Development of Curcumin Chewable Gels

Nattapaul Rattanamusik

A Thesis Submitted in Partial Fulfillment of the Requirements for the
Degree of Master of Pharmacy in Pharmaceutical Sciences
Prince of Songkla University
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This is to certify that the work here submitted is the result of the candidate's own investigations. Due acknowledgement has been made of any assistance received.

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I hereby certify that this work has not been accepted in substance for any degree, and is not being currently submitted in candidature for any degree.

.....Signature

(Nattapaul Rattanamusik)

Candidate

ชื่อวิทยานิพนธ์ การพัฒนาเจลแบบเคี้ยวได้ของเคอร์คูมิน
ผู้เขียน นาย ณฐพร รัตนมูสิก
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บทคัดย่อ

เคอร์คูมินอยด์เป็นสารที่สำคัญพบได้ในขมิ้นชัน (*Curcuma longa* L.) วงศ์ Zingiberaceae โดยหนึ่งในสารกลุ่มเคอร์คูมินอยด์คือเคอร์คูมินที่จัดอยู่ในคลาส II ของระบบการจำแนกชีวเภสัชภัณฑ์ เนื่องจากมีสมบัติละลายต่ำ แต่มีความสามารถในการซึมผ่านสูง การประยุกต์ใช้เคอร์คูมินโดยการเตรียมในรูปแบบของเจลแบบเคี้ยวได้ (chewable gel, CGs) ที่ปราศจากน้ำตาลโดยใช้เจลาตินและสารก่อเจลร่วม เป็นรูปแบบยาเตรียมที่เหมาะสำหรับผู้ป่วยที่มีภาวะกลืนลำบาก ทั้งผู้ป่วยมะเร็งและผู้ป่วยสูงอายุ มีความน่าสนใจในอุตสาหกรรมผลิตภัณฑ์เสริมอาหารในปัจจุบันและเป็นที่นิยมในท้องตลาด การศึกษานี้มีวัตถุประสงค์เพื่อพัฒนาเจลแบบเคี้ยวได้ของเคอร์คูมินในยาพื้นเจลาตินน้ำมันพืชเพื่อเป็นระบบนำส่งทางปากโดยการกระจายตัวของเคอร์คูมินอยด์ในอิมัลชันชนิดน้ำมันในน้ำของน้ำมันรำข้าวและเจลแลนกัม โดยมีสารแต่งกลิ่นรสและวัตถุกันเสียที่เหมาะสม ตรวจสมบัติทางเนื้อสัมผัสของผลิตภัณฑ์กำหนดโดยใช้เครื่องวิเคราะห์พื้นผิว ลักษณะเฉพาะของเจลแบบเคี้ยวได้บ่งชี้ความสม่ำเสมอของน้ำหนัก การทดสอบปริมาณเคอร์คูมินอยู่ในช่วง 90-120% ของปริมาณที่ระบุตามฉลาก สมบัติทางเนื้อสัมผัสและการปลดปล่อยเคอร์คูมินจากเจลแบบเคี้ยวได้ เป็นผลจากเจลแลนกัมและปริมาณเคอร์คูมินอยด์ เจลแลนกัมมีผลส่งเสริมการปลดปล่อยเคอร์คูมินอยด์ เมื่อเทียบกับสูตรตำรับที่ไม่มีเจลแลนกัม นอกจากนี้ในสภาวะช่องปากสูตรตำรับที่มีปริมาณเคอร์คูมินอยด์ต่ำจะมีการปลดปล่อยเคอร์คูมินอยด์ได้เร็วกว่าสูตรตำรับที่มีปริมาณเคอร์คูมินอยด์สูง ผลการวิจัยพบว่าสูตรตำรับเจลแบบเคี้ยวได้ของเคอร์คูมินอยด์ในอิมัลชันชนิดน้ำมันในน้ำของน้ำมันรำข้าวและเจลแลนกัมมีศักยภาพในการนำไปใช้ประโยชน์เป็นระบบนำส่งสารเคอร์คูมินทางช่องปาก

คำสำคัญ : เจลแบบเคี้ยวได้, ภาวะกลืนลำบาก, เคอร์คูมิน, เจลาติน, เจลแลนกัม

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ABSTRACT

Curcuminoids have known as versatile active compounds of *Curcuma longa* L. (Zingiberaceae) reported for anticancer and anti-inflammatory activities. Curcumin, an active compound in curcuminoids, is classified in class II of biopharmaceutic classification system (BCS) as its poor solubility and high permeability. Application of non-sugar gelatin based chewable gels (CGs) as a dosage form of curcumin for dysphagia, cancers and the elderly patients have become interesting as an attractive forms of CGs in dietary supplements and nutraceutical products. This study aimed to develop CGs of curcumin in gelatin base containing vegetable oils as an oral delivery system. The CGs were formulated by dispersion of curcuminoids in oil in water (O/W) emulsions of rice bran oil (RBO) with gellan gum, and other suitable flavoring agents and preservatives. Texture properties of the products were determined by using a texture analyzer. Characterization of the CGs indicated the consistency in weight and assay of curcumin contents was found within 90-120% of label amount. Texture profiles and curcumin release from the CGs were the results of levels of gellan gum and curcumin contents. The CGs with gellan gum contributed faster curcumin release compared with the CGs without gellan gum. In addition the CGs with lower curcumin contents exhibited faster curcumin dissolution compared with the CGs with the higher contents. The results from this study revealed that CGs of gelatin based with O/W emulsion of RBO and gellan gum can be useful to be applied as oral delivery system of curcumin.

Keywords : chewable gel, dysphagia, curcumin, gelatin, gellan gum

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Nattapaul Rattanamusik

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LIST OF ABBREVIATIONS AND SYMBOLS

CGs	Chewable gels
Cur	Curcumin
OM	Oral mucositis
RBO	Rice bran oil

CHAPTER 1

INTRODUCTION

Background and Rationale

Head-and-neck squamous cell carcinoma (HNSCC) is a type of cancers found in oral cavity, esophagus, larynx, pharynx, oropharynx and nasopharynx. HNSCC is the highest morbidity rate in Thai males (22.2% of cancer patients) as reported by the Thailand national cancer institute in 2019. Mortality rate from HNSCC is predicted to rise up to 595,000 in 2030 worldwide according to the World Health Organization (WHO), and approximately 324,000 lives in South East Asia. Oral mucositis is a common adverse effect of cancer. Chemotherapy (CRT) and radiation therapy (RT) basically improve survival rates of the HNSCC patients in addition to operative surgery. However, RT and CRT can cause clinical problems in HNSCC patients such as acute mucositis of the oral cavity, pharynx, and larynx. These problems can enhance the risks of local and systemic infection.

Natural products have been known to give benefits to geriatrics and cancer patients for various symptoms which cannot be adequately controlled by modern therapies. *Curcuma longa* L (Zingiberaceae), is recognized as a versatile ayurvedic herbal medicine. Curcumin is one of the main compounds in curcuminoids, the main active compound of Curcuma longa extract. It is known to have anti-inflammatory, antioxidant, anticancer activities.

Chewable gels are a dosage form suitable for elder adults and patients with difficulty of swallowing, dysphagia and oral wounds. This dosage form is official in the monograph of USP 42. Chewable vitamins are available and become popular in thepharmaceutical markets. Development of chewable gels of curcumin gains a big attraction. Curcumin-based drugs are currently being developed to allow the drug to be

available dosage forms as soft oral solutions, gels in soft gelatin capsules. These dosage forms are difficult in drug administration for some patients, including those who have difficulty swallowing and the elderly. Chewable gels are able to slowly dissolve and allow absorption through the mucous membrane in oral cavity. Suitable formulations of the chewable gels can help the release active substances and increase their permeability through the oral mucosa, directly to the bloodstream through buccal or sublingual. This dosage form can deliver the low-solubility and high first-pass metabolism drugs to the administration of difficult-to-swallowing patients and the elderly. The chewable gels may solve the difficulty swallowing and unsuitable doses of medication for these people, as well as the cancer patients after the radiation treatment, especially head and neck cancers. Actives in a unit dose of chewable gels can slowly dissolve in the oral cavity. Chewable gels can sustain drug release and enhance permeability through the oral mucosa. The actives can be directly absorbed to the bloodstream through buccal or sublingual routes. Therefore, the chewable gels can be benefit delivery for the low-solubility and high first-pass metabolism actives and support the administration of difficult-to-swallowing patients and the elderly.

Objectives

1. to formulate chewable gels containing curcumin
2. to evaluate physico-chemical properties and stability of the curcumin chewable gels

CHAPTER 2

REVIEW OF LITERATURE

Head-and-neck squamous cell carcinoma (HNSCC)

Most head and neck cancers are squamous cell carcinomas. This type of cancer begins in the flat squamous cells that make up the thin layer of tissue on the surface of the structures in the head and neck. Squamous-cell carcinomas arising from mucosal surfaces of four major anatomical sites: the oral cavity, esophagus, larynx, pharynx, oropharynx and nasopharynx are shown in Fig. 1 (Vokes et al. 1993; Chow 2020).

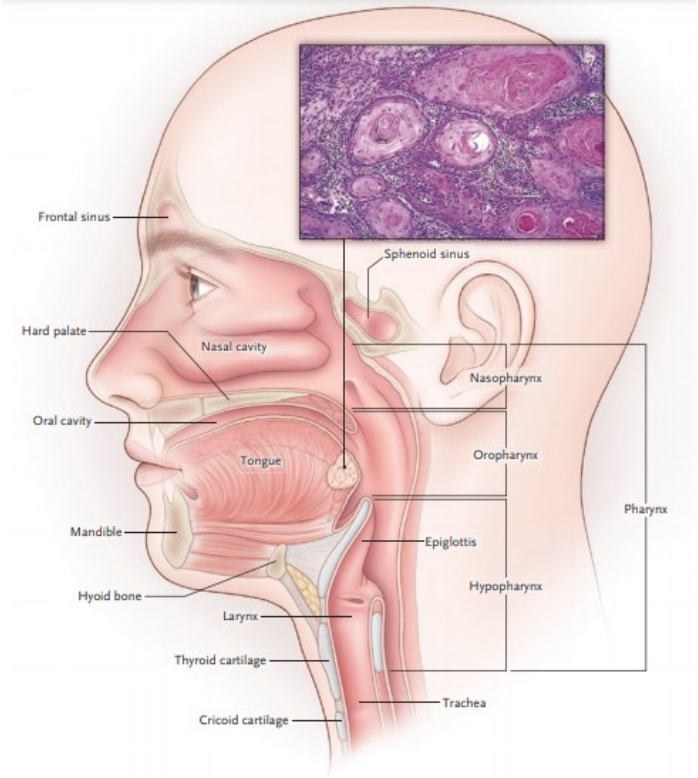

Figure 1 : Major anatomical sites of squamous-cell carcinoma of the head and neck cancers (Chow 2020).

HNSCC is the seventh most common cancer worldwide (890,000 new cases and 450,000 deaths in 2018). In Asia, the estimated number of new cases was 415,000 cases

with 231,000 deaths, accounting for 55% of cancer cases (Bray et al. 2020). The Thailand national cancer institute reported in 2019 that HNSCC was the most common cancer in 2019 (22.2% of cancer patients) (National cancer institute 2019). HNSCC was reported in 2016 as 3% of all cancers and over 1.5% of all cancer deaths in USA (51,540 new cases and 10,030 deaths) (Siegel et al. 2016). The incidence of oropharyngeal cancer was elevated in economically developed countries (Grénman et al. 2010). In Thailand HNSCC patients are reported to be associated with the high incidence of oral cancer in Northeast provinces (Fitzmaurice et al. 2017; Chaturvedi et al. 2013; Tangjaturonrasme et al. 2018). The major risk factors associated with HNSCC include smoking, heavy alcohol consumption and betel nut chewing. The prevalence of HNSCC has been increasing among patients aged over 60 years (Mountzios 2015; Smith et al. 2009). Human papilloma virus (HPV) is also one of the causes of HNSCC (Schroeder 2017; Ang et al. 2010; Kreimer et al. 2005; Muñoz et al. 2003). The evidences from epidemiological, pathological and molecular studies have led to the implication of HPV as an etiological factor for HNSCC, especially oropharyngeal sites (Mehanna et al. 2013; Termine et al. 2008).

Radiation therapy (RT) is a normal treatment course for patients with HNSCC. RT for HNSCC generally involves with daily fractions of 6,000–7,000 cGy total doses over 6–7 weeks (Pfister et al. 2013; Lalla et al. 2017), It is known to cause many oral complications including oral mucositis, oral pain, xerostomia (dry mouth), hyposalivation, increased risk of dental caries, reduced mouth opening, and osteoradionecrosis (Buglione et al. 2016a; Buglione et al. 2016b; Jensen et al. 2019). Intensity-modulated radiation therapy (IMRT) is considered to decrease the radiation dose to adjoining structures (such as the salivary glands, gum areas), potentially reducing the incidence and/or severity of oral complications (Duarte et al. 2014). The inflammation of oral cavity cells decreases the quantity and quality of saliva after completion of radiotherapy. Their salivary flow rates, pH, and buffering capacity are preposterously low. Consequently, the patients regularly suffer from dry mouth symptoms with poor oral conditions and other significant oral health problems (dental caries, atrophic mucosa, altered taste sensation, and traumatic ulcer) (Arrifin et al. 2018; Tarapan et al. 2019; Epstein et al. 2012). After patients

receivingchemotherapies, oral mucositis (OM) is one of the frequently important side effects. This side effect can be found in 30%–70% of patients who treated with RT of the head and neck area and in 40%–80% of patients who undergo chemotherapies. Beside that the cancer patients who were predicated with neurodegenerative disease such as Parkinson's or Alzheimer's disease, show the highly frequent dysphagia report. (Alvarez-Berdugo et al. 2016; Cuba et al. 2017; Barkokebas et al. 2015; Miyamoto et al. 2015).

Oral mucositis (OM)

OM manifests as extremely painful ulcerations or erythema of the oral mucosa. The classification of oral mucositis recommended by the World Health of Organization (WHO) or the National Cancer Institute Common Toxicity Criteria (NCI-CTC) are accepted to diagnosis patients (Table 1). The clinical features vary according to the type of cancer therapy used and the health of the patients (Bonomi et al. 2015; Al-Dasooqi et al. 2013).

Table 1 : The classification of oral mucositis according to WHO criteria

Score	WHO	NCI-CTC
GRADE 0	No sign or symptom	No objective findings
GRADE 1	Erythema and slight pain	Erythema with pain without ulceration
GRADE 2	Presence of ulcers and pain, still able to eat	Ulceration with pain requiring a solid food diet (preferably moist)
GRADE 3	Presence of ulcers and pain and unable to eat solid food	Greater ulceration with pain requiring a liquid diet
GRADE 4	Presence of ulcers, unable to swallow, with need of parenteral or enteral support	Severest ulceration or necrosis that prohibits alimentary intake

OM can enormously affect the quality of life of patients as well as the course of their cancer therapy. Oral pain is a normal symptom, making it difficult or impossible to eat, essential in some cases to malnutrition and undernourishment. Moreover, the

consequence of oral inflammation lesions area allows port to entry for opportunistic pathogens, leading to infections that may require antibiotics, hospitalization, and even discontinuation of cancer course treatment. The specifically effective therapy has not been developed to date. Some interventions are successful, although most of them are palliative treatment for reducing the pain and increasing the quality of life. Patients should be encouraged to maintain good oral hygiene and use anti-inflammatory agents, antibiotics, topical anesthetics, and preventive products for the mucosa (Bonomi et al. 2015; de Araújo et al. 2015). The pathogenesis of OM is significant to the development of new preventive and alternatives therapy. Oxidative stress and pro-inflammatory cytokines (such as TNF-α) are directly involved in mucosal destruction secondary to cancer treatment. Specifically, an increment in reactive oxygen species (ROS) emerges after RT or chemotherapy with a subsequent number of events that cause directly to tissue damage (Sonis 2004).

Five stages of development of OM are shown in Table 2. The progression of OM is not only as a direct to cell damage result but also as a sequence of complex biological events in the tissues and cells of the submucosa (Sonis et al. 2004; Sonis 2013). The formation of ROS rising from CT and RT activity would be capable of generating an oxidant-antioxidant imbalance and thereby activating proinflammatory cytokines responsible for tissue damage. Therefore, alternative strategies of prevention and treatment of OM have been aimed at the control or reduction of oxidative stress (Yarom et al. 2013; Aghamohamamdi et al. 2016).

Table 2 : Phases of development of oral mucositis (Sonis et al. 2004)

Phase 1	Initiation: Formation of reactive oxygen species (ROS) due to CT or RT oxidant–antioxidant imbalance
Phase 2	Response to primary damage: Activation of transcription factors such as NF-kB
Phase 3	Signaling and amplification: Regulation of proinflammatory cytokines: (TNF-a, interleukin 1-b and interleukin 6)
Phase 4	Ulceration: Ulceration of mucosa, inflammatory infiltrate rich in macrophages, neutrophils, mastocytes and bacterial colonization
Phase 5	Wound healing: Differentiation of cells and tissues with restoration of integrity of mucosa

Dysphagia

Dysphagia means difficulty in swallowing. It is related to the symptoms associated with the act of swallowing of solid and liquid foods which is related to the signs of coughing and choking (Walker 1990). Dysphagia can be found at any age with 4% of the population (Bhattacharyya 2014). It is estimated to be more prevalent in 15% of the elderly population (Haidt 2012), and 68% of the elderly living in nursing homes (Steele 1997).

Swallowing is a mechanism for transporting food from the oral cavity to pharynx, esophagus, and stomach with function of skeletal muscle system and nervous system. After that foods flow to the lower gastro-intestinal tract such as the small intestine. It is divided into 3 phases i.e., oral, pharyngeal, and esophageal phases involving both voluntary and involuntary movement. Oral phase is the first phase of a deliberate swallowing with biting and chewing. The jaw and tongue cavity are controlled to push the smaller pieces to the oropharynx. Foods will pass through to the pharyngeal stage regulated by automatic reflex in addition to mental power. Foods activate receptors along

the pharynx walls, signaling the swallowing center in the brain to deliver nerve impulses to the muscles. Buccopharyngeal contraction results in the movement of food down the esophagus. It is also controlled by the contraction of the soft palate and uvula, causing the epiglottis to slide to close the trachea. This mechanism takes very little time around 1-1.5 seconds. When foods enter the esophagus, the esophageal stage will begin with the upper esophageal sphincter is moving with peristalsis processes push food into the stomach (Jean 1984; Jean 2001; Thexton and Crompton 1998).

Dysphagia rehabilitation can be done by starting with the classification of patients to determine the cause of difficulty swallowing from various health problems. If dysphagia is caused by some diseases, it has to treat the diseases before starting the rehabilitation plan. Dysphagia rehabilitation can be divided into two processes, indirect and direct therapies. Indirect therapy focuses on rehabilitation of the muscles of the oral cavity and throat, by giving the patient breathing and muscle exercises to provide mechanisms for recovery. Masako maneuver is administered to promote the strength of the base of the tongue and the walls of the pharynx which are compressed and help to push the foods from the mouth into the throat. Vocal cord adduction exercise is a method of exercising the base of the tongue by using the sound of speaking to make the base of the tongue move better to help swallow Jaw opening exercise. Other exercises recommended the physiotherapists are necessary to improve and increase swallowing potency (Logemann 2008; Sze et al. 2016; Wada et al. 2012). Patients can feel the urge to swallow more by using this in conjunction with exercises on the tongue and throat muscles (Byeon 2016). Direct therapy of dysphagia focuses on the use of foods or fluids to practice swallowing for the patients. It is needed to adjust the foods to be easier to eat, such as grinding or cutting the foods into small pieces. Addition of colors can help the foods to look appetizing. Changing the solid foods into liquids can help the foods to flow down the

stomach more easily by gradually feeding the patient. The direct therapy can be used in conjunction with indirect therapy process (Thiyagalingam et al. 2021; Pelczarska et al. 2020; Jongprasitkul and Kitisomprayoonkul. 2020).

Curcuminoids

Turmeric (*Curcuma longa*) is a medicinal plant in the family of Zingiberaceae (Alexander 2016). Curcumin, an important substance in curcuminoids of the terpene functional groups has been reported on its anti-inflammatory, antioxidant and anti-cancer effects. It has a synergistic potential with CBD, with the mechanism of inverse agonist with CB1 receptors (Gertsch et al. 2010), inhibiting P-gp efflux and reducing drug destruction through the liver by hepatic first-pass metabolism (Alexander et al. 2014).

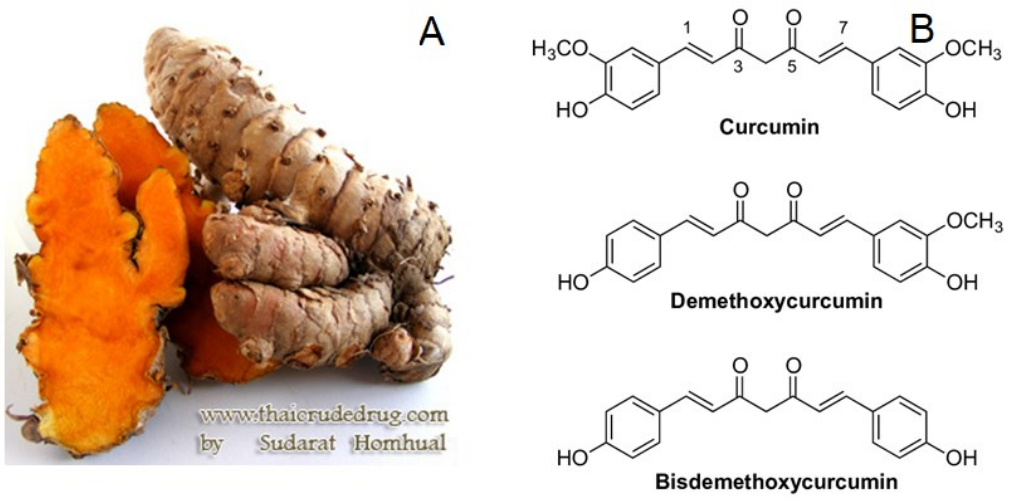

Figure 2 **:** A.) Turmeric (*Curcuma longa* L.) B.) Curcuminoids chemical structure
https://apps.phar.ubu.ac.th/thaicrudedrug/main.php?action=viewpage&pid=34

Curcumin has been reported to prevent and reduce oral mucositis in patient who treatment head and neck cancer. Schmidt et al. (2018) have reported mucoadhesive formulation containing curcuminoids (MFC) from *Curcuma longa* L. extract on oral mucositis in hamster. Overexpression of TGF-β1 in keratinocytes has been associated with chronic inflammation in the wound, which leads to delayed healing. MFC group was

exhibited lower labeling of this cytokine in epithelial tissue compared with all the other groups. (Schmidt et al. 2019; Pakyari et al. 2013)

David and Shree (2019) have reported the results of turmeric mouthwash compared with sodium bicarbonate mouthwash among oral mucositis patients. The formulas for research were prepared by mixing 5 g of turmeric powder with 50 ml of water for turmeric mouthwash and mixing 1.5 g of sodium bicarbonate powder with 50 ml of water for sodium bicarbonate mouthwash. Both of mouthwash solution were administration to patients and given twice times per day for 1 week. The results revealed that turmeric mouthwash was more effective than sodium bicarbonate mouthwash to reduce the level of oral mucositis (David and Shree. 2019).

Thomas et al. the efficacy of turmeric mouthwash on the OM patients with head and neck cancer and receiving radiation therapy. Turmeric mouthwash was prepared by dissolving the standard turmeric capsule (400 mg) in 80 mL of water. Compared with the positive control of benzydamine mouthwash. The OM patients were evaluated by WHO criteria. Turmeric mouthwash could induce anti-inflammatory and antioxidant properties by scavenging the free radicals, inhibiting tumor necrosis factor, and reducing the production of reactive oxygen species. It was more effective than positive control group on reducing the onset and severity of oral mucositis (Thomas et al. 2022).

Boven et al. (2019) have reported the efficacy of curcumin gum as a novel the formulation for protection of oral cavity in head and neck squamous cell carcinoma in clinical trial study on healthy volunteers. In this study, curcumin gum formulation was involved the use of claims approved with US Patent No. 9,700,525. As claimed in this patent, curcumin powder (10 g of curcumin for each batch) was mixed with peppermint chewing gum base with liquid corn syrup. An administration dose of 4 g of curcumin gum was used as it exhibited to be safe in humans and provided adequate serum levels on antioxidative effects (Nathan and Boudreaux 2015). The curcumin gum provenulated for improving curcumin release, prolonged mucosal contact, and increasing mucosal

absorption into the bloodstream. CXCL1 and TNF-α have been shown as potential biomarkers for curcumin chemoprevention study. Two chew methods, initial chew and revised chew, were used to estimate curcumin release. The initial chew method was to chew 4 g of curcumin gum for 30 min. The revised chew method included in first priming the mouth by chewing one 250-mg piece of gum, followed by chewing eight pieces (250 mg each for a total of 2 g) for 6-8 times, and finally leaving the gum with the buccal mucosa for 4 minutes. The chew-and-park cycle was repeated for 30 minutes. Then the gum (2 g) was spited out and the process was repeated again with a remaining gum (2 g) to receive the gum of an administered dose of total 4 g over 60 minutes. Higher curcumin release and absorption was found in revised chew samples. Chewing the gum helped to enhance curcumin release, while leaving the gum on the buccal mucosa involved in the higher serum levels at 4 hours. The serum levels of CXCL1 (GRO-α) and TNF-α were significantly decreased after administration of curcumin gum (Boven et al. 2019).

Delavarian et al. (2019) have reported the efficacy of oral administration of curcumin micelles for prevention of radiotherapy-induced mucositis in head and neck cancers. The clinical trial was performed in the patients during the radiation therapy. The patients received 80 mg/day of oral curcumin (nanoparticles) and the oral mucositis evaluation was scaled according to the National Cancer Institute Common Toxicity Criteria version 2. An ordinal score ranging between 0 (none) and 4 (the highest) was observed at any site within the oral cavity. Efficacy of oral curcumin micelles in prevention and management of oral mucositis by anti-inflammation was approved. In the group of patients receiving oral nanocurcumin, the delayed onset of mucositis and reduced severity of mucositis without grade 4 score, as compared to the control group receiving placebo was observed.

A variety of enzymes closely associated with inflammation and cancer, such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), 5 - LOX, and phospholipases A2 (PLA2) are known to be modulated by curcumin (Zhou et al. 2011). It

has been interested to apply curcumin in dentistry and oral health. Mechanisms of curcumin in anti-inflammatory in dental diseases have been reported (Molayem 2021). Curcumin can inhibit cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), expression. COX-2 is known to catalyze the formation of prostaglandins, which are important mediators in the inflammatory response, while iNOS is a key for the production of nitric oxide, an important signaling molecule that participates in the pathogenesis of inflammation in gingival. Curcumin is known to enhance degradation and reduce synthesis of both iNOS and NF-κB. (Ben et al. 2011; Zhou et al. 2011; Molayem 2021). Moreover, curcumin is known as a high potency antioxidant and strong free radical scavenger compounds, including reactive free radical oxygen species and reducing lipid peroxidation (Zhen et al. 2014). These mechanisms of curcumin contribute to the reduction of oxidative stress and cells damages, one of the signs of inflammation (Maheshwari et al. 2006).

Other interesting mechanisms of curcumin have been reported in management OM and the other symptoms such as dysphagia or xerostomia. The receptors type TRPV-1, TRPV-3, TRPA-1 are detected in human oral cavity such as oral mucosa, tongue, oral floor, gingiva and buccal. (Alvarez-Berdugo et al. 2016; Kiss et al. 2020). The sensory facilitation can be induced the swallowing reflex faster with agonist transient receptor potential (TRP) channels. Curcuminoids can induce TRPA-1 and TRPV-1 (Nalli et al. 2017; Leamy et al. 2011; Dong et al. 2013; Yeon et al. 2010; Mistretta et al. 2014). Therefore, Curcuminoids can stimulate the swallowing reflex and reduced dysphagia symptom in elders. (Talavera et al. 2020)

Developments of Curcumin dosage forms

Bioavailability of oral curcumin is low (Hu et al. 2015; Prasad et al. 2014). It has been reported that hydrophilic carriers, cellulosic derivatives, and natural antioxidants can significantly increase curcuminoid bioavailability compared to curcumin standard (Jäger et al. 2014). Several surfactants have been found to be useful in the lipid-based formulas to

increase solubility and absorption of curcumin. Different kinds of surfactants, including cationic, anionic, amphiphilic, as well as non-ionic surfactants are of interests for increasing the oral bioavailability. (Chaudhari and Dugar 2017).

Curcuminoids are considered as BCS class II of low solubility but high permeability drugs. Emulsions, lipid-based systems, comprising of oil and water phases with suitable emulsifying agents (surfactants as true emulsifiers, and polymers as auxiliary emulsifiers) are one of the efficient ways to improve solubilization and permeability of these low water solubility substances. The oil phase in water phase emulsion (o/w) can encapsulate the active ingredients dispersed in the fine droplets. Permeability and bioavailability properties of the actives can be improved. Not only that, suitable emulsions can provide a valuable oral lubricant property in the oral cavity, thereby reducing the patient dysphagia by this mechanism (Malone et al. 2003; De Hoog et al. 2006). Lubrication performance of the emulsions was found to become strongly dependent on the contents of the oil particles (Torres et al. 2018). The major problem of emulsion stability is the aggregation of oil droplets and creaming. It has been shown that surfactants have the properties of “steric effect” and “polarity of functional groups”. Steric effect is resulting in encapsulation of the oil droplet and protection of the droplet aggregation (Zhang et al. 2020a). The charges of functional groups indicate the charge of the surfactants, which cause the repulsion of the surfactant molecules of the same charge resulting in the distancing between the oil droplets (Dille et al. 2018; Zhang et al. 2020b).

Emulsions are the colloid systems between oil, water or the other immiscible liquids, but thermodynamically unstable systems. Small spherical (internal or dispersed phase) are dispersed in another phase (external or continuous phase). Emulsions are formed either, oil in water (o/w) or water in oil (w/o). Normal emulsions can be prepared by using mechanical forces such as mixing with a mixer (mixer), homogenization with

homogenizer or colloid mill machine. Most emulsions are instable in which coalescence, flocculation of internal phases, oil droplet aggregation or creaming are the main problems. Surfactants or emulsifiers or emulsifying agents can be stabilized to emulsions in order by reducing the surface tension of both parts of the liquids. Because emulsifiers have both hydrophobic and hydrophilic parts in their structure, they can conjugate polar liquids with non-polar liquids. Emulsions are useful in food, pharmaceutical and cosmetic manufactures (McClements 2004; McClements et al. 2007; Achouri et al. 2012, Mollakhalili et al. 2017). Emulsifiers are classified based on their chemical structure, mechanism of action, and sources ,such as synthetics, semi-synthetics, and naturals. Synthetics are further classified into anionic, cationic, amphoteric, and non-ionic emulsifiers (Mistry and Sheth 2011). Anionic emulsifiers, hydrophilic part of molecule is polar which is negatively charged in aqueous solutions or dispersions. These are either a carboxylate, sulphonate, sulfate or phosphate functional group in molecules. At neutral or acidic pH, or in the presence of heavy metal ions, decrease in the solubilizing efficacy of carboxylate group of the emulsifiers is found. The solubility of anionic emulsifiers is influenced by ionic environment in solutions. Both sodium and potassium salts are generally more soluble in water and less soluble in hydrocarbons. Conversely the calcium, barium, and magnesium salts are more compatible with hydrocarbon solvents and less with water. Ammonium and amine salts i.x. tri-ethanolamine improves the compatibility of anions with water and hydrocarbons. In addition, to improve the solubility of anionic emulsifiers, reducing of hydrophobic molecular weight is designed for using at higher electrolyte concentrations (Shah et al. 1994; Chang et al. 2005).

Natural emulsifiers are natural products which derived from plants, animal tissue, semi-synthesis or synthesis base on natural polymers. These emulsifiers hydrate as lyophilic colloids (hydrocolloids), disperse and swell in water to high viscosity gel layers that can conjugate with oil phase to form emulsions. Hydrocolloid type of emulsifiers has

no effect or less on reducing interfacial tension, but has protective colloidal effect, reduce the potential for coalescence of oil droplets by high viscosity system, fix merging of oil droplets by forming sheath around the oil droplets, imparting a charge to the dispersed droplets. In general hydrophilic colloids are limited to be used as emulsifiers in o/w emulsion. The naturally hydrocolloids have the advantages of being non-toxic to edibles, easy to handle and non-expensive. However their disadvantages including the large quantities to be effective as emulsifiers and the need of preservatives to inhibit microbial growth can limit their applications.

Natural emulsifiers from plants are starch, konjac, acacia, agar, alginate, tragacanth, guar, pectin, carrageenan, lecithin, etc. Emulsifiers from animal derivatives can be found as gelatin, lanolin, cholesterol, etc. Bacterial source can be found as xanthan, gellan or curdlan (Dickinson 1993; Sharma et al. 2007; Ozturk and McClements 2016; Chung et al. 2017; Taheri and Jafari 2019). These natural emulsifiers are useful in food, pharmaceuticals, etc.

Gums, the polysaccharides are found in nature such as botanical (trees, shrubs, or seeds), algae, and microbial sources. Plant based sources are used more and well known due to the variety of their structural and functional properties. Natural polymers are used in the pharmaceutical and food industries to control or adjust the rheological properties, texture properties and stability of products. The definition of gums are hydrophilic substances, which form a colloidal solutions or dispersions, colorless, tasteless and nontoxic. Highly molecular weights and their intermolecular interactions make the gums swell in water but can not dissolve to clear solutions.

Gum arabic, the other known as gum acacia, is consisted of highly branched and has plenty of carboxyl groups from polysaccharide such as D-galactose, D–glucuronic acid, L-rhamnose and L-arabinose. Carboxyl functional group on gum arabic molecules are dissociated at neutral pH and shows negative charge. Gum arabic easily dissolves under

stirring in water, producing colorless, bland-tasting mucilage. The dispersion gum has low viscosity-imparting property, which can be assembly made up to concentrations of 50% w/w with texture gel-like. Normal pH of gum arabic mucilage is about 4.5-6.0. Rheological properties of gum arabic exhibit newtonian fluid but contractions up to 40% acquire pseudoplastic character. Emulsifying property of gum arabic is effective to prepare oil-in-water emulsion which can be stable by prevent the coalescence of the oil droplets with gum viscosity.

Gum arabic mucilage can be added on the other polymers such as tragacanth, karaya, gellan, alginate, or xanthan for increasing the viscosity. An interest functional feature of arabic gum is capability to operate as an emulsifier for oils and flavors (Anderson and Stoddart. 1966; Whistler 1993; BeMiller 2002; Hosseini et al. 2015; De Oliveira et al. 2018). Yavaşer et al have been reported the composition between gum arabic and sodium alginate in loading of melatonin, BCS class II drug. Formulation of gum arabic and sodium alginate could entrap melatonin with entrapment efficiency of 77.82±4.47% at the drug concentration of 3.0 mg. The release of melatonin was 45% in the first 5 hours at pH 1.5 medium, and 40% in pH 7.4 medium (Yavaşer et al. 2016).

Tragacanth gum can be found in Astragalus spp. such as *A. gummifer*, *A. parrowianus*, *A. fluccosus* etc. It has a molecular weight about 840,000 daltons and an elongated shape of 4500 Å, providing a high viscosity. This appears to be a molecular chain of (l-4)-linked a-D-galacturonopyranosyl units, some of which are substituted at 0-3 with ß-D-xylopyranosyl units, some having either ß-D-galactopyranosyl end units or a-L-fucopyranosyl units as nonreducing terminals. Tragacanth gum is a branched polysaccharide consisting of insoluble tragacanth acid or bassorin (major fraction) which creates a gel and water-soluble tragacanthin. This gum has emulsifying properties that are due to a small amount of protein molecules in the gum. The pH of a gum tragacanth dispersion is normally 5-6. However, the tragacanth gum has excellent acid stability (down

to pH 2) and better thickening property than the other gums. Gum tragacanth is one of the effective suspending agents for pharmaceutical products. The increasing of viscosity in external phase can prevents and slows down undissolved excipient particles in oil phase from separation. The emulsifier properties effectively absorb the poorly water soluble substances, such as steroid and fat-soluble vitamins (Whistler 1993; Dickinson 2009; Kulkarni and Shaw 2016; Philp 2018; Taheri and Jafari 2019; Nejatian et al. 2020)

Sheorain et al have reported ionic complexation between tragacanth gum and chitosan which can be carriers in nano-formulation of thymol. The ratio of 1:2 tragacanth gum:chitosan showd the smallest particles of particles with average of 278 nm particle size from the particles under with 98% encapsulation efficiency. Thymol released with Korsmeyer–Peppas model at pH 7.4 drug with the sustained release profile (Sheorain et al. 2018).

Mohamed et al. developed the formulation of Tragacanth/acrylic acid loading with a low aqueous solubility amphotericin B. The researchers used γ-irradiation-induced copolymerization process to prepare tragacanth-acrylic acid hydrogel and load amphotericin B 5 mg/ml. Drug particles were suspended in hydrogel. Amphotericin B hydrogel did not show drug release at pH 1, whereas the drug release occured as soon as the hydrogel transferred to buffer solution of pH 7. Drug release was not only pH dependent, but also under the influence of the copolymer composition. With increasing acrylic acid in formulation, the release rate and total released drug increased. These results were attributed to the swelling behavior of copolymer in hydrogel (Mohamed et al. 2018).

Cikrikci et al. have reported delivery of insulin with hydrogel formulation by development alginate-gum tragacanth system. Ionotropic gelation method was selected for preparation the system and chitosan was chosen for the polyelectrolyte complexation

for increasing gel strength. Hydrogels were prepared by immersing the polymer including alginate and gum tragacanth with different ratios into the gelation solution containing $CaCl_2$. This hydrogel could entrap insulin and protected it from acid pH. The cumulative release of insulin in simulated intestinal fluid (pH 6.8) was 70% as controlled release manner.

Most of the gums can disperse and swell easily in water. Colloidal solutions depending on their chemical properties are useful as thickening, gelling, emulsifying and the controlled release of active compounds, nutrients and flavors (Nussinovitch 2009; Saha and Bhattacharya 2010; Valencia et al. 2019).

As most oral emulsions are a liquid dosage form, some disadvantages such as uncomfortable for portable, low compliance and difficulties in pediatrics, geriatrics and dysphagia patients. Therefore, it is ideal to incorporate the emulsions in a solid dosage form as the chewable gels of edible gelling agent such as gelatin.

Gelatin, a one of natural material, is derived from collagen, which is the most abundant structural protein (biowaste), which can be extracted from skins, bones or connective tissue of animals. Gelatin can be divided into two types according to the production process. The acid extraction process can produce gelatin is type A. Another process using alkali for extraction can produce gelatin type B. The gelatins A and B have different physicochemical properties such as gel strength, viscosity, pH gelatin and Isoelectric point. Gelatin type A has Isoelectric point ≈ 9.0 and type B has about ≈ 4.7 (Ahmad et al., 2017; Van Nieuwenhove et al., 2016; Huang et al., 2019; Ma et al., 2019). Gelatin is gathered by amino acids as the most group as glycine (27–35%), proline and hydroxyproline (20–24%) to combined hydrolysate polymer chains and to build the structure of gelatin by α – chains (80–125 kDa), β - chains (160–250 kDa) and γ-chains (240–375 kDa) (Gudipati, V. 2013).

Table 3 : Gelatin A and gelatin B properties (GMIA 2012)

	Type A			Type B		
	Gel strength (g)	Viscosity (mp)	pH	Gel strength (g)	Viscosity (mp)	pH
Hard capsule	240-300	44-55	4.5-5.5	200-250	45-60	5.3-6.5
Soft capsule	150-200	25-35	4.5-5.5	125-175	30-45	5.3-6.5
Tablet	75-150	17-35	4.5-5.5	75-150	20-35	5.3-6.5
Photographic film	-	-	-	240-300	78.0-95.0	5.65-5.85

Gelatins have many advantages for the foods, cosmetics and pharmaceuticals, because they are nutritional proteins, edible and easy to be cross-linked and modified with the other functional groups by their amine and carboxyl functional groups. The biodegradability and biocompatibility are important properties to guarantee the safety of gelatin (Foox, 2015; Song et al., 2018). The structure of gelatin has amine functional group to cross-linked with the other polymer with H-bond in chains or amino acid chains. Uranga et al. have reported FTIR analysis of gelatin showing the broad absorption band characteristic at 3500–3000 cm^{-1} which can be attributed to the free and bounded -NH groups of gelatins and -OH groups of gelatin can be able to catch hydrogen bonds (Urangaet al. 2020)

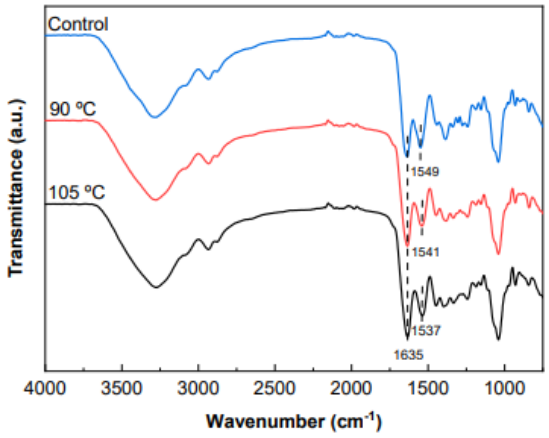

Figure 3 : FTIR spectra of control and thermally treated gelatin CGs (Uranga et al. 2020)

For the interested example for the gelatin modification is phenolic modification. Phenolic compounds are widely present in plants, including the leaves, fruits and seeds, Hydroxyl groups of phenolic compounds can interact with the carboxyl groups of gelatin with hydrogen bonding, and hydrophobic interactions may occur between aromatic rings of phenolic and the hydrophobic side chains of gelatin as shown in Fig 4. (Huang et al., 2019).

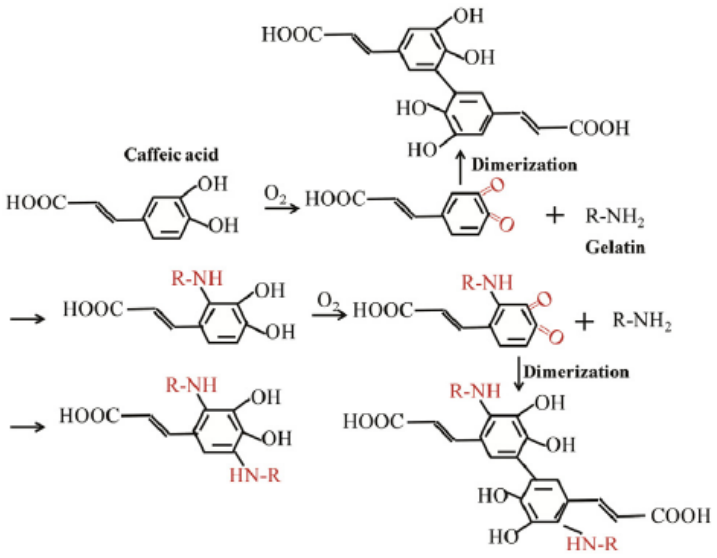

Figure 4 : Reaction of a phenolic acid with amino side chains of gelatin (Huang et al., 2019)

Gelatin interaction with oil has been reported. In Fig 5 the oil is inserted into the gelatin matrix. Hydrogen bonds from protein–protein interactions are reduced and a change of gelatin matrix takes place. Then, amino acids in the chains are moved to bond between their hydrophobic phase or hydrophilic phase (Tongnuanchan et al., 2014; Ramos et al., 2016).

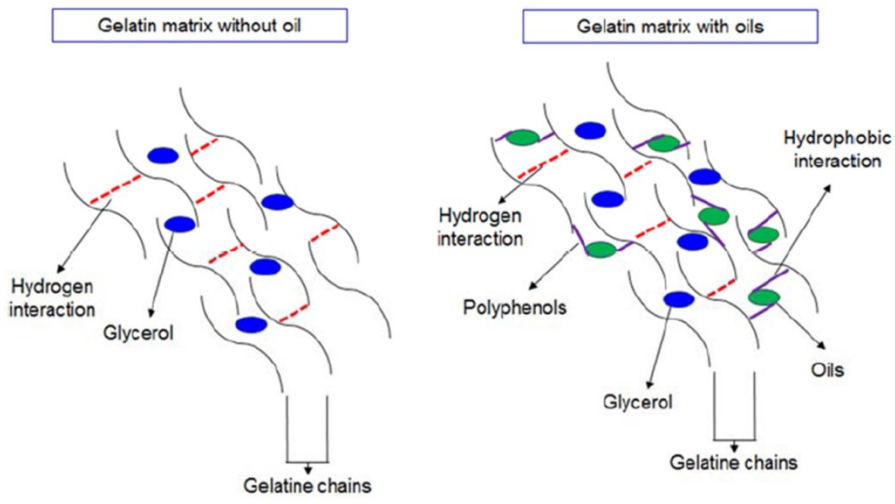

Figure 5 : Oil and gelatin interaction with hydrophobic interaction (Ramos et al., 2016)

The gelatin can be applied to deliver the active ingredients by using the many properties of gelatin to encapsulate actives or nutraceutical ingredients and formulation to the new products. The active substance can be combined in chewable gels in 3 forms, i.e., suspended throughout the gel matrices as solid aggregates particles, dissolved in the water phases of the gel matrices, or dissolved in or dispersed as lipid-based emulsion droplets, which are then suspended throughout the gel matrices (Dille et al. 2018). The emulsion systems may increase stability of the actives when they are conjugated or entrapped with gelatin matrices. Gelatin can support emulsion stability by thickening the water phase along with provide the steric hindrance to prevent the oil droplet aggregation and thus decrease the creaming of emulsions (Huang et al. 2020; Zhang et al. 2020b; Zhang et al. 2020c).

Chewable gels

The United State Pharmacopoeia (USP) defines the chewable gels in general chapter <1151> (USP42-NF37, 2019). Chewable gels are used to deliver the drug substances and dietary supplements via the oral route. They are elastic which can

maintain their molded shapes and yield to mastication. The chewable gels are considered to be chewed before swallowing. Their compositions are of all or some of the following excipient compositions, gelling agent(s) such as gelatin, pectin, and agar (5-8 %), water (15-20%), sugars (28-50%), sweeteners such as corn syrup solids (40-55 %), and suitable flavoring agent(s). Gummies are the term of chewable gels in the confectionary and dietary supplement industries. They are not used as the official article titles. Examples of chewable gels official in USP monographs are Ascorbic Acid Chewable Gels, Cholecalciferol Chewable Gels, Cyanocobalamin Chewable Gels, and Oil-and Water-Soluble Vitamins with Minerals Chewable Gels. The USP monographs have issued the requirements for chewable gels with important quality audits, such as label amount of product, weight variation, dissolution, etc. These standard requirements can be used to assess the quality of the chewable gels.

Dille and Draget 2021 studied the oral lipid delivery with gelatin-based gelled emulsions. Gelatin acting as both emulsifying and gelling agent in the same system. A direct connection between oil and water was achieved, keeping droplets of oil arrested and stable throughout the gel during storage. Gelatin gelled emulsions were prepared by 80% of the water and gelatin were mixed and kept in a water bath with magnetic stirring at 60 °C. When the gelatin was fully dissolved, corn oil was added and the solution was kept stirring at 60 °C for a further 10 min, before emulsification was performed using a homogenizer. Then, the solution was split in two part and the remaining water was add (with or without sodium-***κ***-carrageenan pre-dissolved). This system is advantageous for slowly digested oils to increase oral bioavailability. (Dille and Draget 2021; Zhang et al. 2015; Cho et al. 2015)

Chewable gels can encapsulate both hydrophobic and hydrophilic active ingredients. The bitter or untasted flavors of drugs can be reduced by gelling agents which cover the drug particles and customised by sweetening agents and flavoring agents.

Matulyte et al. 2021 developed chewable gel for delivery nutmeg essential oil. Emulsions were prepared using sodium alginate, maltodextrin, water, and nutmeg essential oil. Essential oil concentrations in the emulsion were 0%, 20%, and 25%. Sodium alginate and maltodextrin ratio ranged from 1:0 to 1:10. The basis of the gel tablets were prepared using gelatin, water, and glycerol (ratio 1:1:1) or gelatin and water (ratio 1:2). Gelatin was poured in either distilled water, or distilled water mixed with glycerol, and swollen for 10–15 min. Gelatin (27% w/w) was melted, and thyme-sugar syrup (68.5% w/w) and thyme extract (2.5% w/w) were added. Then, citric acid 50% solution (2% w/w) was added. The nutmeg essential oil (0.469% w/w) or nutmeg essential oil microcapsules (3.75% w/w) were added in the basis of chewable gel tablets before pouring the mixture into forms. After chewable gels were poured and removed from silicone mold, they were kept in an airtight box in the dark at room temperature (25 ± 2°C). The release of volatile compounds from chewable gel tablets were analyzed by headspace-gas chromatography with mass spectroscopy in control and artificial saliva conditions in vitro. Nutmeg essential oil microcapsules had influence on the physical properties. Chewable gels could prolong the release of nutmeg oil (Matulyte et al. 2021).

Niam et al studied the formulation of chewable gummy with three active ingredients for dietary supplement, Bastard Cedar Leaves (*Guazuma Ulmifolia*), Senna Leaves (*Cassia Angustifolia*) and Lime extracts (*Citrus limon* L.). These herbs had flavonoid compounds and phenolic groups are pharmaceutical compounds with antihyperlipidemic, laxatives, and anti-obesity activity. Those herbs were advantaged for obesity patients. Gelatin, potassium sorbate, sorbitol, nipagin, xanthan gum, citric acid, propylene glycol, and aquadest water are the main ingredients in the base. Researchers were varied xanthan gum (0, 1, 2, 3, 4 g), Syrup simplex (60, 59, 58,57, and 56 g) and used each trio herb 20 g. The chewable gummies were prepared by dissolving gelatin and xanthan gum according to the concentration then, according to the formula's prescribed concentration, add the

three active ingredients, lime juice, potassium sorbate, sorbitol, nipagin citric acid, propylene glycol, coloring, and lemon taste. Stir until homogeneous. After that put it in the mold. Let stand for 1 hour at room temperature, then put in the refrigerator for 24 hours. pH, viscosity, weight uniformity, and texture were tested in this research. the results shown pH value of gummy candies was in the range of 4.26–4.57, the viscosity value of the gummy preparations was in the range of 1–5 mPa.S, weight uniformity test met the requirements. The texture test results were concluded that the addition of xanthan gum in various variations affected the hardness, gumminess and chewiness of the chewable gummy preparation. (Niam et al. 2022) The non-polar volatile oil can be encapsulated by gelling agent and chewable gels.

As the formulas of the chewable gels contain water, addition of preservatives should be considered to prevent the growth of microorganisms. Preservatives such as antimicrobials, antioxidants, chelating agents along with buffering systems suitable in foods are needed to improve storage stability of the products. Preservatives can be used in limited quantities to reduce microorganism contamination in foods, i.e., benzoic acid, sorbic acid, propionic acid, nitrites, and nitrates. Anti-oxidation and chelating agents can prevent oxidation and discoloration during processing and storage (Carocho et al. 2014). The antioxidants work under two mechanisms of action, direct delivery of electrons to free radicals, such as butylated hydroxy anisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), tocopherol and tert-butylhydroquinone (TBHQ). Another mechanism is to accelerate the prooxidant reaction. Chelation of metal ions, classified as prooxidant, can be performed by chelating agents such as ascorbic acid, citric acid, ethylenediaminetetraacetic acid (EDTA) as antioxidants. Among the most popular commercial foods were BHT, BHA, TBHQ, gallates, tocopherols, ascorbic acid, citric acid, and EDTA (Shahidi 2015). The production of chewable gels required heating process. In the manufacturing process of the formulation containing thermal degradative substances

must be taken into account. Synthetic antioxidants were more resistant to heat than natural antioxidants, but they may be evaporated quickly, except for BHA and BHT, due to their melting points below 100°C, which may decompose to form toxic degradation products (Kiewlicz and Szymusiak)

CHAPTER 3

RESEARCH METHODOLOGY

Methods

Preparation of CGs Rice bran oil (RBO) was selected as the oil phase of the primary emulsion. The emulsion gels of RBO was prepared in 5 steps as followed. The first step was to prepare primary emulsions by using wet gum method using gum acacia as an emulsifying agent. The weight ratio of oil: water: acacia was fixed as 4:2:1. The second step was to slowly add the solution of the rest components except gelatin into the primary emulsion and continuously mixed until homogeneous emulsion is obtained. The third step was to mix the emulsion with the prewarmed gelatin gel at 60°C. After emulsion gel was obtained, the natural flavoring agent was added drop by drop under mixing. The fourth step was to fill the warm mixture in silicone molds. The filled molds were kept in the refrigerator at 4-8°C for 24 hours. The last step was to remove the obtained the Chewable gels (CGs) from the molds and stored in tight-light resistant glass containers in the refrigerator for further characterization.

Table 4 : Chewable gel formulas

Ingredients	F1	F2	F3	F4	F4M	F4L	F5	F5M	F5L	F6	F6M	F6L
Curcuma longa L. extract (Cur)	5	5	5	5	2.5	1	5	2.5	1	5	2.5	1
Acacia	5	5	-	-	-	-	-	-	-	-	-	-
Tragacanth	-	-	1	1	1	1	1	1	1	1	1	1
Sodium alginate	1	-	1	-	-	-	-	-	-	-	-	-
Gellan gum	-	1	-	1	1	1	1	1	1	1	1	1
Gelatin	20	20	20	20	20	20	25	25	25	30	30	30
Rice bran oil (RBO)	20	20	20	20	20	20	20	20	20	20	20	20
Glycerin	10	10	10	10	10	10	10	10	10	10	10	10
Xylitol	1	1	1	1	1	1	1	1	1	1	1	1
Flavoring agent	1	1	1	1	1	1	1	1	1	1	1	1
Citric acid	1	1	1	1	1	1	1	1	1	1	1	1
EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Benzoic acid	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water q.s.	100	100	100	100	100	100	100	100	100	100	100	100

Determination of average weight Average weight of the CGs was determined according to weight variation test in the general chapter <2091> weight variation of dietary supplements of USP44-NF 39, (2021). Not less than 20 CGs were collected randomize. Each of CGs was weighed individually and their weights were recorded. The average weight of the CGs and the standard deviation were calculated. The requirements were met if

individual weight varied from the average weight, not more than 7.5%. In case that more than 1 unit exceeded the specified limit, the test failed. If 1 unit fell outside of the limits, the procedure was repeated with an additional set of not less than 20 and not more than 30 individual CGs. The requirements were met if none of the units tested in the second set differed from their average weight by more than 10%.

Analysis of texture properties Textures of the CGTs were analyzed using the texture analyzer (TA.XT.plus Texture analyser, Stable Micro System, Surrey, UK) at room temperature (25°C). The condition of measurement was set as followed: cylindrical probe (25 mm diameter), compression rate at 2 mm S^{-1}, withdrawal rate at 2 mm S^{-1}, maximum strain of 75%, waiting time between the first and the second compression for 5 seconds. Hardness is the maximum force during the first compression. Stickiness is the work/force necessary to overcome the attractive forces between the surface of the product and the surface of the material (the probe) with which the product comes in contact. Firmness describes a product which displays substantial resistance to deformation. Springiness or elasticity is the ration of the distance to the peak force during the second compression and the distance to the peak force during the first compression.

UV-visible spectroscopy Curcumin concentrations were determined by UV-visible spectroscopy (Kadam et al. 2018). The standard curcumin 10 mg were accurately weighed and transferred in a 100 ml volumetric flask. The Stock solution was diluted to 10 ml with ethanol to obtain the concentrations of 0-250 μg/ml. Ethanol was used as blank. Wavelength corresponding to maximum absorbance of curcumin in ethanol was monitored at 424 nm. The standard calibration curve of curcumin was obtained by measuring the absorbance of curcumin solutions in concentration ranges prepared from stock solutions in ethanol at 424 nm with triplicate. Calibration curve of curcumin concentrations and their absorbance was plotted.

Curcumin contents CGs were weighting ,cutting into small pieces and dissolve them in 15 ml of water. Dispersion CGs were added to warming water bath for 1 hour at 60°C or until CGs complete dissolve. After CGs dissolve pipetted 5 ml of the sample and diluted in ethanol until the volume is 15 ml. The CGs solutions were sonicated with Ultrasonic bath for 1 hour and brought to test UV-absorbance.

Dissolution study Dissolution study of the CGs was performed according the general chapter <2040> Disintegration and Dissolution of dietary supplements, USP44-NF 39, (2021). Compliance requires the testing of 6 individual units, measuring the dissolution of the CGTs ingredient as the average of the 6 units tested. Dissolutions were observed in a medium of 200 ml of artificial saliva (pH=7.0±0.5), apparatus 2 at 100 rpm for CGs for 24 hours at 37± 0.5°C and medium of 900 ml of Stimulated gastric fluid (SGF) (pH=1.2±0.5), apparatus 2 at 100 rpm for CGs for 24 hour at 37± 0.5°C. Aliquot parts of 5 ml were withdrawn at a predetermined time interval with replacement (0, 30, 60, 90, 120, 180, 240, 360, 720, and 1440 minutes). All samples were filtered through membrane filters of 0.45 μm pore size and determined for curcumin release (Figueiras et al. 2010; Xu et al. 2020). Artificial saliva was prepared by dissolving Disodium hydrogen phosphate (2.382 g), Potassium dihydrogen phosphate (0.19 g), Sodium chloride (8.0 g) in 1000 ml of distilled water and then adjust pH to 6.75±0.05 with Phosphoric acid (Pan et al. 2015). SGF was prepared by dissolving Sodium chloride (3.0 g) in 1450 ml of deionized water and then adjust pH to 1.2±0.1 with Hydrochloric acid (Koland et al. 2011). Both of the mediums were added Sodium Lauryl Sulfate (SLS) 2% w/w for increase the solubility of curcumin. (Rahman et al. 2009).

Morphology and microstructure characterization All sample of the CGs were dried by freeze-dried and cross cutting. The microstructures of the samples were characterized by Scanning Electron Microscope (SEM) Thermo Fisher Scientific -QUANTA 400.

Microbial limit test Microbial limit test is performed according the general chapter <61> Microbiological examination of non-sterile products: microbial enumeration tests and chapter <62> Microbiological examination of non-sterile products: tests for specified microorganisms (USP42-NF 37, 2019). The microbial enumeration tests are according to the requirements of USP 42. The aqueous preparations for oral use route contain total aerobic bacteria content of not more than 10^2 cfu/g and total molds and yeasts not more than 10^1 cfu/g. The CGTs are collected for microbial enumeration tests by most probable number method and tested for specified microorganisms by checking *Escherichia coli*, *Staphylococcus aureus*, Clostridium spp., and Salmonella spp.

- Growth promotion test

The test is used the same solution as the sample preparation for testing, after insertion of bacterial growth must be observed.

- Negative control

The test is used the same solution as the sample preparation for testing, after insertion of bacterial growth must not be observed.

- Sample preparation

CGs are weighed for 10 g. CGs are dissolved in NaCl-Peptone solution pH 7.0, Phosphate Buffer Solution pH 7.2 or 90 g of Soybean-Casein Digest Broth and mixed well. The solutions are diluted to concentrations (10^{-2}-10^{-3}) by same diluent and mixed well.

- Most Probable Number (MPN) method

Sample solutions are prepared at least 3 concentrations, each concentration 10 times apart (0.1, 0.01, 0.001 g/ml). 1 ml of each concentration of samples are transferred by pipette and added them to 9 ml of Soybean-Casein Digest Broth by 3 repetitions. The samples are kept in suitable conditions at 30-35 °C for up to 3 days and compared the results by table MPN values of microorganisms from USP.

Test for specified microorganisms

- *Escherichia coli*

CGs are weighed for 1.0 g. CGs are dissolved in Soybean-Casein Digest Broth 9 ml and mixed well, then cultured at 30-35 °C for 24 hours. After 24 hours, all samples are transferred 0.1 ml by pipette into MacConkey Broth 9.9 ml and mixed well, then cultured at 42-44°C for 18-24 hours. After that, 1 ml of each sample is transferred for subculture with a MacConkey Agar and incubated at 30-35°C for 18-48 hours. The products are complied with the test if no colonies are present or if the identification tests are negative.

- *Staphylococcus aureus*

CGs are weighed for 1.0 g. CGs are dissolved in Soybean-Casein Digest Broth 9 ml and mixed well, then cultured at 30-35°C for 18-24 hours. After that, all samples are transferred 1 ml for subculture on a Mannitol Salt Agar and incubated at 30-35°C for 18-72 hours. The results are complied with the test if no colonies are present or if the identification tests are negative.

- Clostridium spp.

CGs are weighed for 1.0 g. CGs are mixed with sterile polysorbate 80 (1:5) at 40-45 °C. All samples are transferred 2 ml by pipette into Soybean-Casein Digest Broth 18 ml and mixed well. All sample are divided 10 ml to A and B samples. All of A sample are heated at 80 °C for 10 minutes, then cooled rapidly. All of B samples are incubated in Reinforced medium for Clostridia and cultured with anaerobe condition at 30-35 °C for 48 hours.
Both A and B samples are transferred 1 ml for subculture on a Columbia agar and incubated with anaerobe condition at 30-35 °C for 48-72 hours. The results are complied with the test if no colonies are present or if the identification tests are negative

- Salmonella spp.

CGs are weighed for 1.0 g. CGs are dissolved in Soybean-Casein Digest Broth 9 ml and mixed well, then cultured at 30-35°C for 18-24 hours. After 24 hours, all samples are transferred 0.1 ml by pipette into Vassiliadis Salmonella Enrichment Broth 9.9 ml and

mixed well, then cultured at 30-35 °C for 18-24 hours. After that, all samples are transferred 1 ml for subculture on a Xylose Lysine Deoxycholate Agar and then incubated at 30-35°C for 18-24 hours. The results are complied with the test if no colonies are present or if the identification tests are negative

Stability study The 6-pieces CGs are stored in the tight, light resistant aluminium foil ziplock bag in stability chamber (Memmert HPP260, Germany) under the conditions of USP accelerated stability (30.0±0.2°C, 75±5% RH). The sampling is randomized and the samples are analyzed for curcumin contents at day0, day15, day30, day60, day90 and day180. The data are calculated and presented as percentages of remaining contents of curcumin. The CGs are submitted to be characterized and compared to the initial properties. The Accelerated condition for 6 pieces of CGs are stored in the tight, light resistant aluminium foil zip-lock bag in stability chamber under the conditions of USP accelerated stability (30.0±0.2°C, 75±5% RH) for 12 hours and refrigerator (4-8°C) for 12 hours. The sampling is randomized and the samples are analyzed for curcumin contents at day0, day15, day30. The data are calculated and presented as percentages of remaining contents of curcumin. The CGs are submitted to be characterized curcumin content and compared to the initial properties.

Statistical analysis. The data were presented in the form of mean±standard deviation (at least in triplicate). Comparisons of more than two data groups were analyzed using an analysis of variance (ANOVA). If there are differences, the mean of each group is compared using Duncan multiple range test. The results are considered to show a statistically significant difference. if *P*-value≤0.05 using a SPSS program for statistical analysis.

Materials and Equipment

Materials *Curcuma longa* L. extract (Antiox® Government Pharmaceutical Organization (GPO), Bangkok Thailand), Acacia, Tragacanth, Gelatin type B (Pharmaceutical grade: Sigma, Missouri, USA), sodium alginate, gellan gum, Rice bran oil (King, Bangkok, Thailand), Glycerin, Mannitol, Flavoring agent: lemon extract (McCormick, US), Citric acid, Benzoic acid, Polysorbate 80 (Tween 80), EDTA, 70% Ethanol, Disodium hydrogen phosphate (Wellington new Zealand), Potassium dihydrogen phosphate(Auckland, new zealand), Sodium chloride (Pathumwan, Bangkok Thailand), Hydrochloric acid 1M (RCI labscan limited, Bangkok Thailand)

CHAPTER 4

RESULTS AND DISCUSSION

CGs of curcuminoids in o/w emulsions of RBO were prepared using gum acacia and tragacanth as emulsifying agent in gelatin CG base. Acacia, a polysaccharide hydrogel, was known as a good emulsifying agent of low toxicity and one of the most selected emulsifiers in primary emulsion. General ratio of oil: water: acacia as 4:2:1 was used in emulsification of the vegetable oil in which curcuminoids, the lyophilic actives, could be incorporated in this oil phase. Gum tragacanth was known to confer very high viscosities in an aqueous solution, and it was described as a complex, highly branched, heterogeneous hydrophilic polysaccharide. high viscosity o/w emulsion made the texture like mucus and lubricant for dry mouth (Gavlighi et al. 2013; Godarzi et al. 2021). Incorporation of tragacanth in primary emulsion could help to enhance the emulsion stability of Cur.

Physical appearance of CGs

Physical appearance of the Cur CGs is shown in Fig 6. CGs were difference in Cur contents incorporated. F1-F3 were formulated at 5% w/w Cur. Different Cur contents in which 1% w/w Cur in F4L, F5L, and F6L, 2.5%w/w Cur in F4M, F5M, and F6M, and 5% w/w Cur in F4, F5, and F6 were designed. Consistency of the CGs was found in shape without unevenness. The CGs has smooth surfaces in mustard-yellow color, lemon flavor and sweet-sour taste without bitter or unpleasant flavors. The CGs were kept in strip sealed PP plastic bags and stored protect from light in refrigerator at 4-8°C for further studies.

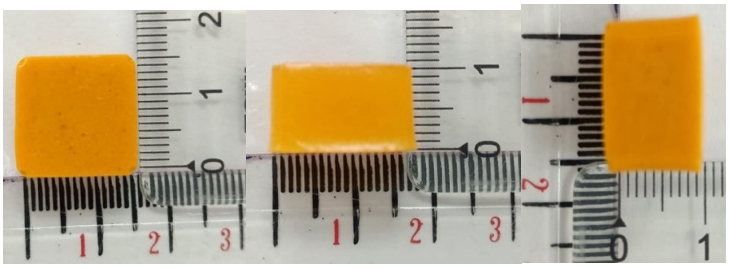

Figure 6 : Physical appearance of curcumin CGs

Data of average weight, pH, and curcumin contents of CGs were shown in Table 5. Consistency of weight of the CGs was found. The curcumin contents of CGs were in the range of NLT 90% and NMT 120% Label amount. All CGs had pH around 4 of which pH values were not significantly different (p-value≤ 0.05). Acidic pH value of CGs is known to enhance stability of the active ingredient (Kumavat et al. 2013). Degradation study of curcumin at various pHs (1, 1.2, 6.8, 7, and 7.4) was studied. It has been reported that decomposition of curcumin was pH dependent and occured faster at neutral-basic conditions. Higher stability of curcumin reported at acidic pH was claimed to be contributed the diene functional group in curcumin structure. However, when the pH was adjusted to neutral basic condition, proton removed from the phenolic group leaded to the destruction of this structure (Kumavat et al. 2013). Citric acid was used as sour flavoring

in food industrial. Sour flavor of the CGs could be compensated bitter taste of turmeric extract.

Table 5 : Average weight, pH and curcumin contents of CGs

CG formulas	Average weight (g)	pH	Curcumin content (%w/w)	Curcumin content (mg/g)
F1	2.34 ± 0.04	4.46 ± 0.06	4.72 ± 0.28	48.48 ± 2.97
F2	2.29 ± 0.04	4.34 ± 0.01	4.66 ± 0.37	46.59 ± 3.39
F3	2.28 ± 0.05	4.36 ± 0.02	4.68 ± 0.42	46.79 ± 3.82
F4	2.30 ± 0.05	4.46 ± 0.06	5.14 ± 0.28	51.39 ± 2.58
F4M	2.38 ± 0.05	4.34 ± 0.01	2.51 ± 0.04	25.09 ± 0.36
F4L	2.38 ± 0.04	4.34 ± 0.02	1.01 ± 0.06	10.10 ± 0.55
F5	2.46 ± 0.05	4.47 ± 0.06	5.12 ± 0.24	51.17 ± 2.24
F5M	2.34 ± 0.04	4.34 ± 0.01	2.50 ± 0.15	24.97 ± 1.38
F5L	2.36 ± 0.04	4.35 ± 0.02	1.13 ± 0.06	11.32 ± 0.56
F6	2.40 ± 0.03	4.35 ± 0.01	4.96 ± 0.11	49.64 ± 1.00
F6M	2.37 ± 0.04	4.34 ± 0.02	2.81 ± 0.25	28.14 ± 2.29
F6L	2.36 ± 0.03	4.36 ± 0.05	1.00 ± 0.04	10.04 ± 0.34

Table 6 : Texture properties of CGs

Parameter	F1	F2	F3	F4	F5	F6
Firmness (g)	1567.32± 91.30	1525.03± 595.27	2307.43± 48.32	1403.92± 89.01	3788.09± 395.74	6247.40± 329.35
Springiness (g)	67.56± 11.67	38.25± 5.15	50.51± 4.81	49.61± 5.85	108.52± 11.39	46.26± 1.49
Hardness (g)	6913.90± 547.43	7483.21± 1677.77	8533.03± 1618.54	7391.80± 904.92	9091.78± 1096.41	13306.65± 484.95
Stickiness (g)	41.78± 13.37	60.75± 0.18	50.36± 9.19	49.63± 2.79	55.13± 8.07	52.86± 73.33

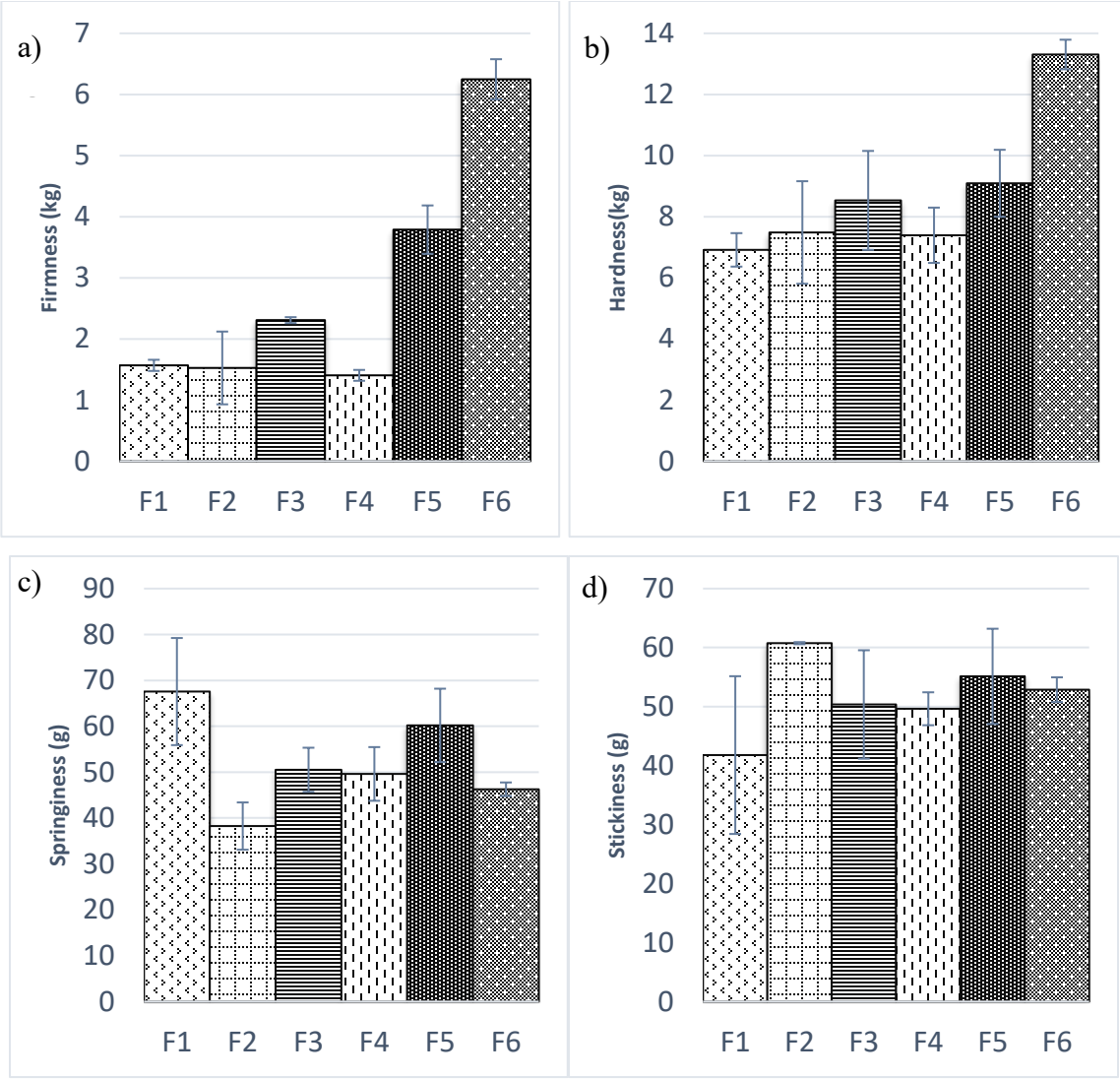

Figure 7 : Texture properties of CGs formula

a) firmness, b) hardness, c) springiness, and d) stickiness

Texture properties of CGs are shown in Table 6 and Fig. 7 Both F2 and F4 exhibited low firmness properties (p-value≤ 0.05). Gellan gum contributed to the reduced firmness of CGs. Firmness and hardness of CGs could be the results of gelatin contents. Springiness is the flexibility of the CGs after exerted to pressure and then recovered its shape. Stickiness was the adhesiveness of CGs after the first bite.

Texture properties of CGs of various %curcuminoid contents are shown in Table 7 and Fig. 8. It was found that enhancing Cur contents was related to increasing of firmness and hardness (p-value≤0.05) but not springiness and stickiness of the CGs.

Table 7 **:** Texture properties of CGs of varied curcumin contents

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F4	1403.92±89.01	49.61±5.85	7391.80±904.92	49.63±2.79
F4M	849.95±479.41	22.99±4.63	2177.36±1093.96	30.84±5.20
F4L	662.09±257.50	33.95±6.02	3925.25±1088.68	44.22±17.92
F5	5788.09±891.27	60.19±8.00	9091.78±1096.41	55.13±8.07
F5M	2847.56±864.85	35.21±6.44	4492.07±473.11	28.67±2.14
F5L	1195.49±509.20	35.77±2.13	3389.14±543.63	36.21±11.82
F6	6247.40±329.35	46.26±1.49	13306.65±484.95	52.86±2.10
F6M	2657.64±130.12	55.65±6.95	5366.68±214.66	28.42±5.89
F6L	1520.69±86.41	50.53±2.45	3309.72±78.57	20.73±1.95

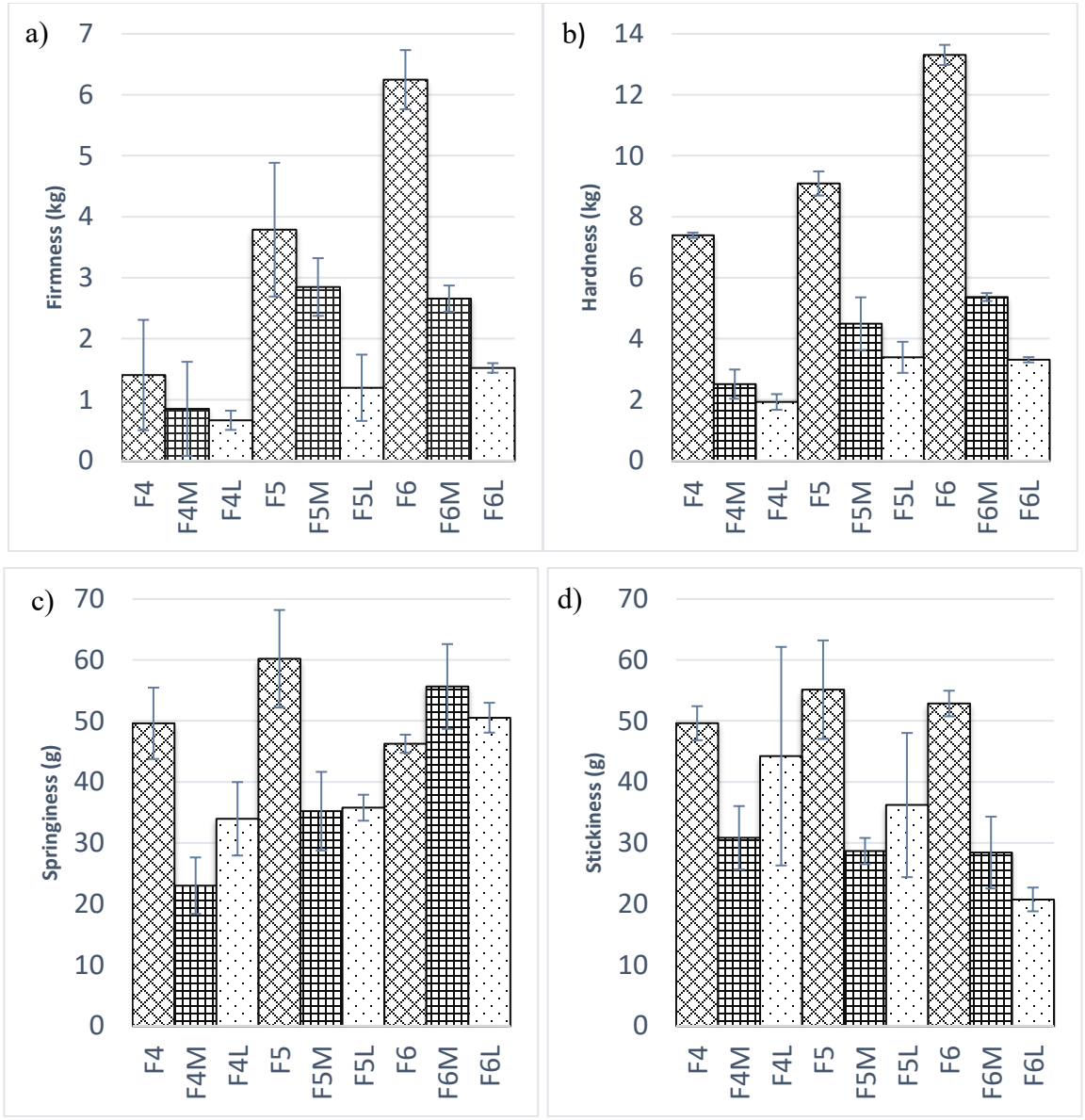

Figure 8 : Texture properties of varied %curcuminoids CGs

a) firmness, b) hardness, c) springiness, and d) stickiness

Hardness of gelatin based CGs was altered by incorporation of acacia and sodium alginate. According to the study of Zainol et al. (2020) on formulation of pastilles consisting of gelatin and acacia, the hardness of the samples was significantly decreased when reducing the gelatin amount in the formulation. Hardness had been reported to be dependent on the contents of active ingredients, aqueous phase, gelatin/ acacia contents as well as dehydration process (Zainol et al. 2020; Delgado and Bañón. 2015).

In this study, at low dose Cur, CGs contained higher water content compared with the CGs with medium and high doses. It can be possible that contents of curcuminoids in solid form contributed to the hardness of the formulation. The data of firmness, and springiness of the CGs are shown in Table 6. The objects were prone to deformation when compressed if its flexibility was too low. In this test, the strains of texture analysis were set as 10%, 25%, and 50%, and the trigger forces were 5 and 10 g, respectively. It was found that firmness of CGs was directly variable to hardness of the samples as hardness was the highest peak force measured during first compression and firmness was the slope of the force-deformation curve at compression force (Abbott and Liljedahl 1994; Bourne 1978; Jarimopas and Kitthawee 2007). Firmness of CGs has been reported to be related to the stability, as the formulation contained water and oil phases, as well as several gelling agents. Poor mixing of ingredients might cause adverse separation of water and oil phases, causing the gel structures to be unstable under introduced pressure from texture analyzer and leaking the oil or water phases. This property is therefore an interesting point for further stability testing where, if the chewable gels deteriorate during storage, the firmness will be reduced compared to the freshly prepared chewable gels (Jarimopas and Kitthawee 2007).

Dissolution study

Cumulative release of curcumin in SGF from the F1-F6 CGs with fixed dose of 5%w/w Cur was shown in Fig 9. The prolonged release of CGs at least 12 hours in SGF is shown. It was found that at the beginning the chewable gel swelled in the medium and later

fragmented into smaller pieces, where large amounts of curcuminoids were released. The contents of CGs were then gradually released in unstable amounts. As shown in Fig. 9, F1 and F3 exhibited the slowest release of Cur. Both formulas showed the higher firmness compared with F2 and F4 of which higher Cur released from the higher swollen CGs. It was found that gellan gum CGs which were less firmness compared to the alginate CGs exhibited the faster release of curcuminoid.

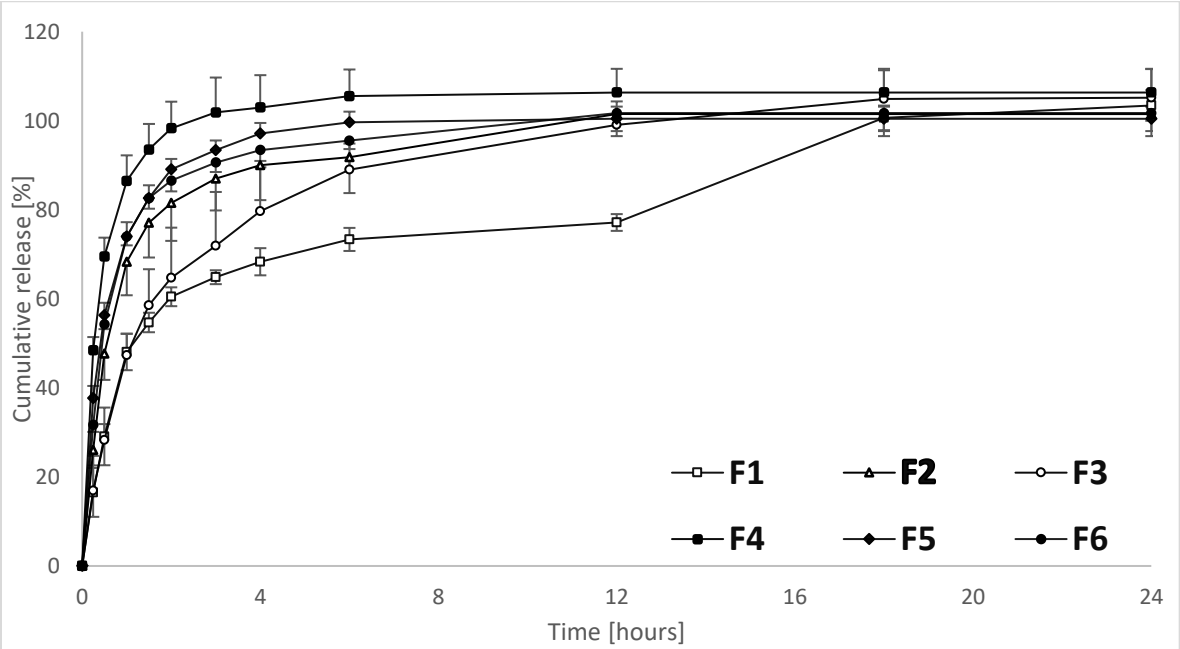

Figure 9 **:** Dissolution of CGs in SGF900 mL at pH 1.2±0.05 at 37.0±0.5 °C

Figures 10-12 show dissolution profiles in SGF of F4, F5, and F6 at low, medium and high doses of Cur. The results show that the lower Cur contents, the faster Cur release was obtained. As discussed above, the lower Cur contents contributed to lower firmness and hardness of CGs which could be related to higher swelling and dissolution of Cur from the test samples (Abbott and Liljedahl 1994; Bourne 1978; Jarimopas and Kitthawee 2007).

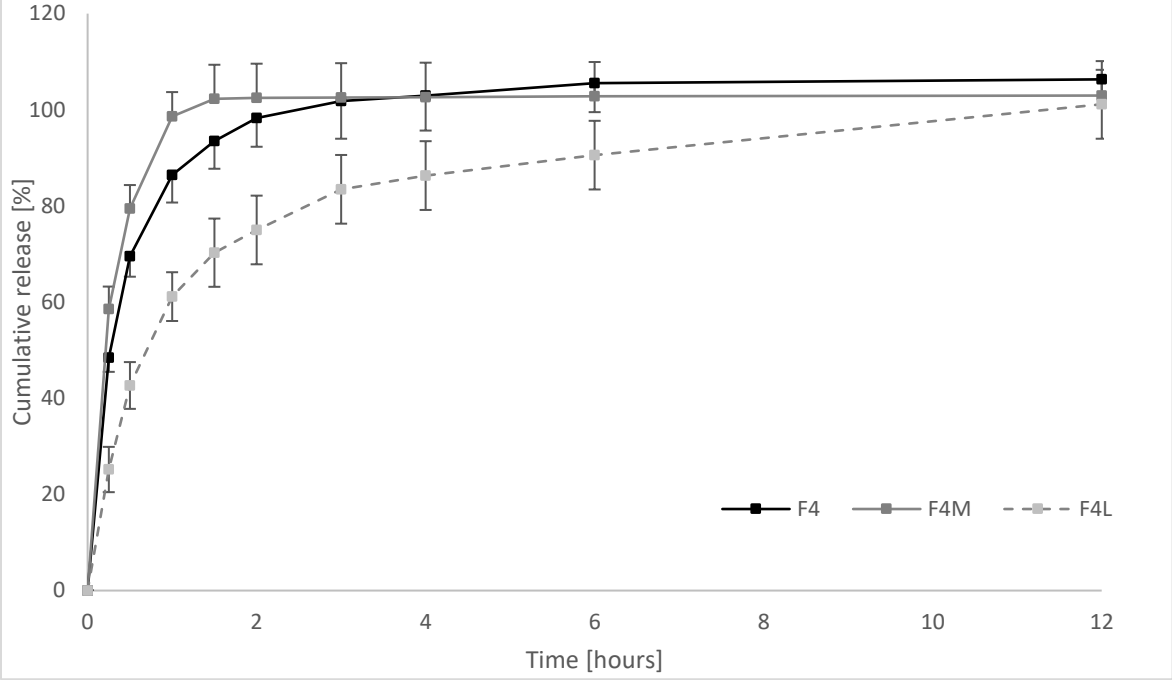

Figure 10 : Dissolution of F4 CGs in SGF 900 mL, pH 1.2±0.05 at 37.0±0.5 °C

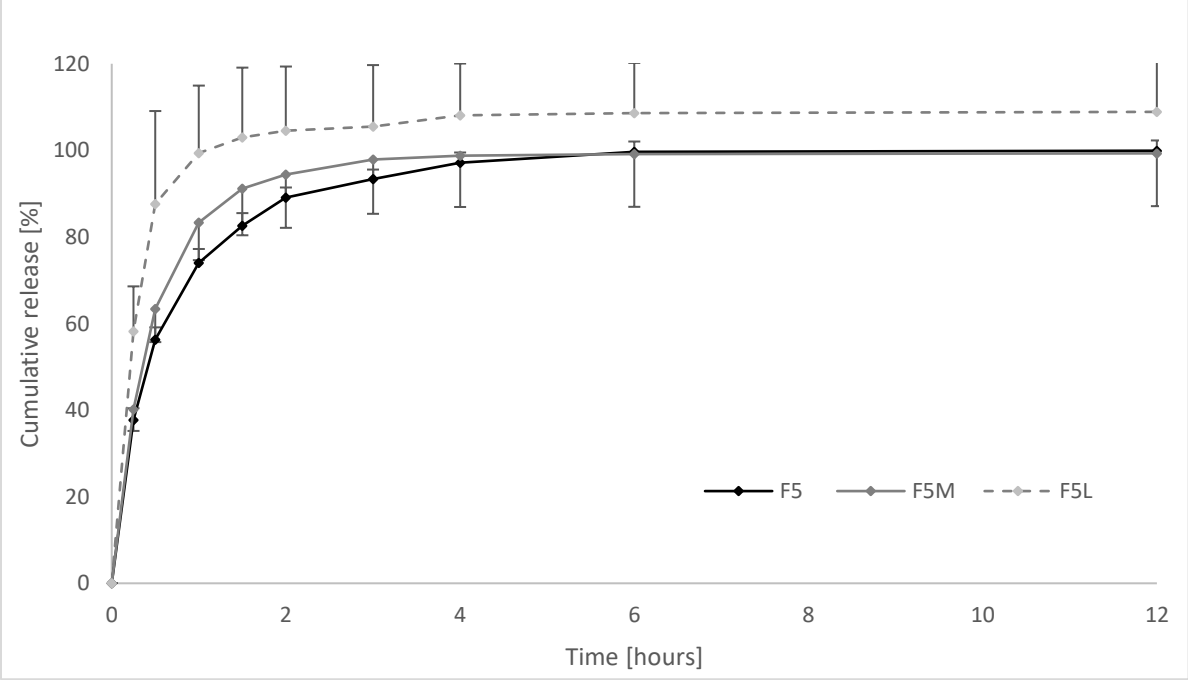

Figure 11 : Dissolution of F5 formula in SGF 900 mL, pH 1.2±0.05 at 37.0±0.5 °C

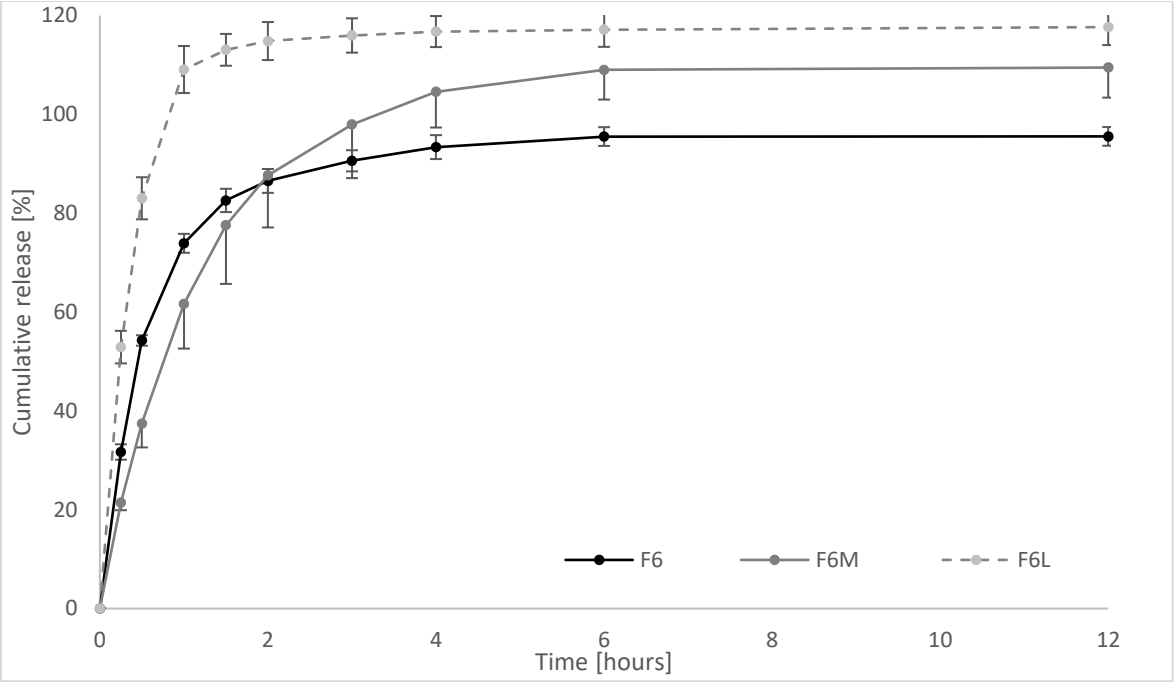

Figure 12 : Dissolution of F6 formula in SGF 900 mL, pH 1.2±0.05 at 37.0±0.5 ºC

Cumulative release of curcumin from the GCs in artificial saliva is shown in Fig. 13. In artificial saliva, all CGs in artificial saliva exhibited limit dissolution. As the low solubility of Cur, the active could be slowly released from the CGs until the saturate solution. As the CGs were incompletely dispersed and dissolved in this medium, retarding release of the active ingredients would achieve.

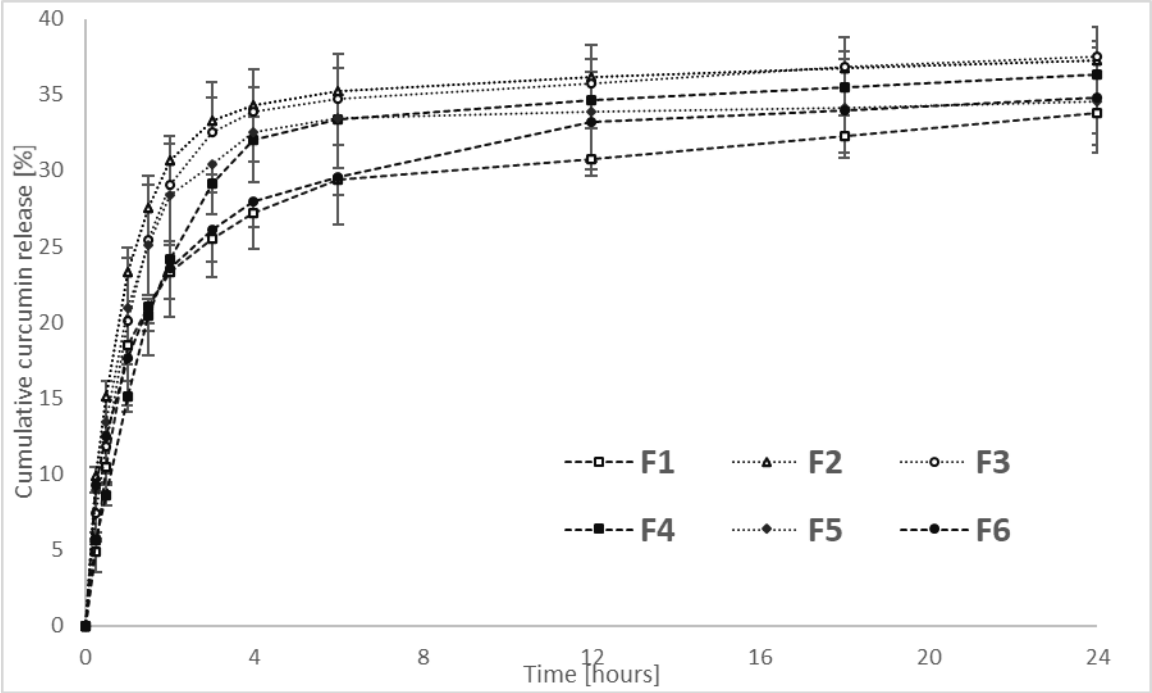

Figure 13 : Dissolution of CGs in saliva fluid 200 mL pH 6.75±0.05 at 37.0±0.5 °C

Dissolution profiles of the CGs of different Cur contents are shown in Figures 14-16. It is interesting that the lowest dose CGs (F4L, F5L, and F6L) exhibited complete dissolution and the fastest release in the artificial saliva. The results are interesting for development of the next generation of CGs with low dose of Cur.

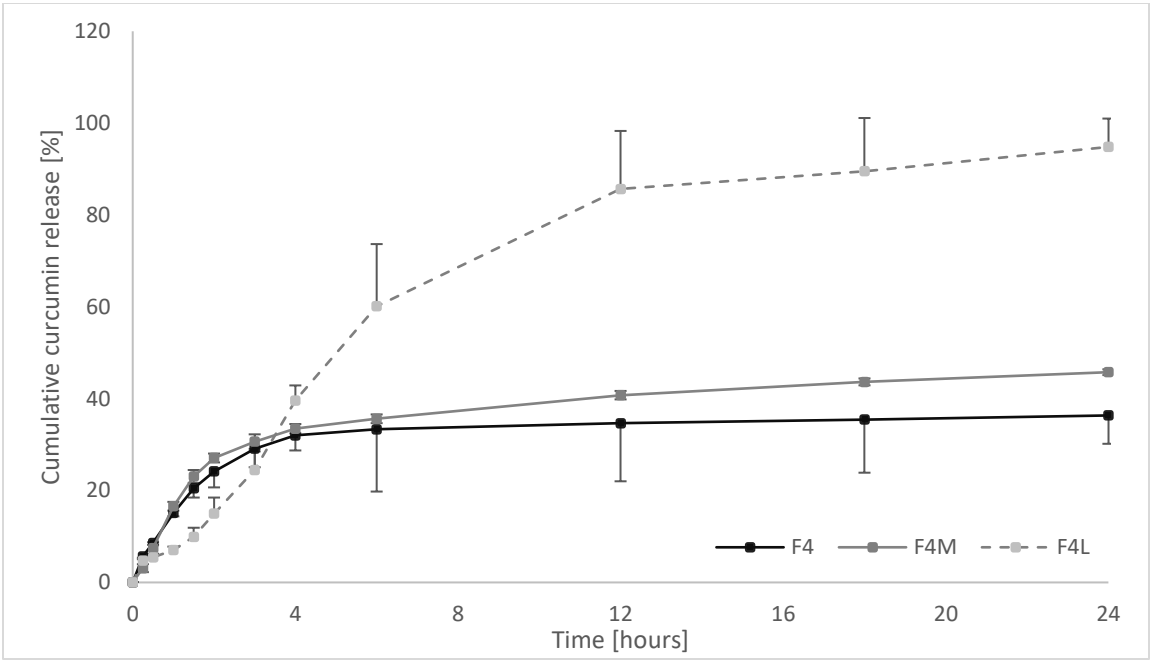

Figure 14 : Dissolution of F4 in saliva fluid 200 mL, pH 6.75±0.05 at 37.0±0.5°C

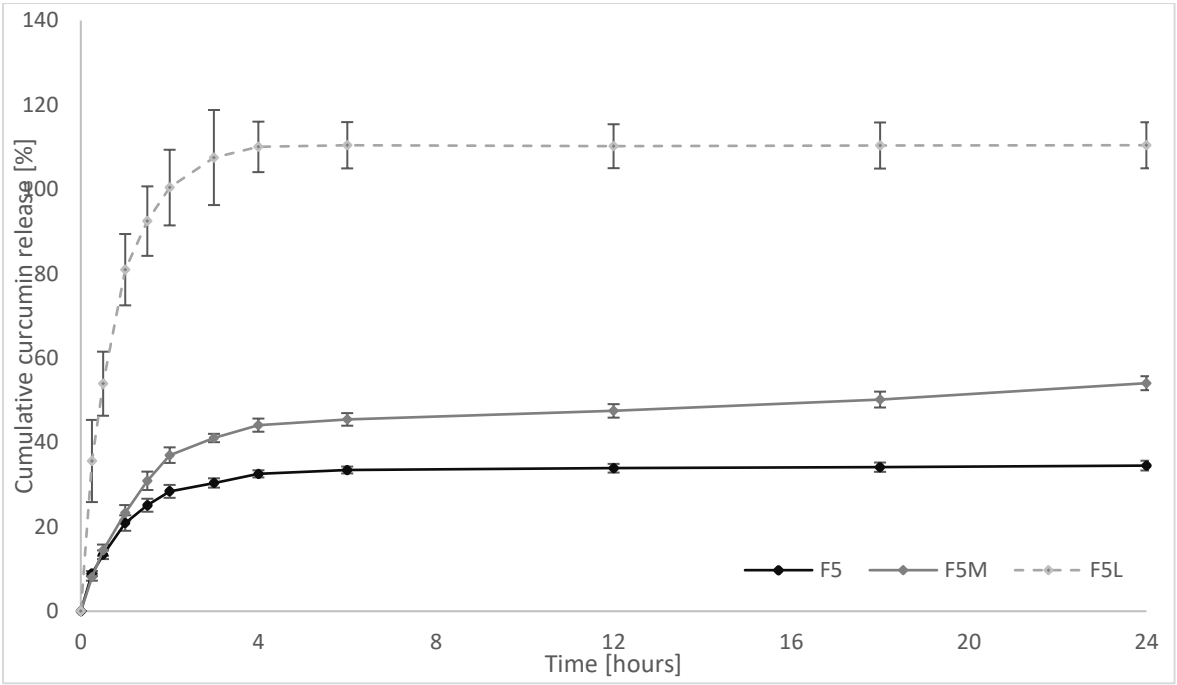

Figure 15 : Dissolution of F5 formula in saliva fluid 200 mL pH, 6.75±0.05 at 37.0±0.5°C

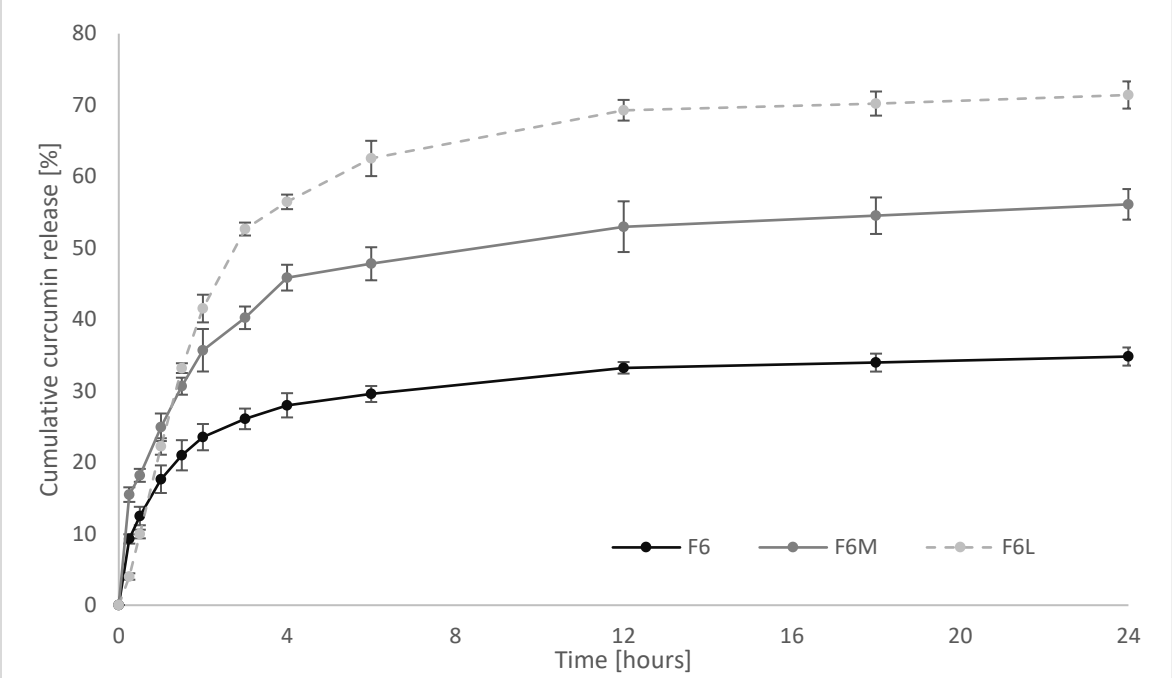

Figure 16 **:** Dissolution of F6 formula in saliva fluid 200 mL, pH 6.75±0.05 at 37.0±0.5°C

Morphology and microstructure characterization

Microstructures of CGs is shown in Fig 17. The results show the porous structures of the CGs in the cross-section samples. F1 was the porous with the smallest pore size compared with the other CGs. Incorporation of sodium alginate in F1 can be accounted to make the thicken layer of the CG in which could delay release of Cur from the samples. In addition, the formula with alginate needed longer duration of melting process and incorporation of Cur as active ingredient (data not shown). The F1 formula was found to be thick, unbreakable construction which may contribute to less swollen and slower release of F1 compared with other formulations. In addition, As shown in this figure, loading of Cur in all formulas resulted in larger pore size of the CGs compared with the plained ones. The F4 exhibited the largest porous structure. The interaction of gelatin with gellan gum made the mixed-gel structure more compact (Petcharat & Benjakul. 2017; Wang et al. 2021). Addition of gellan gum would reduce the dense and thicken of the

foam structures which could stabilize the porous foams and help to stabilize the dispersion of CGs in the dissolution media. Addition of gellan gum resulted in larger CGs cavities (Petcharat & Benjakul. 2017; Wang et al. 2021). This result was in good agreement with the firmness in texture properties of the gellan gum formula which was lower than the alginate formula. The porous structure of CGs is beneficial for rapid diffusion of actives and nutrients throughout the network layers to improving the release efficacy (Zheng et al. 2018; De France et al. 2018; Le et al. 2017).

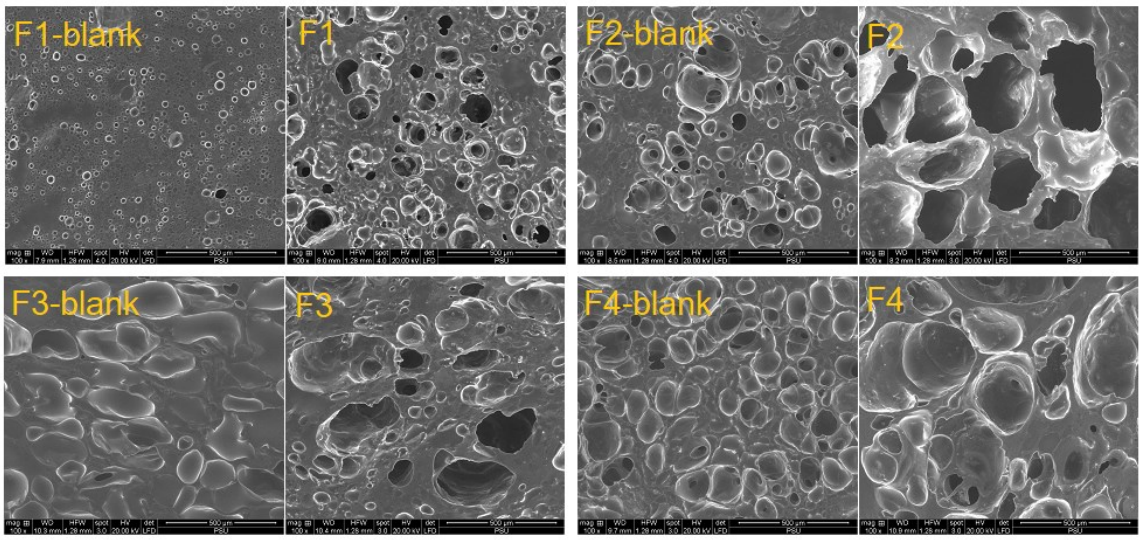

Figure **17 :** SEM micrographs of F1-F4 CGs and their plain bases

Microbial limit test

Microbial limit test is essential to assure the quality and stability of the CGs. The CGs have high water contents in formulation and need preservatives to control the number of microbial in acceptable criteria. The contamination of microbial between production is possible due to the contact of the persons, equipment and the environment. The uncontrollable of number microbial is major cause for spoilage or degradation to

dosage forms especially the active ingredients (reduced shelf-life, change of appearance, colors, taste, etc.) (Mugoyela and Mwambete 2010).

The results of microbial limit test of the CGs (F5L, F5M, F5, F6L, F6M, and F6) after stability test are shown in Table 8. All of the test samples were stable after stability testing indicating the appropriate formulas to maintain and control to prevent the growing of microbes and pass the criteria of microbial limit test. The microbial limit test for microbial contamination in the formulation was performed according to the method shown in USP44 under chapters of the microbial enumeration test. The total aerobic bacteria content has not to be more than 10^2 cfu/g and the total molds and yeasts have not to be more than 10^1 cfu/g. The results indicated that the test samples passed the specified microorganisms test showing not detected *Escherichia coli*, *Staphylococcus aureus*, *Clostridium* spp. and *Salmonella* spp. As 0.1 %w/w benzoic acid was used as a preservative in the CGs formulation, this concentration was proven to be efficient to control the microbial contamination in the formula. The usual level of benzoic acid in foods ranging from 0.05 to 0.1% as an antimicrobial additive (Zeece 2020). The notification of ministry of public health (No. 389) C.E. 2018 on food additives is noted that the specified concentration of benzoic acid in confectionery products is not more than 1,000 mg/kg or 0.1%w/w. Benzoic acid is used as a preservative in a wide variety of foods. Benzoic acid can retard the growth of yeast and molds. The effective agent is in the undissociated acid form. The major food groups contributing to dietary intake of benzoic acid are a wide variety of foods permitted at the following levels; various foods 200–1,000 mg/kg (prepared salads, confectionery, etc. 1,500 mg/kg; food supplements, preserved vegetables 2,000 mg/kg). The acceptable daily intake (ADI) for benzoic acid is 5 mg/kg body weight. (Wood et al. 2004). The interesting properties of curcuminoids is their antibacterial and antifungal activities. It can be inhibited bacterial DNA replication and alter gene expression. This damages impact on the reducing motility of microorganisms and the strength of bacterial cell membrane (Tyagi

et al 2006; Teow et al 2016; Kaur et al. 2010). Antibacterial properties of curcumin as a major compound of curcuminoids has been reported (Adamczak et al. 2020). The minimum inhibitory concentrations (MIC) of curcumin against *Streptococcus pyogenes* (median MIC = 31.25 µg/mL), methicillin-sensitive *S. aureus* (250 µg/mL), *Acinetobacter lwoffii* (250 µg/mL), and individual strains of *Enterococcus faecalis* and *Pseudomonas aeruginosa* (62.5 µg/mL) have been studied. Self-preservative of curcumin can be considered as a promising antibacterial agent (Adamczak et al. 2020). It has been in accordance with the requirements of Thai FDA and the notification of ministry of public health (No. 293) C.E. 2005 on food supplements defined to be less than 3 MPN/g of *Escherichia coli* and must not be detected. 0.1 g *Staphylococcus aureus*, 0.1 g *Clostridium* spp. and 25 g *Salmonella* spp.

Table 8 : Determination of microbial limit test of F5

Microorganisms	Results			Remark
	F5	F5M	F5L	
Total bacterial count	<10	<10	<10	CFU/gm
Mold and Yeast count	<10	<10	<10	CFU/gm
Escherichia coli	Not Detected	Not Detected	Not Detected	MPN/gm
Staphylococcus aureus	Not Detected	Not Detected	Not Detected	/0.1 gm
Clostridium spp.	Not Detected	Not Detected	Not Detected	/0.1 gm
Salmonella spp.	Not Detected	Not Detected	Not Detected	/25 g

Table 9 : Determination of microbial limit test F6

Microorganisms	Results			Remark
	F6	F6M	F6L	
Total bacterial count	<10	<10	<10	CFU/gm
Mold and Yeast count	<10	<10	<10	CFU/gm
Escherichia coli	Not Detected	Not Detected	Not Detected	MPN/gm
Staphylococcus aureus	Not Detected	Not Detected	Not Detected	/0.1 gm
Clostridium spp.	Not Detected	Not Detected	Not Detected	/0.1 gm
Salmonella spp.	Not Detected	Not Detected	Not Detected	/25 g

Stability test

Stability test is essential to assure the maintenance of product qualities during storage. The refrigerator condition (4-8°C) helped to preserve the Cur content of CGs and protect emulsion instability and integrity of CGs during the periods. The CGs with 25% w/w or higher percentages of gelatin (F5 and F6 series) were chosen in the stability study. At the lower gelatin contents the CGs were found to exhibit deformation of shape and bleeding of the oil at 30°C (room temperature of the hot and humid climate). High contents of gelatin helped the CGs to maintain stable shape at room temperature.

The results are shown in Fig 18. It was found that loading doses of the CGs affected their stability. The higher stability of CGs was found in F5 and F6 with higher Cur loading compared with lower loading in F5M and F5L, as well as F6M and F6L, respectively. As mentioned above, loading of Cur in the CGs strongly affected their firmness and hardness. It is known that the firmness is related to the dense of gel structures. It can be noted that the CGs of higher density are stronger and more stable than those of lower density. Increasing of hardness as shown above could be the results of the variation with the increasing of both Cur and gelatin contents. This character could contribute to enhanced

stability of these CGs. Photodegradation of curcumin is the reason to recommend to keep the products protect of CGs protect from light (Kumavat et al. 2013).

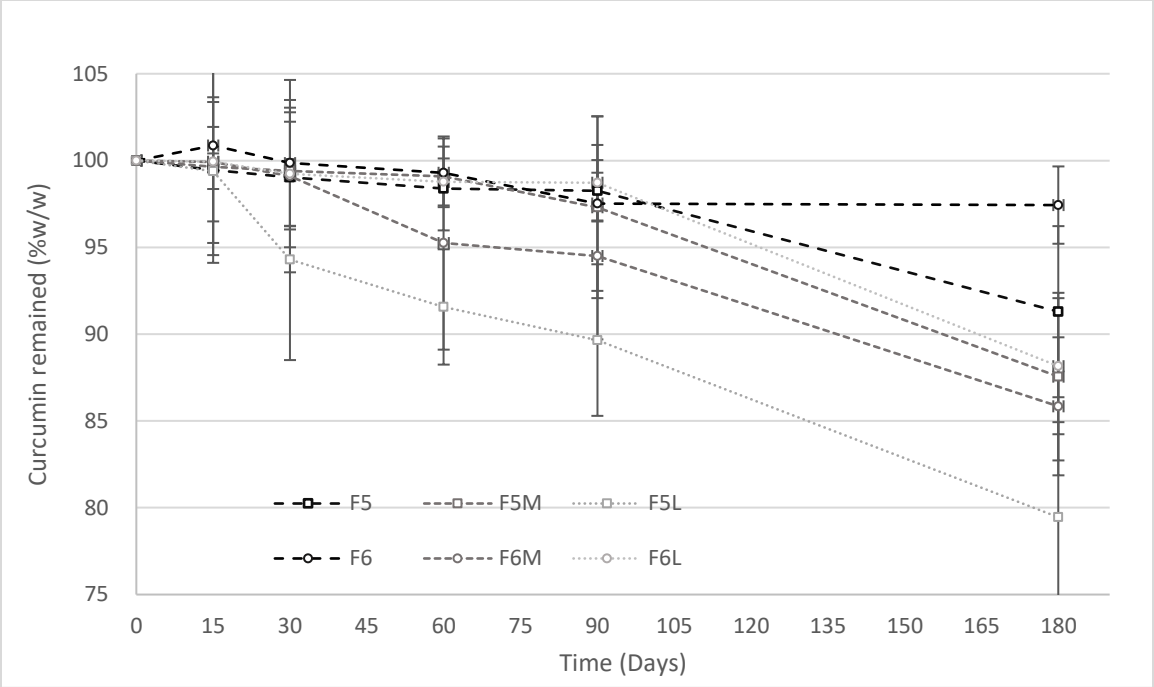

Figure 18 **:** Stability of F5 and F6 CGs at 30.0±0.2°C, 75±5% RH

Since the contents of active ingredients in CGs were reported according to the %label amount of 90-120%, the shelf-life was determined if the curcumin contents decreased to less than 90% LA. All of the samples were found stable after 3 months. However, after 6 months only F5 and F6 with the highest Cur loading (5%w/w) showed the Cur contents remaining higher than 90% LA at at 30.0±0.2°C, 75±5% RH.

CHAPTER 5

CONCULSION

In this study various formulas of CGs in gelatin base with chosen vegetable oil (RBO) were formulated by varying gelling agents (sodium alginate and gellan gum), and emulsifying agents (acacia and tragacanth) and loading of various Cur contents (1%, 2.5%, and 5%). All CGs showed the consistency of their weight and pHs. Curcuminoids contents of CGs were found within 90-120 %LA. Suitable CGs formulas of F5 and F6 with gellan gum and 5% Cur loading were achieved. Stability of the products was studied and the results indicated the physical, chemical and microbiological stable at room temperature (30.0±0.2°C, 75±5% RH), protected from light at least for 6 months of the F6 CGs. Prolonged release of Cur in artificial saliva can be benefit for application of the CGs as oral cavity drug delivery systems. However, further study on the effects of CGs on salivary flow and swallowing, as well as further studies in wound healing and long-term stability profiles of the CGs are needed to support the uses of these CGs.

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APPENDICES

APPENDIX A

General properties

Table A1 : Weight variation

Formula	F1	F2	F3	F4	F4M	F4L	F5	F5M	F5L	F6	F6M	F6L
Weight (g)	2.28	2.22	2.32	2.25	2.35	2.32	2.54	2.33	2.34	2.41	2.35	2.36
	2.29	2.22	2.32	2.25	2.35	2.30	2.55	2.42	2.29	2.42	2.35	2.39
	2.31	2.32	2.31	2.25	2.35	2.40	2.37	2.41	2.37	2.39	2.44	2.39
	2.32	2.24	2.34	2.31	2.31	2.41	2.45	2.40	2.40	2.45	2.33	2.41
	2.33	2.35	2.35	2.30	2.30	2.42	2.38	2.39	2.43	2.38	2.41	2.41
	2.30	2.26	2.26	2.30	2.34	2.33	2.46	2.37	2.40	2.37	2.38	2.44
	2.28	2.27	2.32	2.32	2.32	2.37	2.52	2.29	2.28	2.35	2.39	2.28
	2.26	2.28	2.28	2.30	2.30	2.38	2.38	2.28	2.36	2.35	2.39	2.29
	2.35	2.33	2.23	2.33	2.33	2.38	2.51	2.32	2.35	2.40	2.43	2.33
	2.28	2.32	2.30	2.30	2.30	2.31	2.40	2.28	2.28	2.40	2.43	2.32
	2.32	2.28	2.27	2.29	2.42	2.39	2.50	2.29	2.32	2.41	2.42	2.41
	2.32	2.26	2.25	2.25	2.44	2.35	2.43	2.30	2.32	2.36	2.32	2.33
	2.39	2.27	2.29	2.24	2.39	2.38	2.51	2.30	2.39	2.44	2.32	2.34
	2.30	2.29	2.22	2.34	2.34	2.36	2.45	2.37	2.40	2.43	2.41	2.35
	2.31	2.32	2.22	2.31	2.31	2.36	2.49	2.41	2.41	2.41	2.37	2.38
	2.35	2.22	2.36	2.28	2.38	2.38	2.48	2.29	2.35	2.36	2.35	2.38
	2.37	2.33	2.28	2.29	2.39	2.39	2.46	2.40	2.37	2.45	2.36	2.41
	2.38	2.24	2.27	2.25	2.45	2.31	2.39	2.35	2.38	2.37	2.36	2.31
	2.37	2.35	2.27	2.33	2.33	2.44	2.43	2.33	2.28	2.41	2.40	2.39
	2.29	2.33	2.34	2.39	2.37	2.44	2.50	2.36	2.39	2.39	2.42	2.34
Mean	2.34	2.29	2.28	2.30	2.38	2.38	2.46	2.34	2.36	2.40	2.37	2.36
S.D.	0.04	0.04	0.05	0.05	0.05	0.04	0.04	0.04	0.04	0.03	0.04	0.03

Table A2 : Texture properties of formulas

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F1	1638.68	82.42	7084.13	50.41
	1534.89	59.42	6473.95	50.11
	1691.19	81.63	6418.16	28.24
	1599.02	65.39	7898.44	21.27
	1458.58	55.27	6940.03	50.01
	1481.54	61.21	6668.71	50.66
Average	1567.32	67.56	6913.90	41.78
S.D.	91.30	11.67	547.43	13.37

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F2	2195.19	34.9	7217.05	60.99
	2143.92	32.16	9676.54	60.8
	1768.67	36.34	9251.37	76.02
	852.21	38.42	6768.99	57.2
	1265.24	43.09	6254.22	61.97
	924.96	44.6	5731.08	47.54
Average	1525.03	38.25	7483.21	60.75
S.D.	595.27	4.81	1618.54	9.19

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F3	2230.13	55.41	9629.76	50.31
	2345.48	51.04	10349.67	50.26
	2336.25	56.74	9581.39	50.56
	2263.56	43.89	5868.15	50.59
	2337.86	50.53	7369.85	50.11
	2331.27	45.43	8399.33	50.31
Average	2307.43	50.51	8533.03	50.36
S.D.	48.32	5.15	1677.77	0.18

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F4	1444.75	50.79	8102.46	50.26
	1548.86	52.50	7721.16	50.26
	1327.69	58.99	8498.36	50.61
	1335.41	42.51	5998.66	52.17
	1436.31	45.27	7141.07	44.13
	1330.52	47.57	6889.07	50.36
Average	1403.92	49.61	7391.80	49.63
S.D.	89.01	5.85	904.92	2.79

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F4M	1511.78	29.88	3710.09	25.54
	1236.34	26.09	3256.07	34.78
	542.65	16.66	2082.77	28.47
	951.16	22.50	2048.94	24.79
	655.38	19.88	1865.45	36.57
	202.39	22.94	2100.81	34.88
Average	849.95	22.99	2510.69	30.84
S.D.	479.41	4.63	771.34	5.20

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F4L	993.36	26.45	2083.87	26.53
	562.15	30.41	1960.00	68.32
	873.39	34.35	1949.72	57.88
	402.85	36.15	1971.68	33.09
	478.69	42.38	1661.00	35.28
Average	662.09	33.95	1925.25	44.22
S.D.	257.50	6.02	157.28	17.92

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F5	3507.50	53.01	10171.84	53.42
	3817.09	64.92	9885.32	48.89
	3384.08	65.81	8188.42	69.95
	2988.65	68.14	8840.30	52.91
	3337.89	47.93	7492.09	47.86
	2693.35	61.32	9972.71	57.72
Average	3288.09	60.19	9091.78	55.13
S.D.	395.74	8.00	1096.41	8.07

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F5M	3938.11	46.39	5040.25	27.82
	3036.21	37.24	4246.24	30.31
	3367.05	35.75	4963.04	25.29
	3123.23	33.45	4626.37	28.37
	1904.02	27.97	4268.99	31.50
	1716.71	30.46	3807.52	28.72
Average	2847.56	35.21	4492.07	28.67
S.D.	864.85	6.44	473.11	2.14

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F5L	2110.86	31.54	2868.44	24.40
	1326.05	36.71	2813.44	25.34
	1131.26	35.94	3699.31	37.86
	1128.46	37.31	3081.73	36.32
	823.38	36.18	3728.13	57.14
	652.90	36.93	4143.79	36.22
Average	1195.49	35.77	3389.14	36.21
S.D.	509.20	2.13	543.63	11.82

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F6	6283.18	44.58	12857.39	50.42
	6640.46	48.50	13728.70	53.31
	6345.91	45.89	13450.82	50.99
	6497.74	46.86	13883.80	52.75
	5781.77	44.78	12642.46	53.31
	5935.34	46.97	13276.73	56.35
Average	6247.40	46.26	13306.65	52.86
S.D.	329.35	1.49	484.95	2.10

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F6M	2460.25	47.54	5435.19	26.90
	2760.01	62.07	5707.96	25.31
	2777.94	60.89	5412.29	22.16
	2664.28	48.00	5365.35	39.40
	2541.22	53.20	5094.60	29.27
	2742.13	62.18	5184.71	27.46
Average	2657.64	55.65	5366.68	28.42
S.D.	130.12	6.95	214.66	5.89

Formula	Firmness (g)	Springiness (g)	Hardness (g)	Stickiness (g)
F6L	1646.80	52.63	3332.89	21.04
	1502.75	46.77	3330.13	20.79
	1417.88	48.66	3314.67	17.65
	1441.32	50.26	3164.25	19.55
	1585.07	51.85	3403.05	22.13
	1530.29	53.01	3313.32	23.20
Average	1520.69	50.53	3309.72	20.73
S.D.	86.41	2.45	78.57	1.95

Table A3 : pH of formula

Formula	F1	F2	F3	F4	F4M	F4L	F5	F5M	F5L	F6	F6M	F6L
pH	4.54	4.33	4.38	4.54	4.33	4.33	4.54	4.33	4.34	4.35	4.34	4.34
	4.46	4.33	4.35	4.46	4.33	4.35	4.46	4.33	4.35	4.35	4.35	4.35
	4.39	4.34	4.34	4.39	4.34	4.34	4.49	4.34	4.34	4.34	4.34	4.34
	4.52	4.34	4.33	4.52	4.34	4.33	4.52	4.34	4.35	4.33	4.34	4.35
	4.39	4.34	4.37	4.39	4.34	4.37	4.39	4.34	4.37	4.37	4.37	4.47
	4.44	4.34	4.36	4.44	4.34	4.32	4.44	4.34	4.32	4.35	4.32	4.32
Mean	4.46	4.34	4.36	4.46	4.34	4.34	4.47	4.34	4.35	4.35	4.34	4.36
S.D.	0.06	0.01	0.02	0.06	0.01	0.02	0.06	0.01	0.02	0.01	0.02	0.05

APPENDIX B

Drug content and physical properties

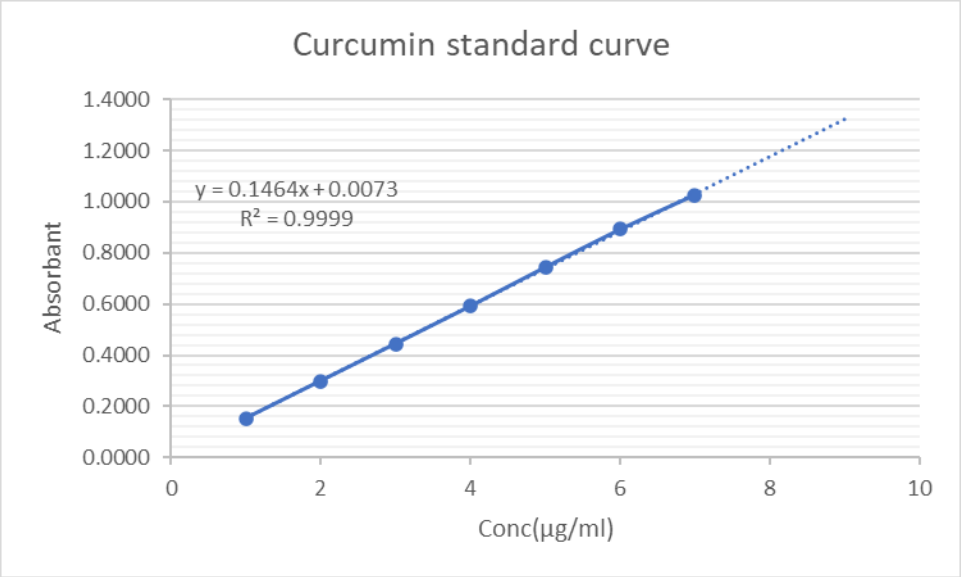

Fig. B1 : Curcumin standard curve at UV 424 nm.

Table B1 : Weight and absorbance of CGs formula

Formula	Weight/piece (g)	Absorbance	Formula	Weight/piece (g)	Absorbance
F1	2.17	0.4875	**F5**	2.23	0.3631
	2.26	0.5073		2.39	0.4285
	2.27	0.5542		2.32	0.3692
	2.18	0.5011		2.31	0.3885
	2.35	0.6019		2.38	0.4065
	2.35	0.6102		2.40	0.4255
F2	2.27	0.4997	**F5M**	2.46	0.1933
	2.19	0.5649		2.51	0.2211
	2.29	0.4896		2.45	0.1995
	2.27	0.4833		2.34	0.1957
	2.23	0.5442		2.48	0.2025
	2.17	0.5098		2.51	0.2306
F3	2.23	0.4955	**F5L**	2.31	0.1615
	2.23	0.5137		2.45	0.1615
	2.25	0.5136		2.36	0.1615
	2.32	0.6252		2.32	0.1615
	2.17	0.5009		2.46	0.1615
	2.35	0.4892		2.34	0.1615
F4	2.33	0.3843	**F6**	2.49	0.3954
	2.23	0.3865		2.40	0.3988
	2.22	0.4174		2.41	0.4067
	2.17	0.3577		2.49	0.4156
	2.35	0.3883		2.41	0.3954
	2.19	0.3641		2.41	0.3912
F4M	2.26	0.3687	**F6M**	2.25	0.2196
	2.29	0.3746		2.47	0.2017
	2.22	0.3741		2.26	0.2191
	2.15	0.3586		2.35	0.2070
	2.05	0.3436		2.42	0.2414
	2.16	0.3667		2.33	0.2423
F4L	2.33	0.162	**F6L**	2.26	0.1584
	2.30	0.1522		2.35	0.169
	2.23	0.145		2.16	0.1509
	2.38	0.1766		2.18	0.1465
	2.35	0.1702		2.25	0.1491
	2.29	0.1507		2.25	0.1489

Table B2 : Drug contents of CGs (%w/w)

Formula	F1	F2	F3	F4	F4M	F4L	F5	F5M	F5L	F6	F6M	F6L
Drug content (%w/w)	4.53	4.45	4.49	4.97	2.46	1.02	4.90	2.32	1.03	4.79	2.90	1.03
	4.53	5.22	4.65	5.23	2.47	0.97	5.42	2.62	1.16	5.01	2.42	1.06
	4.94	4.32	4.61	5.68	2.54	0.95	4.79	2.41	1.15	5.09	2.88	1.02
	4.64	4.30	5.46	4.96	2.51	1.09	5.07	2.47	1.20	5.04	2.61	0.98
	5.18	4.93	4.66	4.98	2.52	1.07	5.16	2.42	1.16	4.95	2.97	0.97
	4.47	4.75	4.20	5.01	2.56	0.96	5.36	2.73	1.10	4.90	3.10	0.97
Mean	4.72	4.66	4.68	5.14	2.51	1.01	5.12	2.50	1.13	4.96	2.81	1.00
S.D.	0.28	0.37	0.42	0.28	0.04	0.06	0.24	0.15	0.06	0.11	0.25	0.04

Table B3 : Drug contents of CGs (mg/g)

Formula	F1	F2	F3	F4	F4M	F4L	F5	F5M	F5L	F6	F6M	F6L
Drug content (mg/g)	45.35	44.45	44.86	49.73	24.58	10.20	49.04	23.24	10.26	47.91	29.00	10.28
	45.34	52.17	46.53	52.27	24.65	9.68	54.17	26.18	11.60	50.14	24.19	10.58
	49.37	43.16	46.11	56.78	25.39	9.49	47.95	24.11	11.55	50.94	28.81	10.22
	46.42	42.97	54.58	49.63	25.11	10.93	50.72	24.75	12.01	50.40	26.12	9.81
	51.85	49.34	46.61	49.83	25.21	10.65	51.56	24.19	11.56	49.50	29.73	9.69
	52.57	47.45	42.02	50.08	25.57	9.62	53.56	27.35	10.97	48.96	31.00	9.67
Mean	48.48	46.59	46.79	51.39	25.09	10.10	51.17	24.97	11.32	49.64	28.14	10.04
S.D.	2.97	3.39	3.82	2.58	0.36	0.55	2.24	1.38	0.56	1.00	2.29	0.34

Table B4 : Stability of F5 in condition 30.0±0.2°C, 75±5% RH

CG formulas	Curcumin content (%W/W)
F5	(Mean±S.D.)
Day 0	100.00±0.00
Day 15	99.45±4.20
Day 30	99.02±4.02
Day 60	98.39±2.41
Day 90	98.26±1.77
Day 180	91.29±4.93

Table B5 : Stability of F5M in condition 30.0±0.2°C, 75±5% RH

CG formulas	Curcumin content (%W/W)
F5M	(Mean±S.D.)
Day 0	100.00±0.00
Day 15	99.64±5.53
Day 30	99.41±3.37
Day 60	99.09±0.34
Day 90	97.31±5.23
Day 180	87.55±4.83

Table B6 : Stability of F5L in condition 30.0±0.2°C, 75±5% RH

CG formulas F5L	Curcumin content (%W/W) (Mean±S.D.)
Day 0	100.00±0.00
Day 15	99.39±1.03
Day 30	94.30±5.79
Day 60	91.57±3.32
Day 90	89.66±4.37
Day 180	79.45±5.48

Table B7 : Stability of F6 in condition 30.0±0.2°C, 75±5% RH

CG formulas F6	Curcumin content (%W/W) (Mean±S.D.)
Day 0	100.00±0.00
Day 15	100.87±1.07
Day 30	99.85±3.64
Day 60	99.29±1.98
Day 90	97.52±5.03
Day 180	97.43±2.23

Table B8 : Stability of F6M in condition 30.0±0.2°C, 75±5% RH

CG formulas F6M	Curcumin content (%W/W) (Mean±S.D.)
Day 0	100.00±0.00
Day 15	99.92±5.36
Day 30	99.10±5.54
Day 60	95.25±6.14
Day 90	94.50±4.80
Day 180	85.84±3.98

Table B9 : Curcumin content of F6L after stability test at 30.0±0.2°C, 75±5% RH

CG formulas F6L	Curcumin content (%W/W) (Mean±S.D.)
Day 0	100.00±0.00
Day 15	99.93±3.44
Day 30	99.24±3.00
Day 60	98.77±1.35
Day 90	98.72±2.18
Day 180	88.15±3.92

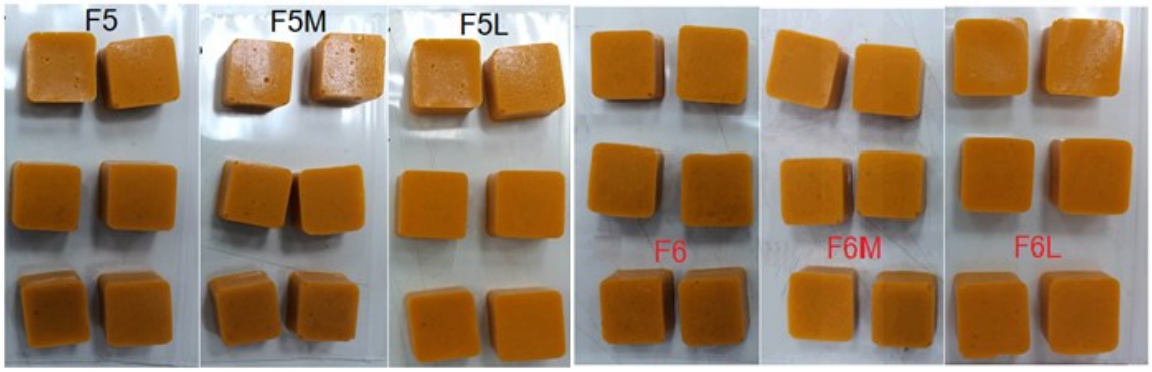

Fig. B1 : Physical appearance after stability test, day 0

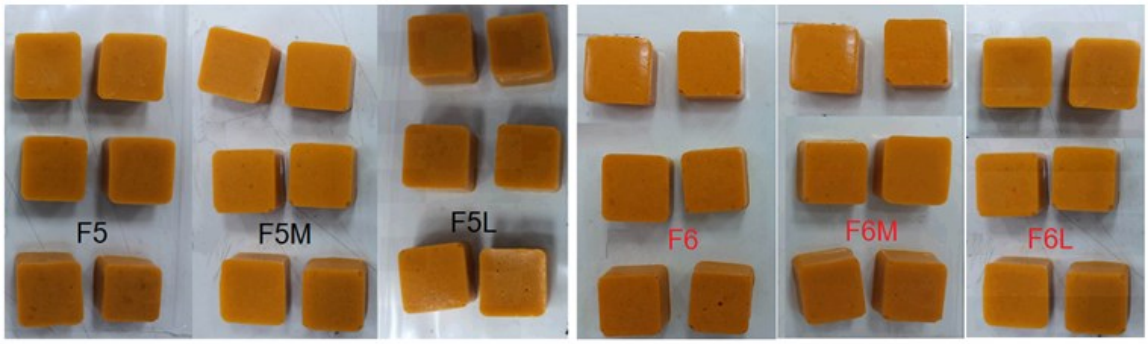

Fig. B2 : Physical appearance after stability test, day 15

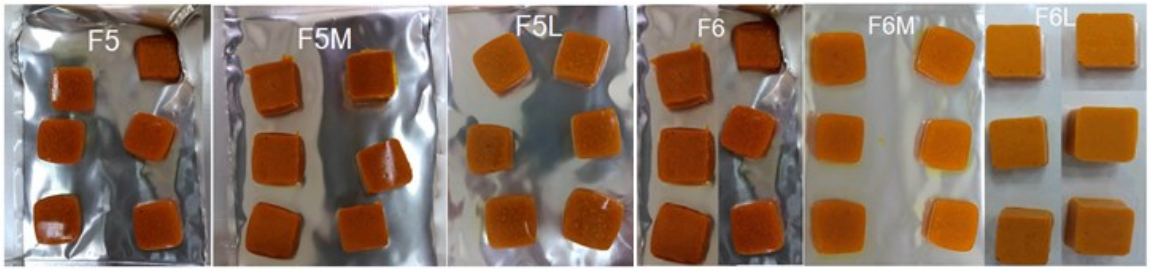

Fig. B3 : Physical appearance after stability test, day 30

Fig. B4 : Physical appearance after stability test, day 60

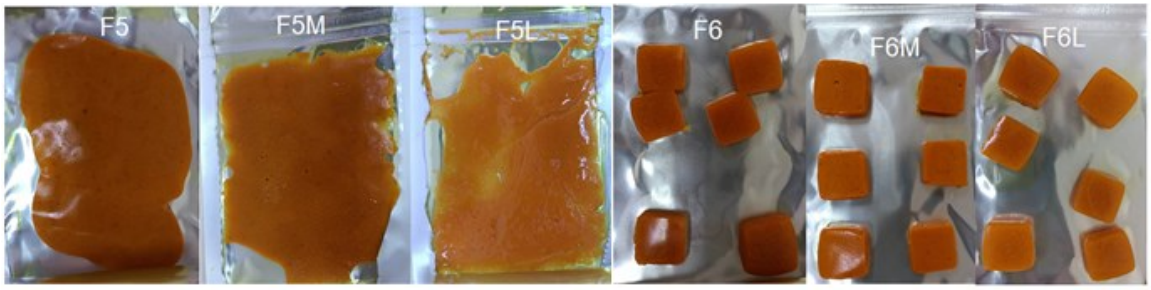

Fig. B5 : Physical appearance after stability test, day 90

Fig. B6 : Physical appearance after stability test, day 180

VITAE

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Educational Attainment

Degree	Name of Institution	Year of Graduation
Doctor of Pharmacy	Walailak University	2019

Scholarship Awards during Enrolment

- Scholarship to support tution fees from Discipline of Excellence in Pharmacy Project, Faculty of Pharmaceutical Sciences, Prince of Songkla University
- Research assistant scholarship from Drug Delivery System Excellence Center, Faculty of Pharmaceutical Sciences, Prince of Songkla University