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## **Human taste testing and evaluation of the physicochemical properties of fine granules of sodium cromoglycate in commercial drug products**

Yutaka Inoue<sup>1\*</sup>, Toru Iwasaki<sup>1</sup>, Kensuke Suzuki<sup>1</sup>, Sujimon Tunvichien<sup>2</sup>, Isamu Murata<sup>1</sup>, Ikuo Kanamoto<sup>1</sup>

<sup>1</sup>Laboratory of Drug Safety Management, Faculty of Pharmaceutical Sciences, Josai University; 1-1 Keyakidai, Sakado-shi, Saitama, 3500295, Japan

<sup>2</sup>Faculty of Pharmacy, Srinakharinwirot University; Nakhon Nayok 26120, Thailand

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### **ABSTRACT**

The purposes of this research were to assess palatability based on human taste testing and to evaluate physicochemical properties of sodium cromoglycate fine granules [a brand-name (CGNa-A) and two generics (CGNa-B and CGNa-C)]. From the results of the human taste testing for the taste evaluation, significant variation in roughness were observed between CGNa-A and CGNa-C and between CGNa-B and CGNa-C. Further, evaluate physicochemical properties, CGNa-A and CGNa-B showed significant difference in solubility. Average granule sizes of CGNa-A, CGNa-B and CGNa-C were of 305.2, 386.6 and 147.2  $\mu\text{m}$ , respectively. In addition, CGNa-B contained granules with smooth surface compared with the two others. CGNa-C had a briefer period of dissolution compared with the other 2 formulations. Further, the repose angle of CGNa-B showed a large. The near infrared measurements, three formulations showed almost the identical absorption spectrum. In conclusion, current results revealed differences in the palatability and physicochemical properties of the three sodium cromoglycate formulations and a correlation between human taste testing results and physicochemical properties of the products was noted.

**Keywords:** human taste testing, palatability, physicochemical properties, sodium cromoglycate



### **INTRODUCTION**

Medical expenses in Japan have been ever-increasing in recent years, therefore Japanese government has recommended to medical institutions for the use of generic drugs (generics) as part of the medical expense reduction projects. In 2015, the targeted volume share of generics has been revised from 60% or above by the end of FY 2017 to 70% or above by mid-2017 as a step toward achieving 80% or above, and it is planned to attain the target goal of 80% or above at the earliest date possible between FY 2018 and 2020 [1]. Although generics contain same active pharmaceutical ingredient as a brand-name drug, different preservatives, excipients, and coloring agents sometimes draw concerns from doctors and pharmacists about the equivalence of the preparations [2]. Different additives, may affect the bitterness that the patient feels. Bitterness is lower the medication compliance of patients. Poor compliance, reduces the treatment effectiveness, it impact on patient's quality of life (QOL). When

patients have difficulty in taking medicine that may be due to bitter taste, doctors and pharmacists tend to lower the dose of the medicine [3, 4]. Selection of safe and effective generics is considered to be an important responsibility of pharmacists. However inadequate information on the clinical efficacy and safety and on the properties of generic drug products [5] make the transition to increase in volume share of generic drugs usage being more retarded. Palatability of drug products is able to be assessed by human taste testing [6-8]. Evaluation of physicochemical properties and human taste testing in loperamide, tulobuterol, and teprenone were conducted in the authors' laboratory previously and correlation between the human taste testing result and physical properties was noted [9-11]. Differences in physical properties among formulations were related to their differences in the sweetness, bitterness, and palatability. In this research, fine granules of sodium cromoglycate, a widely used preventive agent for food allergy, (1 brand-name and 2 generic products) were studied to examine the correlation between their human

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\*Corresponding Author Address: Dr. Yutaka I, Laboratory of Drug Safety Management, Faculty of Pharmaceutical Sciences, Josai University; 1-1 Keyakidai, Sakado-shi, Saitama, 3500295, Japan, E-mail: [yinoue@josai.ac.jp](mailto:yinoue@josai.ac.jp)

taste testing result and physicochemical properties. The analysis of physicochemical properties included dissolution testing, determination of particle size distribution and particle morphology, measurement of repose angle, analysis of sugar content, and near infrared spectrophotometry.

## MATERIALS AND METHODS

1. Materials: Three commercial products of 10% (100 mg/g) sodium cromoglycate were obtained; one brand-name drug INTAL® Fine Granules (Sanofi, Co., Ltd., Tokyo, Japan) and two generic drugs, PULENT® Fine Granules (Tatsumi Kagaku Co., Ltd., Ishikawa, Japan) and ALLERNATE® Fine Granules (Biomedix Co., Ltd., Tokyo, Japan). In this study, they were designated as CGNa-A, CGNa-B and CGNa-C, respectively.

In addition, additive incorporated in each formulation is solely white sugar as claimed in their attached document.

2. Human taste testing: Human taste testing was performed in 40 healthy human volunteers (18 males, 22 females, mean age: 22.7±3.44 years). Detail of the study was clearly explained to potential volunteers and then their consents were obtained. Volunteers were given 0.2 g of each preparation in random order and asked to place it in their mouths for 15 s and then assessed the quality of each preparation. After completing each preparation assessment, volunteers immediately spit out the preparation and gargled with 25 mL of water. Next assessment was commenced 15 min later after gargling to prevent interference from a previous preparation. Evaluation form was a structured rating scale of 6 attributes of preparation, i.e. "solubility," "roughness," "sweetness," "palatability," and "overall impression" (Scheme1). This experiment protocol was approved (H-25-1) by the Ethics Committee of Josai University.

3. Dissolution testing: Dissolution was performed using paddle method as specified in the 16th edition of the Japanese Pharmacopoeia. Dissolution medium was 900 mL of distilled water or artificial saliva (pH 4.8) [11]. The paddle was agitated at a rate of 50 rpm at 37±0.5°C. Sodium cromoglycate should dissolve from fine granules more than 85% in 15 minutes in accordance with guidelines on generics. Ten milliliters of samples were withdrawn at various time intervals and filtered through a 0.45-µm membrane filter. The amount of sodium cromoglycate in filtered solutions was analyzed by means of ultraviolet-visible spectrophotometry at a wavelength of 254 nm. In addition, artificial saliva (pH 6.8) used was the Fusayama-Meyer artificial saliva (AS). It contained

0.4 g KCl, 0.4 g NaCl, 0.795g CaCl<sub>2</sub> • 2H<sub>2</sub>O, 0.78 g NaHPO<sub>4</sub> • 2H<sub>2</sub>O, 0.005g Na<sub>2</sub>S • 9H<sub>2</sub>O and 1 g NH<sub>2</sub>CONH<sub>2</sub> in 1L of distilled water. Artificial saliva was used to simulate dissolution in the mouth.

4. Measurement of particle size distribution: The particle size distribution in each preparation was examined using a dynamic light-scattering instrument (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., Worcs, U.K.). The particle size distribution was characterized using the mass median diameter d (0.5).

5. Observation of particle morphology using SEM: A scanning electron microscope (Hitachi, modelS3000N, Japan) was used to observe the surface and shape of particles in each preparation. SEM was performed with a metal coating and a voltage of 15 kV.

6. Measurement of repose angle: Angle of repose measurement was carried out according to the 16th edition of the Japanese Pharmacopoeia. A [petri dish was placed upside down under a funnel in a manner that the funnel tip was directly pointed at the center of the petri dish. The distance between the funnel tip and surface of the petri dish was 2 cm. After that, mountain such that same type triangle is formed even when viewed from any direction.

7. Near infrared spectrophotometry: Each sample was analyzed using a NIRFlex N-500 analyzer (Büchi Labortechnik AG., Switzerland). The transmittance spectra were recorded using Vision software (Foss NIR Systems, Inc., Laurel, MD, U.S.A.) by integrating thirty two scans taken from 1000 to 2500 nm at 2 nm intervals. A reference (ambient air) spectrum was obtained by integrating thirty two scans in advance in order to compute each dry-syrup powder's transmittance spectrum. The spectral data was processed and analyzed using the relevant NIRWare software modules and the NIRCAl chemometric software.

8. Determination of sugar content: The analysis of sugar content in 1, 10, and 40 mg/mL of sodium cromoglycate solutions of each preparation was performed by sugar refractometry using Atago Master-N1 (Atago Co., Ltd., Japan).

## RESULTS AND DISCUSSION

Human taste testing of CGNa-A, CGNa-B, and CGNa-C was carried out and the results are shown in Fig. 1. Five characteristics, i.e. "roughness", "solubility", "sweetness", "palatability" and "overall impression", of each product were

assessed and significant differences in roughness and solubility were observed. CGNa-B provided a rougher feel in the mouth (roughness score: 6.5) than did CGNa-A and CGNa-C. Significant difference ( $p < 0.01$ ) in the roughness of CGNa-A vs. CGNa-B was noted and also significant differences ( $p < 0.05$ ) in the roughness of CGNa-A vs. CGNa-C and CGNa-B vs. CGNa-C were observed. Additionally, CGNa-A was more soluble (solubility score: 7.6) than CGNa-B or CGNa-C, and significant difference ( $p < 0.05$ ) in the solubility of CGNa-A vs. CGNa-B was revealed. Physical properties of the formulations were evaluated in order to investigate the underlying factors that led to the different in human taste testing results.

Differing dissolution rates of brand-name and generic products of ceftriaxone sodium and clarithromycin dry syrup have been reported [12, 13]. Dissolution behavior of CGNa-A, CGNa-B, and CGNa-C in distilled water and artificial saliva (pH 4.8) was revealed in Figs. 2 and 3, respectively. Eighty five percent or more amount of sodium cromoglycate dissolved from CGNa-A, CGNa-B, and CGNa-C in 15-min in distilled water. This performance has complied with the dissolution standards in the guideline for generics. In distilled water, dissolving of CGNa-C started first and followed by CGNa-A and CGNa-B, respectively. Nevertheless there was no marked difference in dissolution behavior among the three preparations in artificial saliva (pH 4.8). There are presumably 2 reasons for the different dissolution behavior in distilled water and artificial saliva at the beginning of dissolution profiles. The first is because artificial saliva contains sodium ion. The second reason is due to artificial saliva has a pH of 4.8, which is lower than that of distilled water (pH 6.2).

In order to investigate the effects of particle size and particle morphology on solubility, particle size distribution was analyzed and particle morphology was observed using SEM (Figs. 4 and 5). CGNa-A, CGNa-B and CGNa-C had an average particle size of 305.2, 386.6 and 147.2  $\mu\text{m}$ , respectively. In addition, CGNa-C had a wider range of particle size distribution than did CGNa-A and CGNa-B. SEM illustrated particle surface of the 3 formulations, that is, rough surfaced particles in CGNa-A and CGNa-C (Fig. 5 a-2, c-2) and smooth surfaced particles in CGNa-B part (Fig. 5 b-2). CGNa-A particles were longer than those of CGNa-B and CGNa-C (Fig. 5). Basically, the dissolution rate is affected by the wettable surface area of powder [14, 15]. CGNa-B had a larger particle size than those of CGNa-A and CGNa-C, so it had smaller surface area. This may lead to the delayed dissolution of CGNa-B particles in mouth. Although CGNa-A had a larger particle size than

that of CGNa-C, it had a higher solubility score than CGNa-C in human taste testing. This result could be explained that CGNa-C had a wide range of particle size and the larger particles might affect its solubility in mouth.

Angle of repose was measured in order to evaluate flowability of each product (Fig. 6). The repose angles of CGNa-A, CGNa-B, and CGNa-C were 36.7°, 41.3°, and 38.0°, respectively. CGNa-B had significantly larger angle of repose than did CGNa-A and CGNa-C. According to the 16<sup>th</sup> edition of Japanese Pharmacopeia, particles possessing repose angle between 40-36° is categorized in “somewhat acceptable” flowability (CGNa-A and CGNa-C). Only CGNa-B had “normal” flowability. In addition, CGNa-B dissolves little, so it tends to remain in mouth longer. These attributes might lead to high roughness score of CGNa-B in human taste testing.

Typically, larger particle size will reveal a higher absorption spectrum in near-infrared spectroscopy. In the current study, near-infrared spectroscopy was performed in order to determine if CGNa interacted with additives and to verify particle size (Fig. 7). Similar NIR spectra of CGNa-A, CGNa-B, and CGNa-C were observed, indicating that there was no interaction between CGNa and additives in the 3 formulations. Furthermore, peaks due to the OH groups of CGNa were observed between 4700  $\text{cm}^{-1}$  and 5000  $\text{cm}^{-1}$  in all formulations. Larger particle sizes of CGNa-B was also confirmed by the observation of slightly greater intensity spectrum of its NIR spectrum compared with those of CGNa-A and CGNa-C. This finding indicates the correlation between the particle size and the roughness score of CGNa-B.

It has been reported that the difference in physical properties of formulations is due to their additives and granulation. According to package insert, the only additive claimed in the CGNa-A, CGNa-B, and CGNa-C products was white sugar. Sugar content in CGNa solutions at concentrations of 1, 10, and 40 mg/mL was analyzed (Table 1). In 1 mg/mL CGNa solutions, sugar content was 0.0%. In 10 mg/mL and 40 mg/mL of CGNa solutions, the sugar contents were about 1.0% and 4.0%, respectively. Thus, the sugar content in all formulations was about the same. This presumably suggested that different human taste testing results were due to difference in particle surface and particle size of drug itself, not additive.

## CONCLUSION

Although generic pharmaceuticals currently show similar level of therapeutic efficacy as brand-name

pharmaceuticals, different product physical properties may have influence on patient compliance. In this study, size and surface of granules in each formulation dictated their roughness and solubility in mouth, and these quality attributes affected the product's palatability. Three CGNa formulations in this study contain same additive and did not show clear varied compliance. In case of strongly bitter tasted formulation, this could presumably result in less palatability to patients. Thus, the comparison of physical properties of generic pharmaceuticals is a useful approach for a selection of an appropriate formulation in order to provide care to improve a patient's QOL.

#### ACKNOWLEDGEMENT

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#### CONFLICTS OF INTEREST

This study was conducted fairly and impartially and ethical considerations were taken into account. The authors have no relationships with any companies or other commercial entities mentioned in this paper.

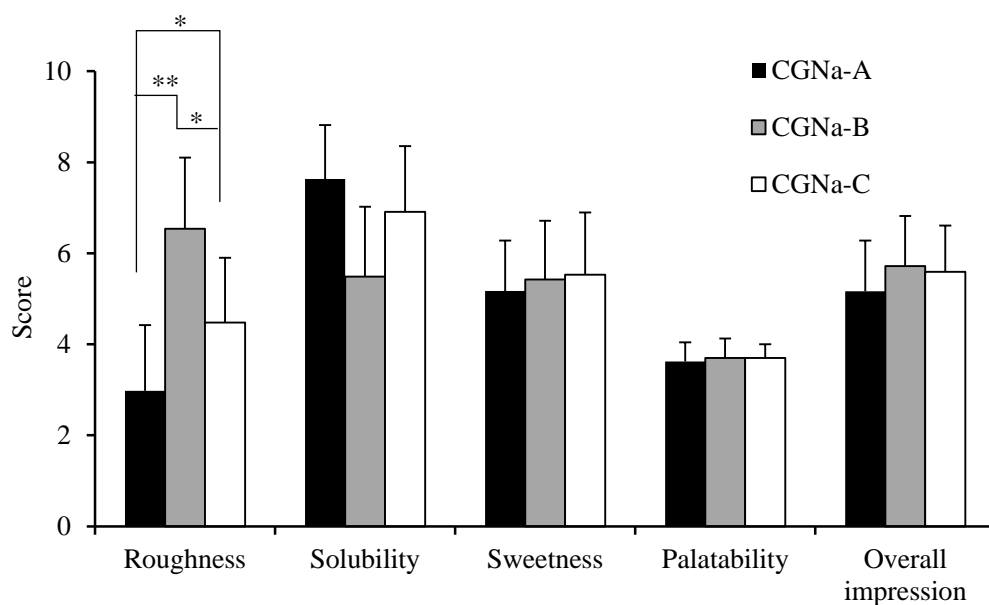


Fig. 1. Result of human taste testing.

\* $p < 0.05$ , \*\* $p < 0.01$  (Tukey Kramer Test,  $n=40$ ,  $\text{mean} \pm \text{S.D.}$ ).

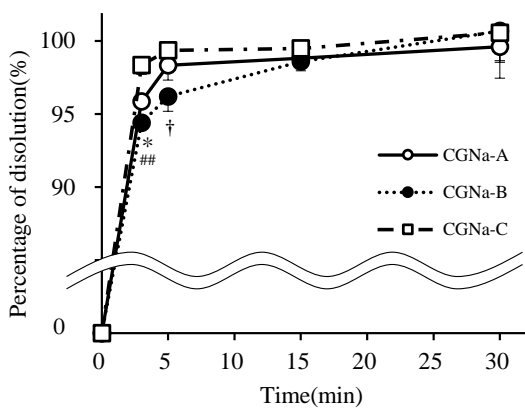


Fig. 2 Dissolution profiles of each formulation in distilled water (n=3, mean  $\pm$  S.D.).

\*p<0.05 CGNa-A vs. CGNa-B,  
##p<0.01 CGNa-A vs. CGNa-C and B,  
†p<0.05 CGNa-B vs. CGNa-C

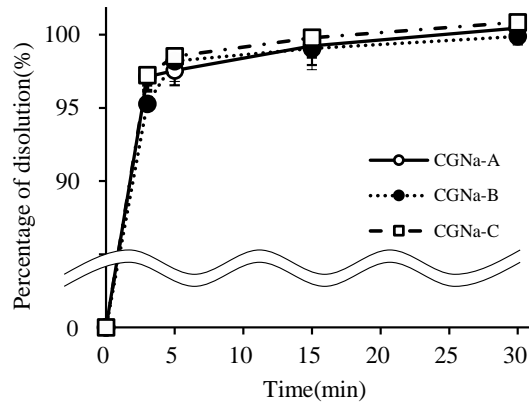


Fig. 3 Dissolution profiles of each formulation in artificial saliva (n=3, mean  $\pm$  S.D.).

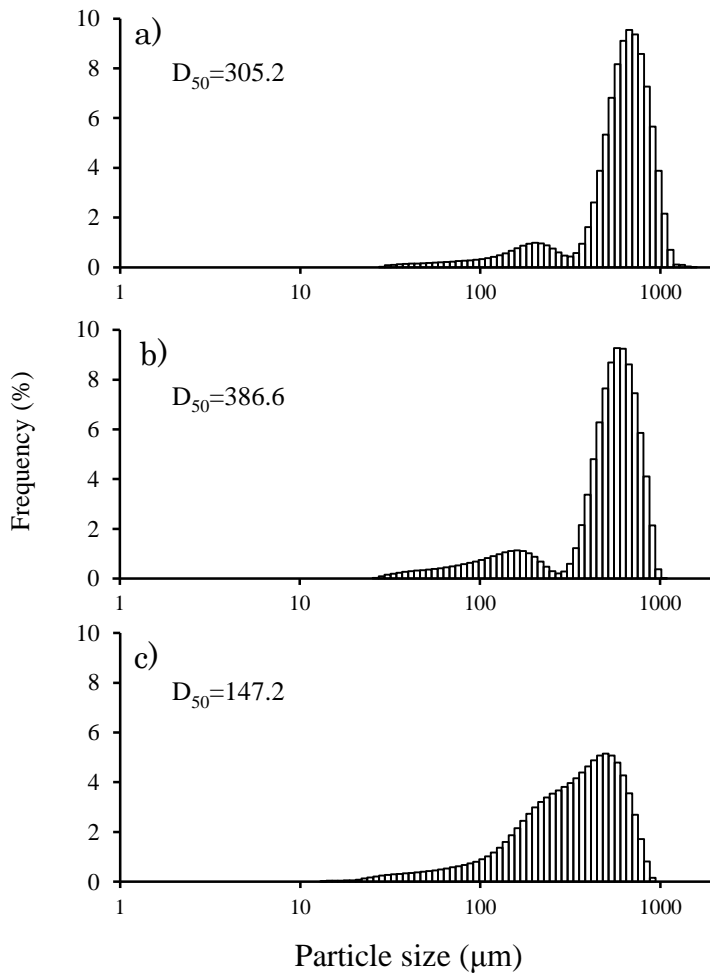


Fig. 4 Particle size distribution for each formulation.  
a) CGNa-A, b) CGNa-B, c) CGNa-C

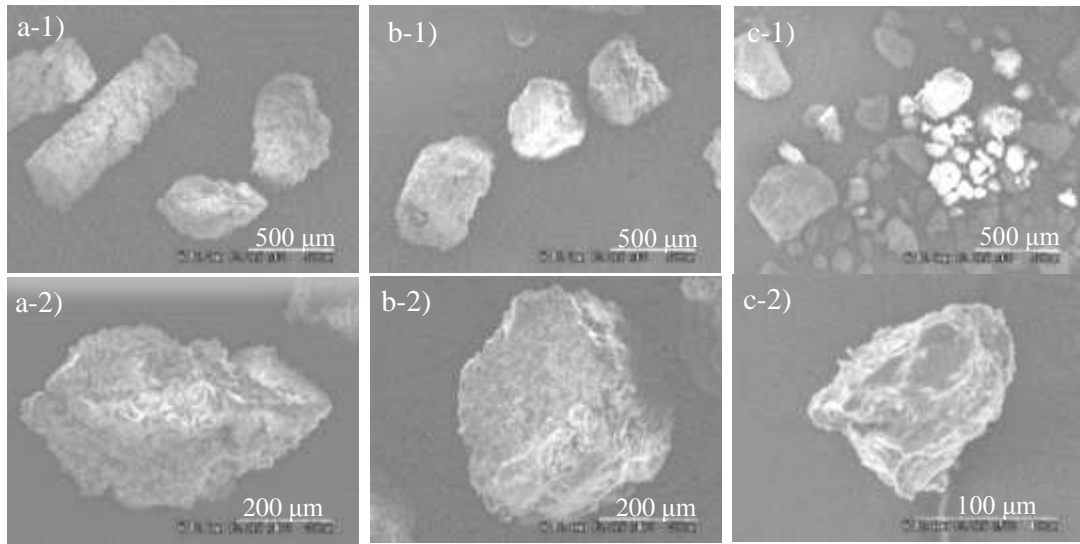


Fig. 5 Scanning electron microscopy photograph of each formulation.  
a-1) CGNa-A ( $\times 60$ ), a-2) CGNa-A ( $\times 170$ ), b-1) CGNa-B ( $\times 60$ ), b-2) CGNa-B ( $\times 170$ ),  
c-1) CGNa-C ( $\times 60$ ), c-2) CGNa-C ( $\times 500$ )

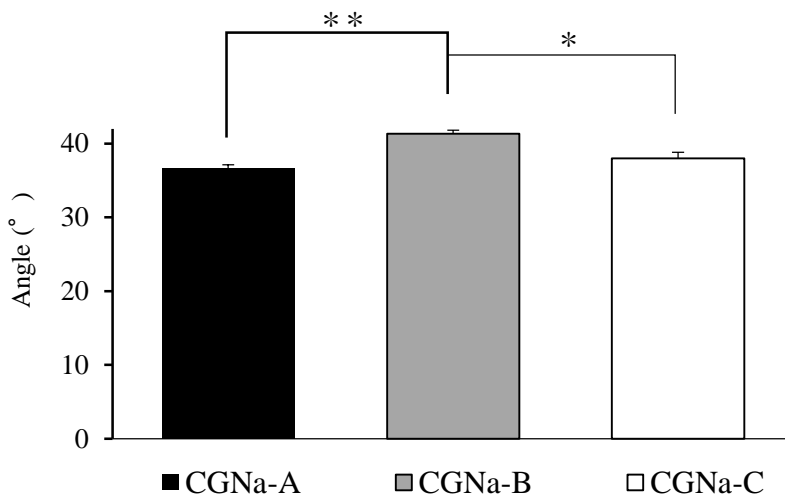


Fig. 6 Angle of repose of each formulation.  
\* $p < 0.05$  \*\* $p < 0.01$  (Tukey test,  $n=3$ , mean  $\pm$  S.D.).

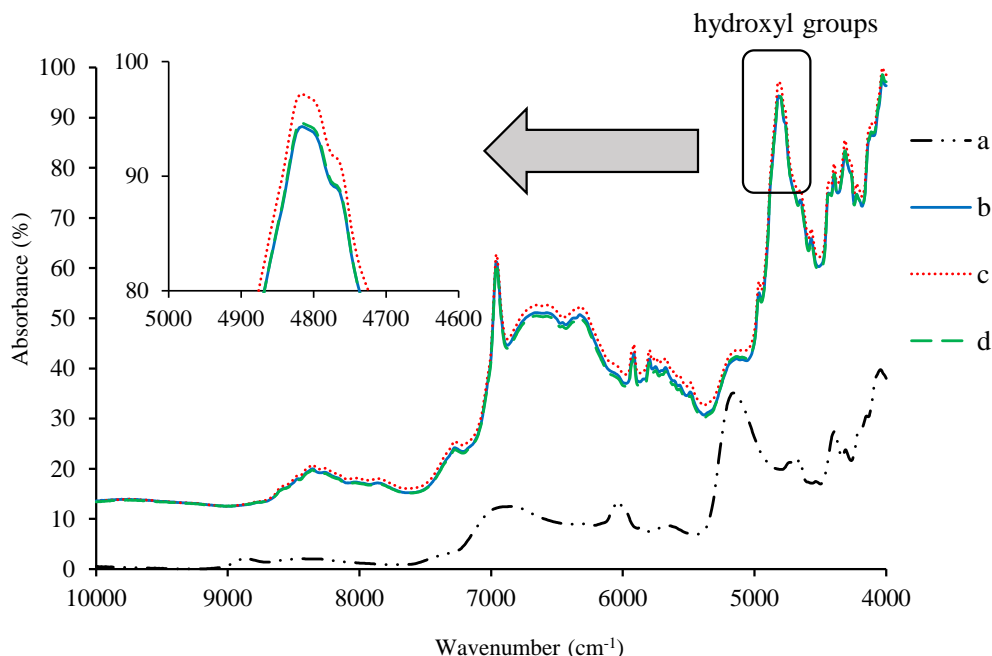


Fig. 7 Near-infrared spectra of each formulation.  
a) CGNa-intact b) CGNa-A, c) CGNa-B, d) CGNa-C

Table 1. Sugar content in each formulation determined by Brix measurement.

Formulation	Concentration of CGNa (mg/mL)		
	1	10	40
CGNa-A	none	0.99±0.01%	4.0±0.0%
CGNa-B	none	0.99±0.01%	4.0±0.0%
CGNa-C	none	1.0±0.0%	4.0±0.0%

n=3, mean ± S.D.

No significant difference between each formulation.

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