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# Formulation, Characterization, and Release Property of Antioxidant Supplement Capsule with Red Ginger Oleoresin Extract-loaded Chitosan Microparticles

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**Abstract.** Ginger is one of the spices that well-known for the health benefit. Ginger containing 6-gingerol and other phenolic compounds that act as antioxidant activity. Bioactive compounds in ginger are sensitive to high temperature, pH, and light so encapsulation is needed for protecting the bioactive compounds from degradation and for controlling the drug release in the gastrointestinal tract. The aim of this study is to get the formulation of the antioxidant supplement capsule containing microparticle chitosan- oleoresin extract from red ginger and excipients that has sustained release in gastrointestinal simulated fluids. Oleoresin extract was obtained by maceration extraction with the yield 6 %, 6-gingerol content of 6 mg/gr dry weight, total phenolic content of 40.6 mg GAE/gr dry weight, and the IC<sub>50</sub> DPPH of the oleoresin of 17 ppm. Oleoresin extract, then was encapsulated using chitosan with the encapsulation efficiency is 95.8% and the loading capacity is 4.9%. Hard gelatin capsule was filled with chitosan-oleoresin microparticle, starch as a disintegrant, and magnesium stearate as lubricant. Dissolution test was done by dissolution tester basket method. The release profile shown the burst release in each gastrointestinal simulated fluid. Antioxidant supplement hard gelatin capsule in formula 2 with the composition consisted of 89.5% chitosan-oleoresin microparticle, 10% starch, and 0,5% magnesium stearate show the lowest release in simulated gastric fluid, but the highest release in simulated intestinal fluid. The bioactive compounds in formula 2 can be released in the small intestine.

*Keywords:* Chitosan microparticles, oleoresin extract, red ginger, supplement capsules, release profile

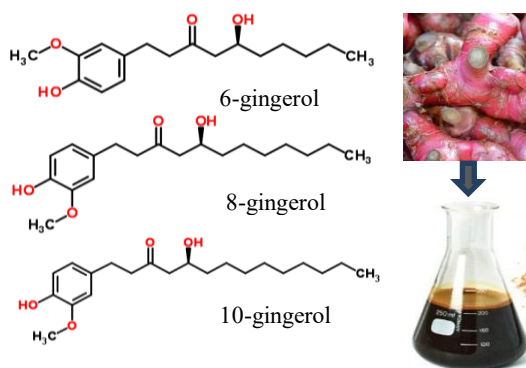
## 1. Introduction

Free radicals are any molecular species that contain unpaired electrons in atomic orbital, that can attack important macromolecules such as DNA, proteins, carbohydrates, and lipids leading to cell damage and homeostatic disruption [1]. The cellular damage can cause chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases [2]. An antioxidant is a molecule that stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing the free radicals' ability to damage other molecules or cells. The requirement of antioxidants for human consumption can be supplied through supplement tablets or capsules.

Red Ginger (0) is a well-known spice in Asia for its medical benefit. The antioxidative and free radical scavenging properties of the ginger extracts have been well established [3], as well as anticancer (4,5), antibacterial [6], for treating rheumatoid arthritis [7]. Ginger extract contains oleoresin and essential oils which have a feature of yellow, oily, and pungent. The oleoresin contains the phenolic



compounds, which has a role in antioxidant activity, such as gingerol, shogaol, and zingerone [8-11]. The gingerol, where 6-gingerol is the major constituent of oleoresin, is susceptible to heat, light, and oxygen. Gingerol and shogaol are the source of the pungency and spicy flavor in ginger. Some of the phenolic compounds in red ginger are shown in Figure 1.



**Figure 1.** Some of phenolics in oleoresin extract of red ginger

Microencapsulation is a technology used to protect the active ingredients in the form of liquid, solid and gas from environmental affect [12]. Microencapsulation can be used for protecting the bioactive compounds of ginger from environment, covering the taste of ginger, and for controlling the release in the gastrointestinal tract. The biopolymer chitosan is known widely used as materials for encapsulation [13,14]. Chitosan is bio-polyamino-saccharide produced from the deacetylation process of chitin, which is the largest source of polysaccharide after cellulose. Chitin is derived from animal's arthropods and marine crustaceans. Chitosan is biocompatible, biodegradable, non-toxic, and unreactive with active ingredients [15-16].

The dissolution of the drug also can be affected by the solubility of the material. Poor solubility of oleoresin in water can limit the drug bioavailability in the gastrointestinal medium [17]. The use of excipient materials in the form of disintegration may increase solubility, absorption, and bioavailability has been reported in some cases of water-soluble drugs [18]. The addition of disintegrant materials in general is in the range 3 - 15% [19]. The differences in mass of disintegrant materials added may influence differences in drug dissolution characteristics [20]. Therefore, in order to produce capsules of antioxidant supplement it is required to study the effect of the composition of disintegrant materials as well as characteristics of the microparticles that encapsulated the antioxidant compounds of ginger oleoresin, hence the capsules can deliver the active compounds into the targeted area in the intestine.

The purposes of this research were to obtain a formulation of antioxidant supplement capsule that contain chitosan-red ginger oleoresin microparticles and excipients, and to determine the characteristics of chitosan microparticles loaded red ginger oleoresin, as well as the property of oleoresin release in gastrointestinal solution. In this research, the red ginger oleoresin extract was produced with maceration extraction in ethanol and the encapsulation of chitosan microparticles was conducted using ionotropic gelation method with sodium tripolyphosphate as cross-linking agent. Various compositions of chitosan microparticles and excipients in alginate capsules were made and the property of oleoresin release from the capsules was assayed in synthetic gastrointestinal solution at temperature of 37°C.

## 2. Material and Method

### 2.1. Chemical and Materials

Fresh red ginger (*Zingiber officinale* var. *Rubrum*) was purchased from a local market in Pemalang, Central Java. Chemicals and reagents used such as ethanol, methanol HPLC-grade, DPPH, chitosan medium molecular weight (MW sodium tripolyphosphate (Na-TPP), gallic acid, Folin-ciocalteu's (FC) reagent, calcium chloride (CaCl<sub>2</sub>), Sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>), hydrochloric acid (HCl), potassium chloride (KCl), monopotassium phosphate (KH<sub>2</sub>PO<sub>4</sub>), sodium hydroxide (NaOH), magnesium stearate, and starch were procured from Sigma-Aldrich, Inc. and Merck.

## 2.2. Extraction of Red Ginger

Fresh Ginger was cleaned, then thinly sliced and dried naturally under the sun. The dry ginger chips were ground using a food grinder and then filtered using a 40 meshes sieve. Ginger powder was macerated in 7 days using 96% ethanol solvent with the ratio of dried ginger powder to the solvent as 1: 3 (g/mL). After filtering, the oleoresin was obtained by drying the filtrate using a Rotary Vacuum Evaporator (EYELA N-1000) at a temperature range of 35-40°C.

## 2.3. Quantification of 6-Gingerol in the Oleoresin

The 6-gingerol content in oleoresin was analysed using High Performance Liquid Chromatography (HPLC). Shimadzu HPLC with a reverse-phase C18 column (240mm×4.6mm, 5µm) was used at temperature of 40° C. The UV detector was used at a wavelength of 282 nm. The mobile phase eluent was a mixture of methanol (90%) and water (10%) with a flow rate of 1 mL / minute and the volume of injected solution was 20 µL. The 6-gingerol standard and the oleoresin samples were dissolved in methanol (HPLC grade).

## 2.4. Quantification of Total Phenolic Content in the Oleoresin

The determination of total phenolic contents was determined using spectrophotometric analysis as reported by Kim et al. [21] with some modification. Small amount of oleoresin extracts was diluted in ethanol samples in several concentrations. An aliquot (0.5 mL) of dilute oleoresin solutions was added to 5 ml 10 % Folin-Ciocalteu reagent and shaken for 5 minutes. The mixture was added to 4 ml of sodium carbonate and mixed thoroughly. The mixture was then incubated at room temperature for 15 minutes. The absorbance was read by visible spectrophotometer (UNICO RS1100) at λ 765 nm. Gallic acid solutions in several concentrations, as standards, had the same treatment as the oleoresin samples. The total phenolic contents of oleoresins were calculated using gallic acid calibration curve and were expressed as mg gallic acid equivalents (GAE)/g dry plant sample.

## 2.5. Antioxidant Activity of Oleoresin with DPPH Assay

The method reported by Mensor et al. [22], was used with modification in order to determine the radical scavenging ability of compounds in oleoresin. The sample solutions of oleoresin extract in methanol were prepared in various concentrations. Each 2 mL of oleoresin sample was added to 1 mL of 0.1 mM DPPH solution in methanol and 1 mL of pure methanol. The mixture was incubated for 30 minutes at room temperature, in a dark place, and the absorbance was read at λ 517 nm at visible spectrophotometer. The blank sample was prepared by mixing 3 mL methanol with 1 mL of 0.1 mM DPPH solution. Various concentrations of ascorbic acid solutions that were prepared with a similar procedure were used as positive controls. The antiradical activity (AA) was determined using the following formula:

$$AA\% = 100 - \left( \frac{(Abs\ sample - Abs\ blank) \times 100}{Abs\ control} \times 10 \right) \quad (1)$$

## 2.6. Microencapsulation of Chitosan-Oleoresin with TPP Cross-linking

The preparation of chitosan microparticle was based on an ionotropic gelation method using sodium TPP as cross-linking agent reported by Yu et al. [23] with some modification. 0.1 g of oleoresin was dissolved in 1 mL of ethanol, then added into a 50 mL of 2.5% acetic solution that contained 1 g of chitosan. The mixture was stirred using a four-blade impeller at a rate of 1000 rpm for 15 minutes to form a chitosan-oleoresin suspension. To form small beads, 100 mL of sodium tripolyphosphate (TPP) solution (1%, w/v) was dropped into the chitosan-oleoresin suspension using a 10 mL syringe, stirred at 600 rpm for 10 minutes and left unstirred for 30 minutes. The particles were separated using Whatman filter paper that connected to a water vacuum pump. After washed with distilled water several times, the

particles were separated and dried using freeze drying equipment. Dried microparticles were ground using a mortar and sieved to obtain microparticles with size < 100  $\mu\text{m}$ .

### 2.7. Encapsulation Efficiency, Loading Capacity and Yield Assay

Filtered water and washing water from the microparticle preparation was used for quantification of phenolic compounds by the same method as the total phenolic content test to obtain the total phenolic content trapped in the microparticles. The encapsulation efficiency and loading capacity are calculated by the equation

$$\text{Encapsulation efficiency (\%)} = \frac{\text{phenolic concentration (initial-filtrate)}}{\text{phenolic concentration initial}} \times 100 \quad (2)$$

$$\text{Loading capacity (\%)} = \frac{\text{phenolic concentration (initial-filtrate)}}{\text{microparticle weigh}} \times 100 \quad (3)$$

### 2.8. Loading Microparticles and Excipient into Hard Gelatin Capsules

Disintegrate excipient used is starch, while as lubricant the material used is magnesium stearate. Capsules used are gelatin capsules no.2 derived from cows. The fixed mass of the mixture in one capsule is 200 mg.

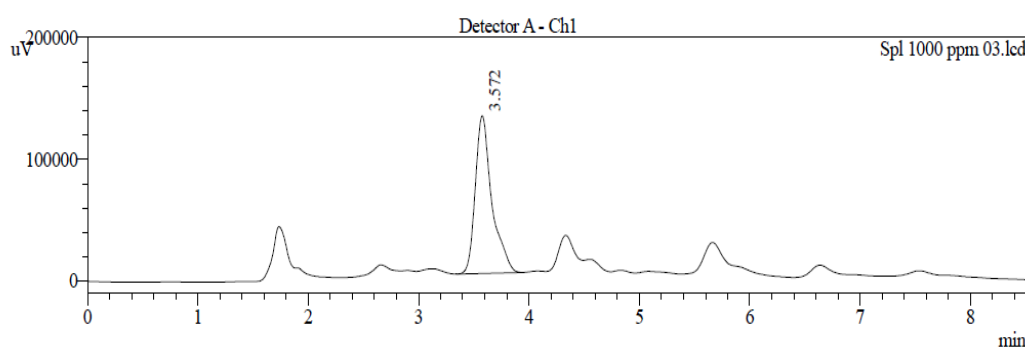
### 2.9. Capsule Dissolution Test

The dissolution test refers to The United States Pharmacopeia (USP 711) which provides guidance for testing the dissolution of hard gelatin capsules using dissolution tester with basket method and 75 rpm rotational speed. The temperature is set at 37 °C and the medium volume of each vessel is 500 ml. The medium used includes three types of gastrointestinal medium, Simulated Gastric Fluid (SGF) pH 1.2, Simulated Intestinal Fluid (SIF) pH 7.4, and Simulated Colon Fluid (SCF) pH 6, 8. Dissolution was performed for 2 h in a simulated gastric fluid (SGF) solution of pH 1.2. Sampling of 4 ml at 30, 60, 90, and 120 minutes was immediately replaced by the same amount into the dissolution vessel. For SIF and SCF solutions were performed for 4 hours with sampling at 30, 60, 120, 180 and 240 minutes. The samples taken were measured by a visible spectrophotometer at a wavelength of 765 nm by treatment such as the total phenolic test. The absorbance obtained is treated as phenolic release.

## 3. Results and Discussion

### 3.1. Red Ginger Oleoresin Quantification and Antioxidant Activity

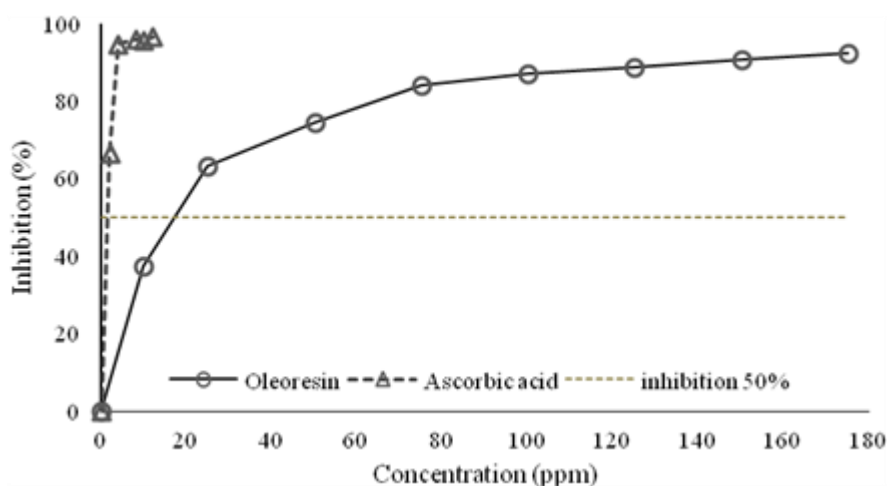
The 6-gingerol content of oleoresin samples tested by HPLC showed a yield of 6.0 mg / g dry weight (DW) of ginger sample. The content of 6-gingerol in oleoresin can be affected by the 6-gingerol properties that are susceptible to high temperatures. This property is due to the presence of  $\beta$ -hydroxy keto in gingerol structure which can cause gingerol dehydrated at high temperature. Degradation of 6-gingerol forms 6-shogaol and other derivatives such as zingerone, gingerdion, and gingerdiol [24].



**Figure 2.** Chromatogram of Red Ginger Oleoresin Extract

The total phenolic content of ginger is expressed as the equivalent of gallic acid or Gallic Acid Equivalent (GAE). For 1 mg GAE / g sample there is 1 mg of gallic acid in a 1 g sample. The phenolic content of oleoresin from ethanol extract was at 40.6 mg GAE / g dry weight plant sample. This result was higher than phenolic content in another type of *Zingiber officinal* [25], which was in the range of 10.2 mg – 13.5 mg GAE/g dry plant sample using methanol extraction. Compare to extraction using petroleum ether and chloroform/methanol the phenolic content was lower, which were 52.2 mg GAE/g and 60.3 mg GAE/g, respectively [26]. It seems likely the total phenolic contents in oleoresin extract was affected by the solvents used during extraction, the polarity of the solvents, the heating during the process of extraction and part of the ginger plant used.

Figure 3 shows the profile of the antioxidant activity of oleoresin, which is expressed as % inhibition, as a function of concentration of oleoresin. At concentration around 17 ppm, the inhibition caused by oleoresin reached 50%. The result of assay on the standard ascorbic acid was much different. The inhibition of 50% was reached at very low concentration of ascorbic acid. i.e. 1.5 ppm. The maximum inhibition of oleoresin was 92% at a concentration of 175 ppm, while ascorbic acid concentration at 12 ppm caused the inhibition 97 %.



**Figure 3.** % DPPH Inhibition of Oleoresin compared to that of Ascorbic Acid

The  $IC_{50}$  parameter is used to represent the ability of antioxidant to inhibit the radical activity up to 50%. Figure 3 shows the  $IC_{50}$  of oleoresin extract and ascorbic acid were 17 ppm and 1.5 ppm, respectively. Based on a study reported by Phongphaicit et al. [27] on antioxidant strength classification, compound with value of  $IC_{50}$  lower than 50 ppm is classified as very strong antioxidant. Therefore, oleoresin extract can be classified as compounds that have very high antioxidant activity. The ascorbic acid has much higher antioxidant activity than oleoresin extract since it has a higher amount of hydroxyl groups than that in gingerols of oleoresin. The presence of antioxidant activity in red ginger oleoresin is due to phenolic compounds such as gingerol, shogaol, and zingeron [28]. The ability of gingerol and shogaol as a source of antioxidants due to its structure containing benzene rings and hydroxyl groups. The hydrogen atoms in the hydroxyl group bind to free radicals, thereby increasing the stability of free radicals. Oleoresin reacts to diphenyl picryl hydrazyl (DPPH) molecules by releasing the hydrogen atom to form a diphenyl compound of picryl hydrazine and causing the decay of DPPH color from purple to yellow [29].

### 3.2. Encapsulation Efficiency, Loading Capacity, and Yield

The encapsulation efficiency shows the amounts of phenolic compounds absorbed in the chitosan-oleoresin microparticles compared with the number of phenolic compounds at the beginning of addition. The higher the efficiency value of encapsulation indicates more and more phenolic compounds are absorbed. The encapsulation efficiency in this study is relatively high, is 95.8%. The high value of the efficiency of encapsulation can be influenced by the low solubility of phenolic compounds of ginger oleoresin in aqueous solution during the preparation of chitosan microparticles. Using the ionotropic gelation method, the hydrophilic active compounds will prefer to be inside chitosan-TPP network, rather than diffuse to the aqueous solution of TPP. The loading capacity indicates the amount of phenolics contained in the microparticles formed. The loading values are generally influenced by the weight of microparticle formed. The loading value on this microparticle is 4.9%. The results of this study were higher than reported by Krisanti et al. [30] with loading of 3.1% for the same ratio of chitosan to oleoresin.

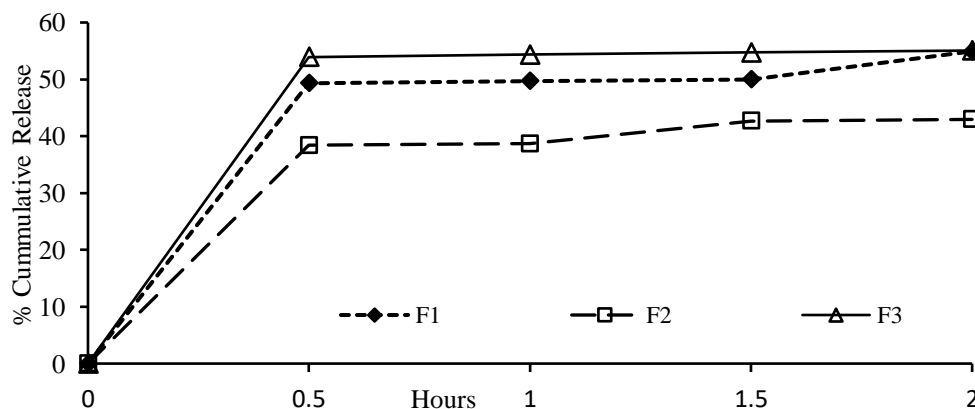
### 3.3. Release Profile of Oleoresin Loaded in Microparticles from Capsule

The oleoresin loaded chitosan microparticles were mixed with excipient, i.e. starch and magnesium stearate. Three compositions of microparticles and excipients were tested for their release properties in synthetic gastrointestinal fluids, i.e. SGF, SIF and SCF. The compositions of the capsule were shown in table 1.

**Table 1.** The compositions of microparticles and excipients in the capsules

Formulation:	F1	F2	F3
Chitosan-oleoresin microparticle	94.5%	89.5%	100%
Starch	5%	10%	-
Magnesium stearate	0.5 %	0.5 %	-

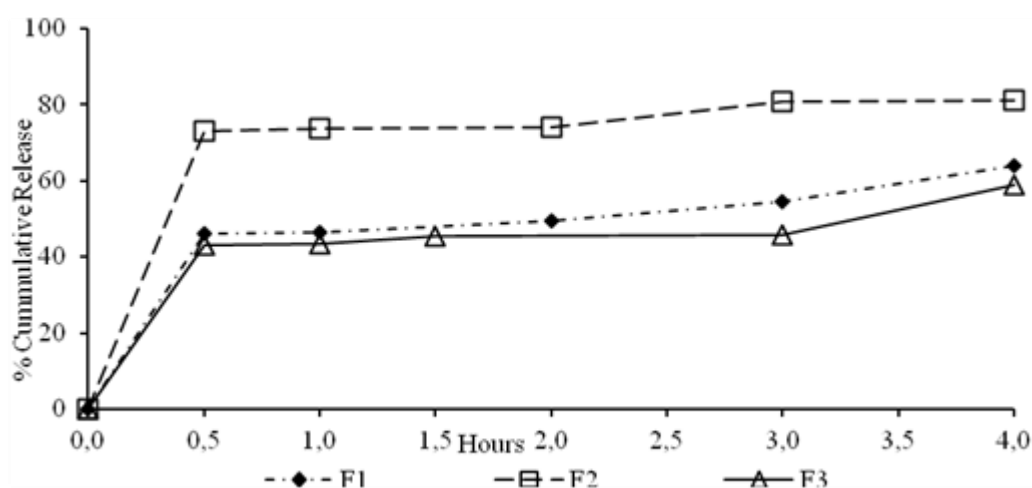
Release of the three formulas of capsules loaded with oleoresin microparticles with excipients in SGF medium was shown in figure 4. Formula F3 which contains no excipients shows the highest release among the three formulas with the increase of starch content in the composition, the phenolic release of the SGF medium decreases. This result was predicted since the absence of starch as disintegrate materials and magnesium stearate as lubricant affected the drug dissolution [20]. Magnesium stearate is known as the lubricant that act as water repellent, hence the presence of magnesium stearate can slow the dissolution process of capsules contain disintegrate starch [31].



**Figure 4.** Release Profile of phenolics in SGF medium from capsule contains oleoresin microparticles and excipients.



The release profile of F2 capsule, with 10% starch, on SGF (figure 4) shows the lowest release. In acidic conditions of SGF, the starch undergoes hydrolysis that reduced swelling capacity [32]. This might be related to the fragmentation of amylose chains in starch during hydrolysis that form irregular structures of starch that cannot retain water ([33]. When the swelling capacity of starch decreased, the water absorption for chitosan microparticles decreases. Thus, in acidic condition, increasing the content of starch in the composition can reduce the contact time between water and chitosan microparticles. The results indicated that in low pH condition, the excipient mixed with chitosan microparticle that encapsulated oleoresin can lower the release to 43%, compared to 55% release of capsule without excipient.

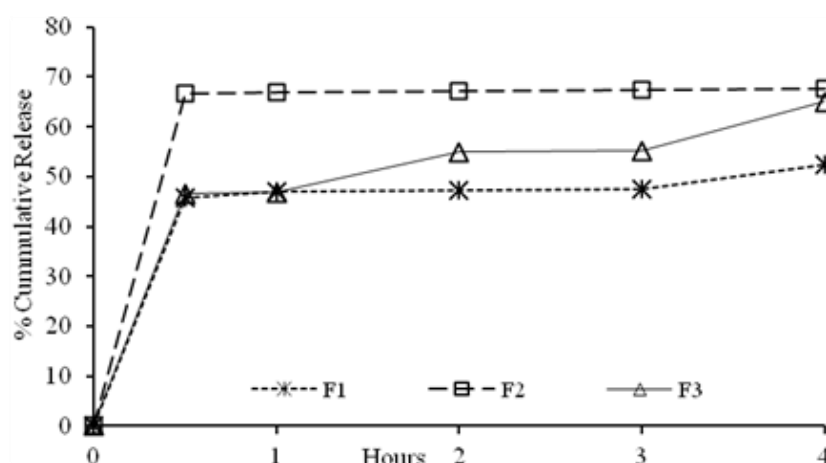


**Figure 5.** Release Profile of phenolics in SIF medium from capsule contains oleoresin microparticles and excipients.

Figure 5 shows that in SIF medium, with pH 7.4, the F2 formula with 10% starch, had the highest cumulative release of active compounds from the capsule. It seems likely that in this pH condition, the swelling of starch is manageable, so the water absorption increases by filling the free volume afforded by the swollen starch. The more water contacts with chitosan microparticles the most active compounds can diffuse through the microparticles and swollen excipient. After immersing in the SIF medium for half hour, the release reached 73% of F2 formula, compare to F1 and F3 which were 45% and 43 %, respectively.

In SCF medium that simulated the condition of the colon, the cumulative release of active compound of F2 formula was the highest as in SIF medium (as shown in figure 6). It reached 66 % in half hours immersed in SCF medium, which was higher than the release from formula F1 and F3 around 47%. The cumulative release results in figure 5 and 6 show that starch and magnesium stearate as excipient increase the release of active compound from oleoresin-chitosan microparticle in SIF and SCF mediums. However, even in these two mediums, the release of active compounds (gingerols) from chitosan microparticles did not reach 100 %. It is reported that the solubility of oleoresin in aqueous solution is very low, which cause the low bioavailability of oleoresin [17]. Formation of chitosan microparticle to encapsulate oleoresin and the use of excipients of starch and magnesium stearate seemed improved significantly the solubility of active compounds in aqueous phase. Figure 4, 5, and 6 indicated the release improvement due to the encapsulation in chitosan microparticles and the usage of starch and magnesium stearate. The use of hard gelatin capsules can also increase the wettability and dissolution of the drug because of its hydrophilic nature [34].





**Figure 6.** Release Profile of phenolics in SCF medium from capsule contains oleoresin microparticles and excipients.

The release of active compounds from chitosan microparticles that are filled in the gelatin capsules in the synthetic gastrointestinal fluids, showed the burst release profile. It reached a maximum release almost in the first half hour immersed in the release medium. Release in synthetic gastric acid showed lower release than intestine or colonic medium. It is reported that a moderate release in SGF will enhance the release in the SIF and SCF medium simultaneously [35]. When swelling of biopolymer slightly occurred in acidic condition, further diffusion of active compounds becomes easier and faster because the chitosan microparticles structures disintegrated greater in alkali condition.

The result of release test also indicates that encapsulation of oleoresin in chitosan microparticle and mixing the microparticles with starch and magnesium stearate excipients has improved the solubility of oleoresin in the aqueous release medium. It is known that the residence time of food in the stomach is less than two hours, so when the release can be kept low in the first two hours in SGF medium, greater the amounts of active compounds of oleoresin can be delivered to the intestine and colon.

#### 4. Conclusions

The oleoresin extract from red ginger showed high antioxidant activity and the preparation of loading the oleoresin into chitosan microparticles resulted in 95.8 % encapsulation efficiency and 4.9 % loading capacity. The release profile of antioxidant hard gelatin capsules containing chitosan-oleoresin microparticle in the gastrointestinal medium (SGF, SIF, and SCF) showed the burst release of the first 30 minutes for all capsule formulations. The capsule formulation of F2 with the composition of 89.5% chitosan-microparticle, 10% starch and 0.5% magnesium stearate showed the lowest release in SGF medium but the highest release in SIF and SCF medium. The formulation of ginger oleoresin encapsulated in chitosan microparticles and then mixing it with the excipients in the gelatin capsules has the potential as formulation for intestine-colon targeted release system for oleoresin.

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