, controlled, and pulsatile release are types of drug release [8]. Many mathematical models are described to determine a drug release kinetic, such as zero and first order models, Baker-Lonsdale, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Noyes-Whitney, Peppas-Sahlin [4], Weibull, Hopfenberg, Gompertz, and regression models [9]. Dissolution is the rate of transfer from the dosage form into a liquid medium per unit of time under certain temperature and solvent composition [10]. Dissolution kinetic can be achieved from calculated drug release.

Drug release itself is one of key parameter to determine the performance of a DDS [11]. Information on drug release kinetics of carrageenan hard shell capsule is still limited. Herein, we report the calculation of salicylamide drug release kinetic from hard-shell carrageenan based capsules combined with alginate (CA) and starch (CS) using first order kinetic model.
2. Experimental Method

κ-Carrageenan and Alginate were purchased from PT. Kappa Carrageenan Nusantara and was purchased in PT. Brataco Chemika Surabaya. Salicylamide was purchased from Sigma-Aldrich. Carrageenan-alginate (CA) and carrageenan-starch (CS) hard shell capsules were produced in PT. Kapsulindo Nusantara, Cibinong, Bogor, Indonesia. Erweka Dissolution Tester type DT 820 was adjusted to 37°C and rate of rotational speed was 100 rpm/min. Three kind of capsules (triplicates) of CA, CS and zero size gelatine capsules were filled with 100 mg of salicylamide and put in the basket holder, which contained 900 mL of medium. The media of dissolution followed the USP (United States Pharmacopeia) at pH 6.8 (phosphate buffer). Sample (5 mL) was taken after 5, 10, 15, 20, 30, 45 and 60 minutes by refilling it with 5 mL of medium. All samples were analyzed using a UV-Vis spectrometer at 299 nm. The data were analyzed statistically to get the kinetic profiles of each types of capsule at mentioned acidity.

3. Results and Discussion

Release profiles between conventional hard shell capsules such as gelatin and CA/CS can be compared in order to study the potential of our capsules in order to be the replacement of gelatin. Fundamental principle of drug release was found by Noyes and Whitney in 1897 with the following equation:

\[
\frac{dM}{dt} = KS (C_S - C_t)
\]

where \(M\) is the mass transferred with respect to time, \(t\), by dissolution from the solid particle of instantaneous surface, \(S\), under the effect of the prevailing concentration driving force \((C_S - C_t)\), where \(C_t\) is the concentration at time \(t\) and \(C_S\) is the equilibrium solubility of the solute at the experimental temperature [9]. Modification of Noyes-Withney equation (1) will result the first order model to describe absorption and/or elimination of some drugs. The equation is mentioned by equation (2).

\[
\frac{dC}{dt} = -Kc
\]

where \(K\) is the first order rate constant [4] expressed in units of time. In order to create a more linear equation, the aforementioned equation should be expressed in logarithmic equation as written by equation (3).

\[
\ln C_t = \ln C_0 + Kt
\]

It was observed that in one hour, all the capsules did not completely dissolved that could affect the result of our graph. Thus, it was shown that gelatin and CA capsules produced similar graph while CS capsules produced a more linear graph. However, it needs to be highlighted that the logarithmic amount of drug released in one hour for CA and gelatin capsules are 1.39 (24.81 ppm or 22%) while the salicylamide in CS capsules only released 3.98 ppm (3.59%) in one hour as shown by Figure 1.
It is observed that both graphs of gelatin (Figure 1a) and CA (Figure 1b) show a non-linear plot (both $R^2 = 0.5682$). One of possible explanations is that slightly high solubility of both gelatin and CA, compared to CS, supports faster absorption and swelling to both capsules. In the first 20 minutes, both graph show a plot with high slope while after 20 minutes, the graphs result the second plots with lower slope. This can be caused by the swelling process have been reaching its maximum point at that time. Yang et al. study the swelling degree of gelatin in 0.001 M of NaCl solution where at pH 6 and 7, the degrees are about 1.2 and 1.45 [12] while alginate has higher swelling degree at range of 43.3 to 197.7, depends on the cross-link used [13]. It is suffice to say that when those capsules are reaching their maximum swelling point, it become saturated that the migration of salicylamide become significantly slower. However, the differences between swelling degree should cause the difference in both release profiles. This will be such an interesting topic to be investigated further in order to explore how the differences in chemical structures and swelling degree of both gelatin and CA capsules could result similar result of drug release profile.

The drug release profile of CS at pH 6.8 shows a different yet an interesting profile will be observed. CS capsules released the drug constantly for one hour, shown by Figure 1c, creating a good linear plot with the correlation coefficient of 0.9939. Amylose from starch of *Manihot esculenta* is in the form of a linear structure, compare to alginate, which means this linear structure (Figure 2) would increase the hydrophobicity this organic molecule in water [14]. It is known from the safety data sheet from Megazyme that the solubility of amylose in water at room temperature is below 1 mg/mL which practically makes amylose insoluble in water.

**Figure 1** First Order Kinetics of Salicylamide Released from (a) gelatin, (b) CA, and (c) CS

![Figure 1](image_url)

**Figure 2** Structure of amylose

![Figure 2](image_url)
This insolubility harden the solvation of water to CS capsules even at high pH. However, the presence of carrageenan at its crosslinker increases the solubility a little bit because of ester sulfate groups contained in the structure. Solubility could be the reason why CS were only 3.59% in water in one hour, which reduces the potential of CS to be used as a good DDS compared to gelatin as conventional DDS. If the linear regression of the graph from figure 1c is extrapolated, there will be about 206.96 minutes (3.5 hours) to dissolve all parts of the capsules completely. In addition, CA contains many acidic groups such as ester sulphate and carboxylic groups. These cause the increase in solubility of the capsules at pH 6.8 compared to CS. It is a good possible explanation since there are significant differences between the drug release profile of CA and CS capsules.

Further researches to study are surely needed to be conducted to study the potential of CS capsules for drugs which need to be released more than 3 hours of consumption. Chen et al. studied the potential of starch for oral colon-specific drug delivery where their DDS can be easily prepared from high-amylose starch [15]. Further development of our DDS could be done by modifying the starch’s functional groups with more polar groups. Quadrado and Fajardo suggest carboxymethyl starch – chitosan composite could provide controlled DDS to a specific region of the gastrointestinal tract [16].

4. Conclusions

According to the discussion and explanation, carrageenan-alginate hard shell capsules has lower stability or easily dissolved to acid medium than another natural polymers from carbohydrate. Salicylamide in carrageenan-alginate and gelatin hard shell capsules is more release in acid medium than carrageenan-starch. Salicylamide in their capsules have smaller percentage of drug release than carrageenan-alginate and gelatin. These results are expected to be the basic of information to help people developing the use of carrageenan based hard shell capsules.

References

[1] Akhgari, A., Abbaspour, M.R., Rezaee, S., Kuchak, A., Evaluation of swelling, erosion, and drug release from polysaccharide matrix tablet based on pectin and inulin, Jundishapur Journal of Natural Pharmaceutical Products, 6(1), 51 – 58 (2011)
[2] L. Li, R. Ni, Y. Shao, S. Mao, Carrageenan and its application in drug delivery, Carbohydrate Polymers, 103, 1 – 11 (2014)
[3] Cole, E.T., Scott, R.A., Cade, D., Connor, A.L., Wilding, I.R., In vitro and in vivo pharmacoscintigraphic evaluation of ibuprofen hypromelllose and gelatin capsules, Pharm Res., 21(5), 793 – 798 (2004).
[4] Carma, M.V.S., Kaushal, A.M., Garg, A., Garg, S., Healthcare technology review: factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems, Am. J. Drug Deliv., 2(1), 43 – 57 (2004).
[5] Zia, K.M., Tabasum, S., Nasif, M., Sultan, N., Aslam, N., Noreen, A., Zuber, M., A review on synthesis, properties, and applications of natural polymer based carrageenan blends and composites, International Journal of Biological Macromolecules, 96, 282 – 301 (2017).
[6] R. Yegappan, V. Selvaiprithiviraj, S. Amirthalingam, R. Jayakumar, Carrageenan based hydrogels for drug delivery, tissue engineering, and wound healing, Carbohydrate Polymers, 198, 385-400 (2015).
[7] Fu, Y and Kao, W.J., Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems, Expert Opin Drug Deliv., 7, 429 – 444 (2010)
[8] G. Singhvi and M. Singh, International Journal of Pharmaceutical Studies and Research, 2, 1, 77–84 (2011)
[9] S. Dash, P.N. Murthy, L. Nath, P. Chowdhury, Kinetic modelling on drug release from controlled drug delivery systems, Polish Pharmaceutical Society, 67, 217 – 223 (2010)
[10] Ghayasi, S., Sheraz, M.A., Anjumi, F., Baig, M.T., Factors influencing the dissolution testing of drug, Pak. J. Health Research, 1(1), 1 – 11 (2013)
[11] W.R. Blakemore, Polysaccharide ingredients: carrageenan, Reference Module in Food Sciences: Elsevier Inc. (2016)
[12] Yang, X.J., Zheng, P.J., Cui, Z.D., Zhao, N.Q., Wang, Y.F., De Yao, K., Swelling behaviour and elastic properties of gelatin gels, *Polymer International*, 44, 448 – 452 (1997)

[13] Lee, K.Y, Rowley, J.A., Eiselt, P., Moy, E.M., Bouhadir, K.H., Mooney, D.J., Controlling mechanical and swelling properties of alginate hydrogels independently by cross-linker type and cross-linking density, *Macromolecules*, 33, 4291 – 4294 (2000)

[14] Green, M.M., Blakehorn, G., Hart, H., Which starch fraction is water-soluble, amylose or amylopectin?, *Textbook Errors*, 52, 729 – 730 (1975)

[15] Chen, J., Li, X., Chen, L., Xie, F., Starch film-coated microparticles for oral colon-specific drug delivery, *Carbohydrate Polymers*, 191, 242 – 254 (2018)

[16] Quadrado, R.F.N., Fajardo, A.R., Microparticles based on carboxymethyl starch/chitosan polyelectrolyte complex as vehicles for drug delivery systems, *Arabian Journal of Chemistry*, DOI:10.1016/j.arabjc.2018.04.004 (2018)

**Acknowledgment:** The authors thank Ministry of Research, Technology and Higher Education, Indonesia for the research support fund through the Penelitian Unggulan Perguruan Tinggi (PUPT) scheme. We also thank PT. Kapsulindo Nusantara for supporting us in the production of hard shell carrageenan-based capsules.

**Conflicts of Interest:** The authors declare that there is no conflict of interest.