T.C.

YEDITEPE UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY

DEVELOPMENT OF LOZENGE FORMULATION OF *PASSIFLORA INCARNATA*

MASTER OF DRUG AND COSMETIC PRODUCTION TECHNOLOGIES THESIS

BAŞAK GİZER

SUPERVISORS

ASST. PROF. GÜLENGÜL DUMAN

İSTANBUL, 2020

THESIS APPROVAL FORM

Institute : Yeditepe University Institute of Health Sciences

Programme : Master of Health Science in Drug and Cosmetic Production Technologies

Title of the Thesis : ‘’Development of Lozenge Formulation of *Passiflora Incarnata*”

Owner of the Thesis : Başak Gizer

Examination Date : 31/01/2020

This study have approved as a Master/Doctorate Thesis in regard to content and quality by the

Jury.

	Unvanı, Adı-Soyadı (Kurumu)	İmza
Jüri Başkanı:	PROF. DR. ECE GENÇ YEDITEPE UNIVERSITY	
Tez danışmanı:	ASST. PROF. DR. GÜLENGÜL DUMAN YEDITEPE UNIVERSITY	
Üye:	PROF. DR. FEYZA ARICI MARMARA UNIVERSITY	
Üye:	ASST. PROF. DR. ETİL GÜZELMERİÇ YEDITEPE UNIVERSITY	
Üye:	ASST. PROF. DR. SAMET ÖZDEMİR ACIBADEM MEHMET ALİ AYDINLAR UNIVERSITY	

BEYAN

Bu tezin kendi çalışmam olduğunu, planlanmasından yazımına kadar hiçbir aşamasında etik dışı davranışımın olmadığını, tezdeki bütün bilgileri akademik ve etik kurallar içinde elde ettiğimi, tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara kaynak gösterdiğimi ve bu kaynakları kaynaklar listesine aldığımı, tez çalışması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığını beyan ederim.

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

DEDICATION

I dedicated my thesis to my mother and father Banu Gizer and İrfan Gizer also my sister Ceren Gizer.

ACKNOWLEDGEMENTS

Foremost, I would like to express to my gratitude to my supervisors, Assist. Prof. Gülengül Duman for her necessary comments. She is really helpful and patient whose always found a solution during my thesis.

Most remarkably, I am thankful of my family for their support through my education. I dedicated my thesis to my mother and father Banu Gizer and İrfan Gizer. They were always in face of me with their encouragement. I am very lucky to have my family. Moreover, I am thankful of my sister Ceren Gizer.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

GI	Gastrointestinal
OTC	Over-the-counter
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
PEG	Polyethylene Glycol
MC	Methyl Cellulose
HEC	Hydroxyethyl Cellulose

ABSTRACT

Gizer, B. (2020). Development Of Lozenge Formulation Of *Passiflora Incarnata.* Yeditepe University Institute of Health Science, Department of Drug and Cosmetic Production Technologies MSc thesis, İstanbul.

The main purpose of the development of chewable and soft lozenge dosage formulation containing *passiflora incarnata* extract as a sleeping agent is to provide an individual dosage form. The other purpose of this study the lozenge formulation is developed for people who suffer from basically insomnia and sleeping disorder based on anxiety.

In this study, *passiflora incarnata* extract is used in developed different lozenge and edible film formulation due to ease of administration, non-invasiveness, adaptability, patient compliance and acceptability of this dosage form. Thus the optimum formulation development of lozenge form is studied and evaluated. The P7 formulation is chosen and this chewable lozenge formulation has composed of 40% glycerin, 15% gelatin, 35% purified water and 10% *passiflora incarnata* extract and it has a pleasant taste for serving purpose of the development. The vitexin amount is analyzed and the efficient lozenge formulation of the *passiflora incarnata* extract can be demonstrated . The P7 formulation is analyzed and according to HPLC study results the P7 *passiflora incarnata* lozenge dosage formulation was containing 1.358 mg/g (n=6) of vitexin. A month later, vitexin amount was found around 1.301mg/g (n=6). P7 formulation disintegration time was found 6.5 min. The taste was masked with simple syrup.

As a result of this outcomes, the chewable lozenge formulation was containing 1.3% vitexin and P7 lozenge formulation will be possible promising optional dosage form for treatment of sleeping disorder problem.

Keywords*:* *passiflora incarnata* extract, insomnia, oral dosage forms, lozenges, vitexin

ÖZET

Gizer, B. (2020).*Passiflora Incarnatanın* Pastil Dozaj Formülasyonunun Geliştirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, İlaç ve Kozmetik Üretim Teknolojileri Bölümü Yüksek Lisans Tezi, İstanbul.

Bu çalışmada *passiflora incarnata* ekstratının çiğnenenebilir veya yumuşak pastil dozaj formunda uyku problemlerinde bireye özgü hazırlanabilen dozaj formunun geliştirilmesi amaçlanmıştır. Bu çalışmanın bir diğer önemli sebebi ise *passiflora incarnata* ekstratının anksiyeteye bağlı uyku bozukluğu rahatsızlığının tedavisinde kullanılmak üzere yeni bir dozaj formunda geliştirmesidir.

Bu çalışmayla *passiflora incarnata* ekstratının farklı pastil ve film dozaj formülasyonları uygulama kolaylığı, hedefe yönelik olması ve hasta uyumluluğu sebeplerinden ötürü geliştirildi. Pastil için optimum fomülasyon çeşitli denemeler sonucunda kanıtlandı. P7 formülasyonu çüğneme pastili olarak en uygun formülasyon olarak bulundu ve bu formülasyon %40 gliserin, %15 jelatin %35 saflaştırılmış su ve %10 etken maddeden oluşmaktadır hem de pastilin amaca hizmete etmesine yönelik olarak seçilen basit şurupla tatlandırlmıştır. Bu geliştirlen pastil dozaj formülasyonundaki uykuya geçişi kolaylaştıran etken madde olan vitexin miktarı analiz edildi. Bu geliştirilen P7 formülasyonundaki vitexin miktarı HPLC yöntemi kullanılarak 6 farklı denemeyle 1.358 mg/g olarak hesaplandı. Stabilite değerlerini koruduğunu göstermek amacıyla Avrupa farmakopesine göre 1.3 olarak hesaplanmış olan vitexin mikrarı 1 ay sonra tekrar 6 farklı denemeyle analiz edilip 1.301 mg/g a düştüğü gözlemlendi. Bu geliştirilen P7 pastil dozaj formunun stabilite değerlerini koruduğu ayrıca Avrupa farmakopesine göre 6-7 dakika bulunması gereken dağılma zamanı 6.5 bulunurak da ispat edilmiş oldu. Geliştirilen bu çiğnenebilir pastil dozaj formülasyonun tadı aynı zamanda basit şurupla maskelendi..

Elde edilen bu sonuçlara göre geliştirilen çiğnenebilir pastil dozaj formülasyonun vitexin miktarının farmakopeyle uygunluğuyla birlikte analiz edilen uygun P7 formülasyonu kullanarak yenilebilir film formu olarak da uyku tedavisi için kullanılabilecek alternatif bir dozaj formu olduğu kanıtlanmış oldu.

Keywords*:* *passiflora incarnata* extract, insomnia, oral dosage forms, lozenges, vitexin

1. INTRODUCTION

1.1. The general information of the oral mucosa

The constitutional and functional features of the oral mucosa have been comprehensively examined by various researchers [1–3]. The lips, cheek, tongue, hard palate, soft palate and floor of mouth have been part of the oral cavity. The oral mucosa contains the buccal, sublingual, gingival, palatal and labial mucosa. The 60% of the oralmucosal surface area constitute the ventral surface of the tongue, the sublingual part and the buccal tissue. The oral epithelium is to conserve the underlying tissue from undesirable agents in the oral mucosa [4]. Lamina propia and submucosa are underneath basement membranes of the epithelium. The oral mucosa also includes taste receptors which are provide the taste perception.

The oral cavity contains three sort of the liningmucosa. These oral mucosa types are the buccalmucosa and the below of the mouth which is sublingual part.

The rear of the tongue has kept privatized mucosa whereas the upper surface of the mouth has kept the masticatory mucosa and the gums [5].The oral mucosal lining contains three part of the surface area in the human of the oral mucosa. First one is the lining mucosa, the masticatory mucosa is the second one and the last one is the specialized mucosa. The lining mucosa comprises the 60% of the total surface area of the oral mucosa, 25% and 15% are the other mucosas constitution percentage respectively. The masticatory mucosa ensures the convenient masticatory system through the position where the upper surface of the mouth. The surface properties of the masticatory mucosa are keratinized, and a thick lamina. These properties firmly attribute the mucosa to the underlying periosteum. In contrast to these properties lining mucosa has a non-keratinized epithelium and an elastic lamina. The dorsal mucosa is related to gustatory. The gustatory mucosa has fine papilla and this mucosa are keratinized or non-keratinized [6].

1.1.1. Drug delivery technologies for oral transmucosa

Various dosage forms such as solutions, tablets or lozenges, chewing gums, sprays, patches and films, hydrogels, hollow fibers and microspheres have been developed by way of perpetual investigation by the researches. They have been still researching the oral transmucosal drug delivery technologies. The classification of these dosage forms are liquid, semi-solid, solid or spray dosage forms [7]. The release of drug is the substantial observation of the drug delivery technologies. For instance, the drug delivery occurs quickly and also the drug delivery into the systemic circulation occurs under the controlled release.

The drug delivery technologies have been developed several companies currently. The solid dosage forms which are tablets and lozenges compose of the greater part of the available dosage forms in market. The film forms or patches have been developed only a few companies.

The oral transmucosal drug delivery technology acquires more researches for these dosage forms such as sublingual tablets, oral strips, chewing gum etc. because the drug is swallowed uncontrollably into the GI (Gastrointestinal) tract.

1.1.2. Mucoadhesive systems

The drug absorption is affected several properties of the buccal cavity because the low or high surface area of the buccal mucosa determines the retention of the drug correspondingly this property affects buccal delivery sytem. The ensuring of the affinitative and elongated contact of the formulation with the oral mucosa related to significant adhibition of mucoadhesive sytems. For instance the release of drug into the oral cavity occurs while permeable product surface available for adhesive systyems. On the other hand, adhesive sytstems which avoid the release of drug delivers the drug just impermeable product surface subjected to the oral cavity.

1.1.3. Physicochemical features of oral mucosa

The release of drug is affected from another property of the oral mucosa which is permeability coefficient [8]. Permeability ranking of the drug in human body is

intestine, buccal mucosa, skin respectively [9]. The relative thickness and degree of keratinization are the factors of the permeability ranking. Aprotinin, 23-Lauryl ether, Benzalkonium chloride, Dextran sulphate, Sodium taurodeoxycholate are permeability enhancers in the buccal drug delivery system. The drug absorption accrues with ease buccal delivery [10].

Oral film absorbed either through intracellular route and intercellular route [8,9]. Stratified squamous epithelium, Lamina propria and Submucosa are the layers of the oral mucosa. Stratified squamous epithelium is found through outermost layer, Lamina propria is found through intermediate layer and Submucosa is found through innermost layer [8].

Mucus which is referred to intercellular ground substance composes the Epethelium of oral mucosa. Mucus include proteins and carbohydrates. Mucosal thickness of hard and soft palates, the floor of the mouth, the ventral tongue and the gingival varies from 100-200 um. Submucosal layer excretes mucous. It contains 1-5% of water insoluble glycoprotein, 90-99% water and other components such as proteins, enzymes, electrolytes etc. and the secretion in the body is related to this this origin of the excrition [8,9].

Mucous pursues of oral cavity hydration hydrating conditions of oral cavity, retains favorable lubrication and maintains concentrated protective molecules also reduces undesirable micro-organisms. Salivary gland consists of lobules of cell. It excretes saliva and parotid through the salivary channel. The lips, buccal mucosa and lining of the mouth and the throat contain minor salivary glands. 1-2 ml of saliva is excreted from the salivary gland [11]. Saliva includes water, mineral salts, salivary amylase (enzyme), mucus, lysozyme, immunoglobulins and blood clotting factors [12]. Saliva and salivary mucin support the barrier features of oral mucosa. Muco-adhesive phenomenon is related to negative charge of mucin [10].

1.2. Dosage forms which are applied to oral mucosa

1.2.1 Liquid dosage forms

Liquid dosage forms contain a mixture of active substance and excipients which can be prepared active substance dissolving in the solvent which is aqueous or nonaqueous. Liquid dosage forms utilization in the oral cavity is the simple dosage form. These dosage forms can be classified as suspension of the drug in appropriate or incorporation of the drug into a liquid phase such as water or oil phase. These dosage form utilization has been several difficulties about targeting to buccal mucosa directly. Also for this forms,the drug releases occur unbounded through the oral mucosa. Results from some researches, polymer containing solutions adsorbed easily and maximum binding was observed in the buccal mucosa. Especially the polymers of Chitosan demonstrate the ultimate binding in the various polymer containin solutions [13].

1.2.2. Semisolid dosage forms

Semisolid dosage forms contain polymer, one ore more active substance dissolved in a suitable base and contain excipients such as emulsifiers, stabilizing agents etc.The administration of these dosage forms ensure the systemic effect directly. typically contain a polymer and drug plus any required excipient dissolved or suspended as a fine powder in an aqueous or non-aqueous base. These dosage forms can be used in order to drug delivery and hydrogels can be utilized as polymer in these dosage forms because hydrogels comprise of polymers and hydration is observed out of dissolution [14]. Semisolid dosage forms are demonstrated along with syringe or finger through the target region on the patient. These dosage forms can be enhanced about ease of handling.

1.2.3. Solid Dosage Forms

Solid dosage forms are essential in pharmacuetical dosage forms. It can be administered easily and also these dosage forms are confidential for patients. There have been several types of solid dosage forms such as capsules, tablets, lozenges, pills etc. Tablets and capsules are frequently using in this dosage form. Commonly capsules are

the greatest types in an other solid dosage forms because these are inexpensive to manufacture and easily serve the purpose [15].

1.2.3.1. Tablets

Tablets are solid dosage forms containing drug substances usually prepared with the care of appropriate excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics. Tablets contain active substance and various ingredients such as binders, lubricating agent, disintegrates, colorings and coatings. Flavorings existence is usually observed in the tablets. The stability of these products can be retained with coating. Correspondingly, appearance of this products can be advanced, swallowing easily, and retain the release of medication. Several and various doses can be applied with tablets. For instance it can be taken as required from patients. Sometimes it must be used one more doses of tablet for observing its effect. Altough tablets have many advantages they are are not favorable for treatment of some diseases related to cholesterol or blood pressure because of its high costs. Also researches are not sufficient for its administration along with significant treatments. Several types of tablets are available in market. One of those are odd-shaped tablets. This types of tablets do not cut easily even if using a tablet splitter. The ingredients using in the tablets can be compressed by Punch-and-die machines. This machines are frequently operated for obtaining tablets. Nowadays, the caplet form of this tablet have been manufacturered hybrid of the capsule and it is also called an oblong tablet . The shape of this caplet form look like a capsule and coated prosedure can be observed like a capsule coated. The caplet and capsule forms can be splitted up according to its inside and outside ingredients. The caplet has a solid inside while the inside of the capsule has a powder granular material. The swallowing easily, high stablization are the advantages of caplet according to compare with the capsules phycochemical properties. The OTC (over-the-counter) drugs of Tylenol and antibiotic erythromycin are the caplet formulations on the market. Tablets are frequently uncoated but some tablets have been a unique outside layer and owing to this layer rupturing is occured at the site of application. Thanks to the coating of these tablets, the bitter taste of a tablet can be masked and also it preserves the stomach from destruction and the

late releasing drug into the instestines cannot be observed. Tablets can be coated with containing sugar, film, or enteric.

Sugar-coated tablets have been outside layer through this layer the medication cannot be delayed and appearance, flavor of tablet properties are enhanced. The taste of the sugar-coated tablets enriches the preferability also ensuring the chance of treatment for patients who comply with keeping on their medication regularly. However, sugar-coated tablets are heavier than the other types of this related to this factor swallowing is not easy for treatment so this is the serious one and only disadvantage of this tablet forms.

The other types of tablet is film-coated tablets. They have been thin outer layer of a polymer and this polymer can be ssoluble or insoluble in water. Film-coated tablet manufacturing is the greatest compared to the sugar-coated tablets because film-coated tablets are thinner than sugar-coated tablets. This affects the light of weight property that identify the cost of its products. The erythromycin which is used for bacterial infections can be developed as an film-coated tablet.

There have been a lots of forms for this sugar-coated tablet. In large part of this tablets designed to utilized with swallowing whole but chewable, under the tongue form and vaginal tablets are also manufactured ready for use.

Chewable tablets are the different form of the tablets. The colored/flavored base is used for its manufacturing. Chewable tablets can be administered using masticatory muscles. Antacids, antiflatulents, vitamins are usually formulated as chewable tablets.

Buccal tablets and gum are located between the gum and the cheek. Dissolution and adsorption of these tablets can be occured by the buccal mucosa.

The last type of tablets named as sublingual tablets which are formulated for using under the tongue. The dissolution profile of these tablets are very high when using under the tongue because the drug absorption is rapidly owing to this property the drug mix quickly with the blood.

1.2.4. Lozenges

The Lozenge is derived from Losenge. In other words a diamond shaped geometry having four equal sides. Lozenges and pastilles formulation have been found since 20th century in pharmacy and this formulation is currently attained a place in markets [16].

Lozenges are dissolved in mouth or pharynx. The have been one or more active substance in a flavored base. They have been using for systemic drug absorption. It medicates irritation or infection of mouth directly. They can both deliver drug into the oral cavity and to the mucosal surface [17,18]

Lozenges can be administered in oral cavity. Buccal lozenges have been developed and utilized directly from the cheek and gums. Lozenge dissolution occurs in 30 minutes but it usually depend on the patients because it is medicated at its sole direction of patient so it has variable dissolution and adsorption time. The delivery of the drug usage is different from each patient also dilution of the drug may be affected from sucking and subsequent production of saliva.[19]

The lozenges can be prepared using molding and compression processes. Pastilles are named as molded lozenges whereas compressed lozenges are referred as troches [18].

Dissolution of lozenge is gradually occured in mouth [20]. Lozenges have been developed differently such as flat, circular, octagonal, biconvex or bacilli which is short rods or cylinders [17].

OTC products are generally produced as a lozenge. Lozenges generally are not required any prescription from a medical paractitioner while some of products have been included direction for us for its medication.

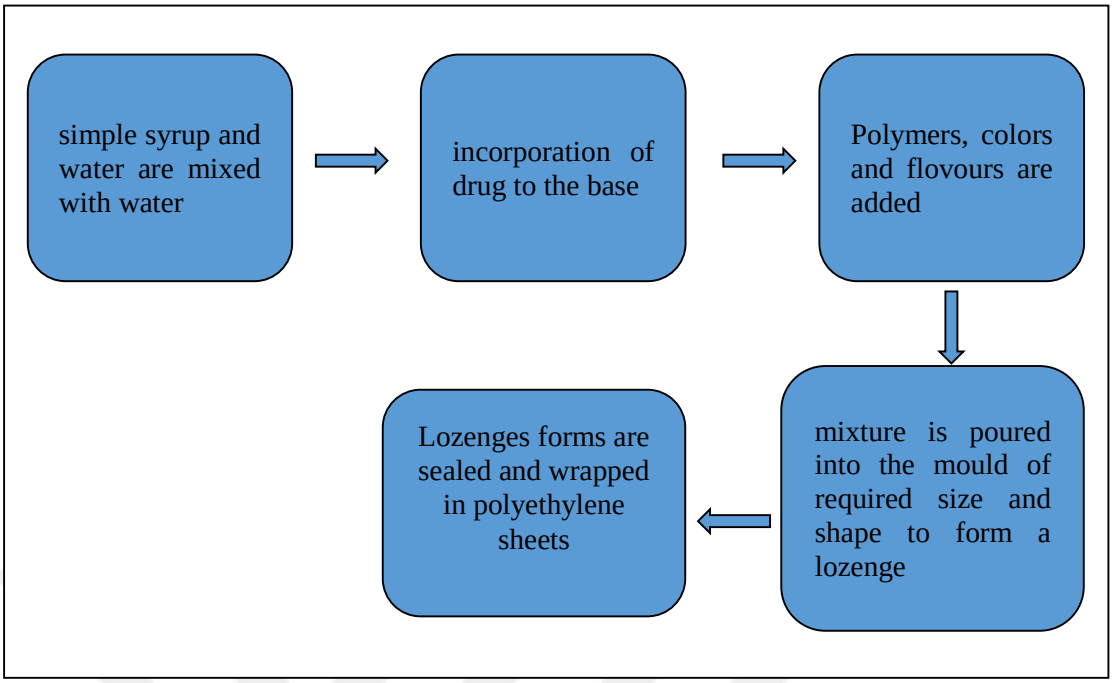

Figure 1.1 Steps of Manufacturing of Lozenge Formulation [21,22].

1.2.4.1. Advantages of Lozenges

- Lozenges are easy to use who suffer from swallowing difficuly [19].
- Lozenges are easy for medication of geriatric and pediatric population.
- The taste of this form is allowable.
- The release of drug actualise in staedy state to obtain effective treatment.
- Lozenges are prepared easily and without expense [23].
- Lozenges can be used without water.
- Although it's a parenteral technique, it is not required invasive for tratment.

1.2.4.2. Disadvantages of Lozenges

- It is not safe for children because of chocking [23].
- The drug distribution is occurred non ubiquitously.
- The nauseation may be observed after its usage.

1.2.4.3. Medicaments of Lozenge Formulation

Antiseptics or local anesthetics have been developed as lozenge formulation. Antibiotics, antihistaminics, antitussives demulcents [17] etc. have been developed as a medicaments of lozenge formulation.

1.2.4.4. Classification of this formulation

Local effect and systemic effect of this formulation are site of action properties. Lozenges have been categorized under the texture and composition properties. Chewable or caramel based lozenges, compressed tablet lozenges and hard candy lozenges are the types of this formulation.

Antiseptics and decongestants are used for the local effect of these formulations. These formulations also used for the systemic effects such as vitamins and nicotine.

1.2.4.5. The Ingredients and Manufacturing of Chewable/Caramel Based Lozenges

Caramel based lozenges have been chewed for medication. This lozenge forms have been candy base, whipping agent, humectants, lubricants, medicaments, seeding crystals and flavors. First ingredient is the candy base. Candy base composed of sugar and corn syrup in a ratio of 50:50 and 75:25 sugar to corn syrup. The whipping agents provide the desired soft chewable lozenge form. Humectants are other ingredient of this formulation. They develop chewing and change the mouthfeel. Lubricants avoid the teeth to stick of candy. Treatment can be added up to 40%.

The manufacturing steps of this lozenge is started with the candy base cooking at 95-125˚C then added to mixer. Mass is cooled to 120˚C. After that whipping agent is added under the 105C˚. The active subtstances transferred into mass at 95-105˚C. Color is distributed in humectant and poured to the above mass at a temperature is about 90ºC. Flavor and seeding crystals are put in simultaneously under 85˚C. Lubricant is transferred at about 80˚C. Consequently, caramel based lozenges can be obtained by rope forming [17].

1.2.4.6. The Ingredients and Manufacturing of Compressed Tablet Lozenges

If the active ingredient is changed by heat , compression factor affects the preparation of this lozenge formulation. Compressed tablet preparation is similar into the granulation [17]. The lozenge tablets and conventional tablets have different properties such as organolepticity, non-disintegrating characteristics and slower dissolution profiles demonstrate of their differences [18]. The manufacturing of this lozenges can be used with heavy compression equipment for give a tablet that is harder formulation and desirable for the troche to dissolution occurs slowly in mouth. They are usually flat faced with sizes, weight, hardness, and erosion time. The flat faced size is ranging between 5/8-3/4 inch , the weigh is between 1.5-4 g and the erosion time is between 5-10min [17].

They contain sugar of dextrose or sucrose. Mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000 and other fillers are di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose are vehicles which are used when sugar is missing in formulation.

Another ingredient of this formulation is the binders. Particles of mass can be holding with binders such as acacia, gelatin, sugar syrup etc.

Lubricants are ingredients that is used to enhancing the mixture of the troches.

Colors and flavors are the last ingredients of this formulation.

This type of lozenges have been developed with the steps of direct compression according to this step the ingredients mixing and directly compressing then mechanical crushing pulverize the sugar as far as obtained a fine powder. Treatment is poured and the formulation is blended well. The blending of this formulation is occurred sugar or corn syrup. Flavor and lubricant are then added then drying an milling processes are performed for obtaining fractional sizes [17]

1.2.4.7. The Ingredients and Manufacturing of Soft Lozenges

Soft lozenges are dissolved slowly in mouth. They composed of polymers such as PEG 1450 or 1000 and sugar-acacia base. Some forms of these lozenges contain both acacia and silica gel. Soft lozenge texturizing and smoothness can be arranged with acacia. Silica gel play a part of prevent materials from settling to the mold cavity through the cooling process. The heating of this formulation is just at about 50˚ [23,24].

Clotrimazole is developed using molding method and physicochemical properties of lozenge can be observed that the hardness of lozenge was ensured with PEG 1500, xanthan gum and xylitol . Moreover it can be observed that both disintegration time and hardness is increased in direct proportion to polymers [25].

1.2.4.8. The Ingredients and Manufacturing of Hard Candy Lozenges

Hard candy lozenges containing sugar and noncrystalline carbohydrates. They can be evaluated solid syrups of sugars. The preparation of this lozenges requires high temperature and materials which are not have heat resistance [17,23].

This type of lozenges include bodying agent or base, sweetening agent, acidulents, colors and flavors, medicaments and salvage. The bodying agent base contains corn syrup. Sweetening agents are maltose, lactose, sucrose and dextrose. Acidulents have been poured to this formulation on order to get impower the flavor characteristics of the lozenge. Acidulent agents frequently using in this type of lozenges are citric, tartaric, fumaric and malic acid. The coloring agents such as red color cubes, orange color paste etc. Cherry, mint, eucalyptus oil agents are commonly used for flovoring. The hard candy lozenges are also included medicaments upto 2-4% and salvage can be liquid or solid in these lozenge froms [17].

The manufacturing steps of this candy base lozenge are as follows;

The required amount of sugar is dissolved in onethird amount of water for preparing the candy base.

The dissolution procedure is kept on up to 110^{o}C is observed on the temperature.Corn syrup is poured into the solution and blended continuosly till the

temperature indicates 145-156˚C. The candy mass is transferred to a container including lubricates and placed on a weight check scale. Then color agent is added in the way of color cubes or pastes. After that, this solution is taken to a cooling table. The solution is mixed and flavor and drug is poured into this formulation. The solution is added both mold and ribbon as far as cooling. Then the desirable length of these form is obtained by cutting [17,23].

1.2.5. Films/Wafers

The manufacturing of the films can be performed by evaporating solvent in the polymer containin solution. Plasticizer can be used arbitrary and this mixture is added into dissolved active ingredient. The convenient substrate is selected and blended.Then this solvent is allowed to evaporate for obtaining a solid polymeric film.

The hot-melt extrusion and direct compression is another techniques of manufacturing these polymeric films.

The manufacturing of these dosage forms have to be performed with using organic solvent so these formulations can be evaluated as environmentally friendly and it demonstrate the one of the major advantages of these dosage forms.

The administration of these formulations is rquired the retentive delivery sytem. The oral cavity mucosa has been ideal for these productions. For instance, mucosal patches are efficacious for administration to the mucosa of the oral cavity. The various types of mucoadhesive patches are designed for rquirements of the treatment also considering the pharmaceutical properties of the active substances. The mucosal patches have been developed especially the local treatment of the oral mucosa [26].

In the adhesion period lidocaine included mucoadhesive buccal patches have been implemented for aneasthesia but the patch was seperated from the buccal mucosa [27]. In the release of miconazole study it was observed that miconazole released rapidyl and seperated from the oral gel [28]. After the first hour of using, it was decreased quicker than the miconazole patches .The ideal patches contain PVA(polyvinyl alcohol) and PVP (polyvinyl pyrrolidone) and steady release is observed. The drug levels are high for both formulations during the 30 min whereas

drug concentration was released from the patch after 4 h. The concentration of the drug in saliva can be detected although the patch has been corroded in 4-4.5h

The minimum inhibitory concentration for miconazole nitrate against *C. albicans* is 5 µg/ml. $T^{>MIC}$ is referred as the lower minimum inhibitory concentration compared to last salivary concentration. $T^{>MIC}$ is noted as 1.3 for Daktarin oral gel, 6.1 h for mucoadhesive patch. (Figure 1.2). According to these data mucoadhesive patches are superior into to the sustaining an elevated drug concentration in saliva. Chitosan containing cetylpyridinum chloride patch is greater than the hydroxyethyl cellulose patch according to the in vivo study buccal residence time.

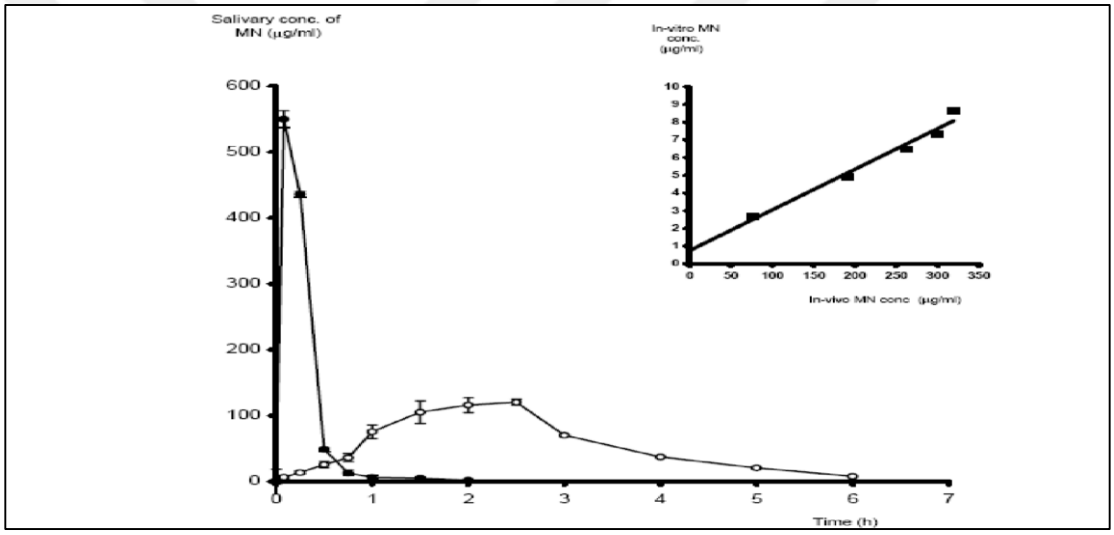

Figure 1.2. The graph of the miconazole concentration with mucoadhesive patch (o) and Daktarin® oral gel concentration released from mucoadhesive patch (●) [29].

1.2.6. Edible Film

Edible films which are dissolved orally in mouth. Firstly, edible films were specified either breath freshener product or personal care products whereas depending on its therapeutic effects they are marketed in the pharmaceutical markets in Europe and United States [30].

Edible films can be named of enhanced solid dosage form. Edible films have been superior to solid dosage forms. They are flexible and active ingredients have been used efficiently, dissolution and disintegration profiles occur in short time as compared to dissolving tablet. The development of thin films allowed to perform delicate drug targets. Since it is not performed with using liquid or solid dosage forms [31].

Oral ingestion is the typical administration route including capsules, tablets etc. However some patients are not sufficient for this ingestion type. For instance bedridden patients cannot administrated of this ingestion or patient who has the fear of chocking [32]. Acording to these disadvantages, bioadhesive mucosal dosage forms have been developed. They contain gels, adhesive tablets, ointments, patches and since 1970 oral thin films in other words fast dissolving films or mouth dissolving films or oro-dispersible films or quick disintegrating films are evaluated in the bioadhesive mucosal dosage forms. Disintegrating films melt in oral mucosa and it has been developed based upon transdermal patches [33].

Today, this dosage forms are utilized as the OTC medications. This formulations have been developed for handling as prescription drug. FDA (Food and Drug Administration) is developed the first oral disintegrating film named as Zulpenz and it has a prescriptions medication [34]. They include absorbtion ability in the buccal cavity with saliva which is used as hydrating agent. The route of administration is not required water. Pregastric absorption is occured in the mouth, pharynx and oesophagus as the saliva passes down into the stomach [32].

1.3. The general information of the plants of genus *Passiflora*

Passiflora plant contains 500 species. It has the largest species in family of Passifloraceae (the Passion flower family) [35]. This plant is distributed in the warm and tropical regions of the New World. They are not observed in Asia, Australia, and tropical Africa. *Passiflora edulis* Sims (Passion fruit or purple granadilla) kinds of these plant are grown in the tropical regions [36]. Another species are grown outdoors in the warmer parts of the world and rarely grown in the glasshouses.

1.3.1. Phyto-constituents of the plants of genus *Passiflora*

They consist of alkaloids, phenols, glycosyl flavonoids and cyanogenic compounds. The species of this plant of *Passiflora incarnata* and *Passiflora edulis* are greatly researched compared to other species of *Passiflora* and also the species of *Passiflora incarnata* is used in this study.

1.3.2. The species of this plant of *Passiflora Incarnata*

Passiflora incarnata is the most commonly used plant among the other species of *Passiflora* in Western phytotherapy [37].

This plant has been used since late Archaic period in North America between 8000 and 20000 B.C.. This plant has been used for its medicinal purpose by the Aztecs of Mexico also the Houmas of Louisiana in America. After its discovering in America this plant has been brought to Europe to benefit from its medicinal advantages. It was introduced to Europeans as a traditional and homeopathic remedy. Europeans have been informed about this plant of its treatments related to sleeping disorder based on anxiety and stress [37]. Commonly, the sedative, antispasmodic and anxiolytic effects can be benefitted from the aerial parts of this plant.

Figure 1.3. Flower of *Passiflora Incarnata* [38].

1.3.3. The Flavonoids of *Passiflora Incarnata*

Flavonoids which are the essential constituent of *Passiflora incarnata* composed of the apigenin, luteolin, quercetin, kaempferol [39], 6-β-d-allopyranosyl-8-β-xylopyranosyl-apigenin [40], C-glycosyl flavonoids vitexin, isovitexin [41], orientin, isoorientin, schaftoside, isoschaftoside, isovitexin-2”-O-glucopyranoside, isoorientin-2”-O-gluco-pyranoside, 2-glucosylapigenin, isoscoparin-2”-O-glucoside, 2-O-glucosyl-6-C-glucosylapigenin, 6-β-d-glucopyranosyl-8-β-d-ribopyranosyl apigenin and swertisin [42].

The more flavonoids are found in leaves. The flavonoid of isovitexin was accumulated between the flowering and pre-flowering part. The liquid extract of *P. incarnata* without ethanol includes higher contents of flavonoids according to compare with commercial preparations. This study is examined and researched on several occasions. Flavonoids of isovitexin content is higher than the other flavonoid concentration in *Passiflora incarnata* [43]. The flavonoid of vitexin (apigenin-8-C-

glucoside) which is also found in *Passiflora incarnata* plant is the c-glycosylated flavone as can be seen Figure 1.4.

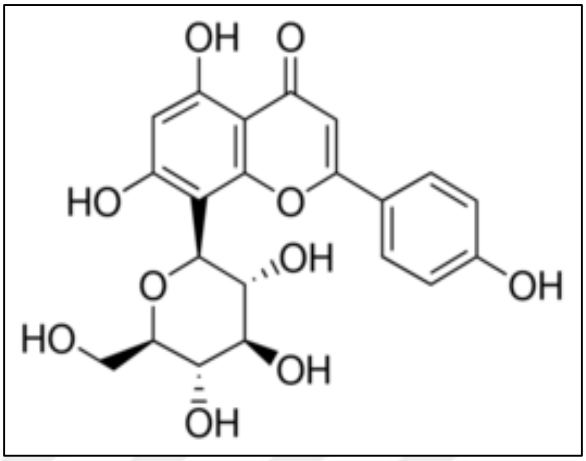

Figure 1.4. The chemical structure of the vitexin [44]

1.3.4. Description of the herbal substances, herbal preparations or combinations according to European Pharmacopeia

The proportions of the herbal subsances

Passiflora incarnata L., herba is the dried parts of *Passiflora incarnata L.* It includes flowers or fruits. The vitexin amount in the *Passiflora incarnata L*., herba is 1.5%. If the *Passiflora incarnata L*., is prepared using 40% – 90% V/V ethanol or 60% V/V methanol or 40% V/V acetone then the vitexin amount is found 2.0% [45].

1.3.5. *Passiflora Incarnata* and Insomnia (sleep disorder)

Insomnia in other words sleep disorder problem is seriously affect people who suffer from retaining sleep or not falling asleep effortlessly. Anxiety, headaches, depression or other physiological problems are the common symptoms of insomnia [46,47]. *Passiflora incarnata L*. plant has been utilized for medication of this problem. There are a lots of researches about this plant related to benefits for insomnia. The

research of placebo-controlled study is occured with 41 participants. They allowed to drink a cup of *Passiflora incarnata L.* herba tea and they are told to record their sleeping diaries for seven days. 10 of these participant even reap the benefit of its tea on last night. The sleep quality was significantly better for the group of drinking tea so the research demonstrated that *Passiflora incarnata L.* is considered to be the potential herbal sleeping drug [48].

2. MATERIALS AND METHODS

2.1.Materials

The materials used in this study are given in Table 2.1.

Table 2.1. List of Materials

Ingredient	**Company**
Vitexin	Fluka, Germany
Acetonitrile	Avantor, Poland
Tetrahydrofuran	Sigma aldrich, Germany
Phosphoric acid, 85-88.0 %	Sigma aldrich, Germany
iso-Propyl alcohol, >=99.5 %	Fisher Scientific, United Kingdom
Drug (*passiflora incarnata*)	Arkopharma, France
Glycerin	Honeywell, Germany
Gelatin	Fluka, Germany
Distilled Water	Polifarma, Turkey
Polyethylene glycol, 1000	Fluka, Germany
Color and flavour qs	-

2.2. Equipment

The equipments used in this study are listed in Table 2.2.

Table 2.2. List of Equipments

Equipment name and model	Company
Lyophilizatior alpha 1-4 LSC	Christ, Germany
High performance liquid chromatography Agilent 100 Series	Agilent, Germany
Water purifier 611 VF	Sartorius, Germany
Ultrasonic Cleaner WUC-D22H	Daihan Scientific, China

2.3 Methods

2.3.1. Preparation of Chewable Lozenge

First of all active ingredient passiflora incarnata extract is dissolved into the water and lyophilized using Lyophilizator (Christ). The *passiflora incarnata* extract lyophilization process the drug of *passiflora incarnata* extract, it was placed into the lyophilizator to make more soluble mixture. For this purpose 100 mg lyophilized sample of *passiflora incarnata* was weighed then disollved in 1 ml distilled water then this chewable lozenge mass was poured to the wellplate and wait for it to dry. Then the different lozenge bases are formulated. The preparation of chewable lozenge components and their amounts are listed in Table 2.3.

Table 2.3. Composition of chewable lozenge formulations (w/w %) and their codes

	Formulation codes						
Components amount (w/w%)	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**
***Passiflora incarnata* extract**	10	10	10	10	10	10	10
Glycerin	40	40		10	10	20	40
Propylene glycol(PEG)	-	-	20	-	-	-	-
Gelatin	10	20	15	-	-	-	15
Methyl cellulose(MC)	-	-	-	2	-	-	-
Hydroxyethyl cellulose(HEC)	-	-	-	-	2	-	-
Gummi arabicum	-	-	-	-	-	20	-
***simple syrup**	40	30	55	78	78	50	35

*: simple syrup 85% (w/v)

The composition of gelatin-glycerin bases which were used into P1 and P2 formulation respectively containing 40% glycerin, 10% gelatin, 40% simple syrup and 10% *passiflora incarnata* extract and 40% glycerin, 20% gelatin, 30% simple syrup and 10% *passiflora incarnata* extract. The lyohilized *passiflora incarnata* extract was distributed throughout the gelatin-glycerin bases (P1, P2) homegenously.

P3 formulation was prepared in the above procedure however 20% of proylene glycol was used instead of glycerin in the P3 base.

P4 formulation was prepared by using methyl cellulose MC (2%). Firstly, the polymer swollen in hot water. The powder was dispersed with high shear in about 1/3 of the required amount of water at 80˚C to 90˚C. Once it was dispersed, the rest of the water (as cold water or ice water) was added with moderate stirring. The maximum clarity, hydration and viscosity would be obtained if the base was cooled to 0-10˚C. P5 formulation was prepared in the same procedure whereas the synthetic polymer of this

base was 2% of hydroxyethyl cellulose (HEC) which was the only difference between P4 and P5. Then, the lyophilized *passiflora incarnata* extract is incorporated into the base.

P6 formulation was prepared with the portions of simple syrup and gummi arabicum (3:1). The 1 part gum was triturated with 3 parts simple syrup to form a mucilage then active ingredients which were glycerin and lyophilized *passiflora incarnata* extract were added into this base.

The P7 formulation base was containing gelatin (15%), glycerin (40%), simple syrup water (35%). The glycerogelatins are plastic masses. They were prepared by first softening the gelatin and glycerin in the water for about 10 minutes, heating on a steam bath at 80˚C until dissolved, then added to lyophilized *passiflora incarnata* extract and allowed the mixture to cool with stirring until congealed and poured into the mold.

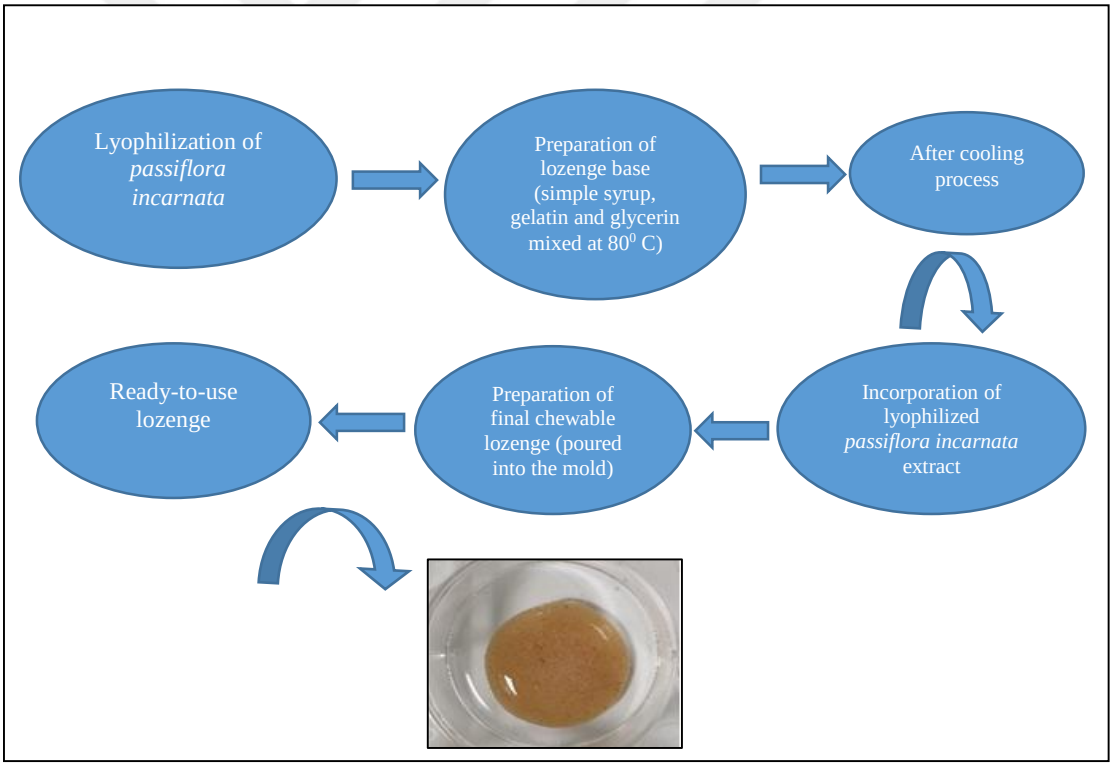

Figure 2.1. Flow chart of chewable lozenge formulation in laboratory

2.3.2. Preparation of Vitexin analysis method

First of all, *passiflora incarnata* extract contained in the capsule was poured to the watch glass then 5 mg and 10 mg extract was weighed respectively following that 50ml of a methanol-water (1:1) solution was prepared. 5mg and 10 mg *passiflora incarnata* extracts which were already weighed was placed into 2 different vial and these dry powdered content was dissolved in 1 ml of methanol-water solution (1:1).

2.3.2.1.Standard solutions and calibration

Firstly, from a vitexin stock solution (260 µg/mL) prepared in methanol-water (1:1,v/v), different standard solutions were prepared as flows: 3.2, 6.5, 13.0, 26.0 and 52.0 µg/mL. All standard solutions were filtered through a 0.22 µm membrane, analyzed in triplicate, and the peak average areas measured.

2.3.2.2.Chromatographic conditions

The HPLC-DAD analysis was carried out using the Agilent (Series 1100 High-Performance Liquid Chromatography – HPLC) system, equipped with an EP Diode Array Detector (DAD), quaternary pump, on-line degasser and automatic sampler. The chromatographic analysis was performed using a ACE C-18 column (150 x 4.6 mm, 5µm) at a temperature of 25˚C and the injection volume was 50µL. The isocratic mobile phase consisted of solvent A (tetrahydrofuran:isopropanol:acetonitrile, 10:2:3, v/v/v) and solvent B (H_3PO_4 0.5%) (12% A in B). The detection wavelength and the flow rate were 340 nm and 1.0 mL/min, respectively.

Figure 2.2. Agilent Series 1100 High- Performance Liquid Chromatography – HPLC

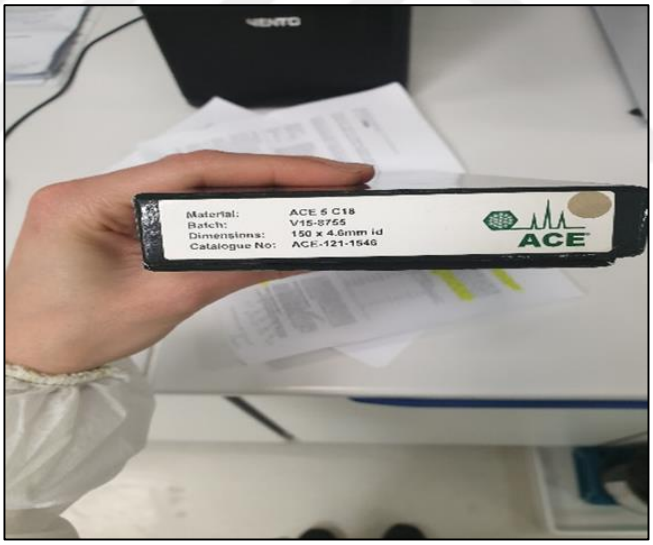

Figure 2.3. ACE C-18 column (150 x 4.6 mm, 5µm) used in this study

2.3.3. Disintegration time test

Disintegration time test was performed by the method described in Eur. Ph. 7.0 in buffer solution with pH 7.2. Pharma Test Disintegration Apparatus was used.

3. RESULTS AND DISCUSSION

3.1. Evaluation of Trial chewable lozenge formulations containing *passiflora incarnata* extract

All formulations are evaluated according to physically appearance as seen in Table 3.1.

Table 3.1. Evalution of chewable lozenge formulations

Formulation codes	Physical evaluation of formulation
P1	Lozenge did not form (liquefy)
P2	Heterogenous (extract was precipitated)
P3	Lozenge was deteroted(fragile)
P4	Heterogenous
P5	Heterogenous
P6	Sticky
P7	Homogenous

The all formulations were evaluated as an physical appearence and content uniformity.

P1 formulation could not be able to solidfy as a lozenge form. The formulation base was not turn like a gel and liquefy. P1 formulation was containing 40% glycerin, 10% gelatin, 40% simple syrup and 10% *passiflora incarnata* extract. The gelatin amount was not sufficient may be affected the texture of this formulation.

The *passiflora incarnata* extract was precipitated into P2 formulation base so it was not found as homogenous formulation. P2 formulation was containing 40% glycerin, 20% gelatin, 30% simple syrup and 10% *passiflora incarnata* extract. The gelatin amount was higher than P1 formulation. The lozenge was harder than the expecting one. Also the precipitation of *passiflora incarnata* extract was observed in the P2 formulation base.

P3 formulation was prepared in the same way of P1, P2 formulation bases however 20% of proylene glycol was used instead of glycerin in the base of this formulation. P3 formulation base was lead to deterioration of the structure. P3 formulation base was fragile.

P4 and P5 lozenge formulations were composed of synthetic polymers (methly cellolose-MC, hydroxyethyl cellulose-HEC). In the P4 and P5 formulation was turned like a film (polymers were film forming agents). Those formulations will be evaluated as an edible films with hydroxyethyl cellulose (HEC) and methly cellulose (MC) in advance with an other polymer options. Its water retention capacity is twice as that of methyl cellulose, and it has better flow property so P5 formulation was more stable in viscosity than P4 formulation. HEC and MC was compatible of the active substance of *passiflora incarnata extract* to obtain edible films so these formulations could not be evaluated as a lozenge. Gummi arabicum was used as a lozenge carrier. It has a other functions as binding, emulsifying and stabilizing roles in the P6 formulation. The final appearence of P6 formulation was found sticky but it was compatible with *passiflora incarnata* extract.

Consequently, all trial formulations were evaluated by physical appearence and chemically. The P7 formulation was found convenient as a homogenous lozange.

P7 formulation composed by 40% glycerin, 15% gelatin, 35% simple syrup and 10% *passiflora incarnata* extract. The extract was purchased from community pharmacy.

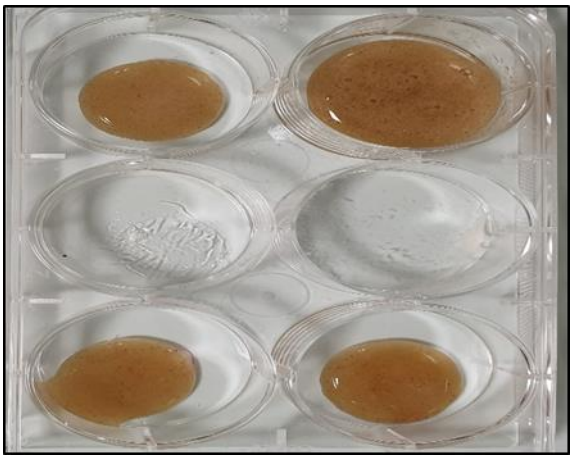

Figure 3.1. Trialed chewable lozenge formulations containing *passiflora incarnata* extract

3.2. Results of Vitexin Analysis

The *passiflora incarnata* lozange formulation (P7) containing vitexin were analyzed by HPLC. The vitexin amount into the P7 formulation were calculated first day and also one moth later. The vitexin amount were found 1.358 and 1.301 % w/w respectively. The chromatogram of the vitexin into the *passiflora incarnata* lozange analysis were shown in Figure 3.2. and 3.3.

Description of the herbal substances, herbal preparations or combinations according to European Pharmacopeia, *Passiflora incarnata* may contain 1.5% of total flavonoids, expressed as vitexin (European Pharmacopoeia, 2012). According to our obtained data vitexin amount was found around % 1.36.

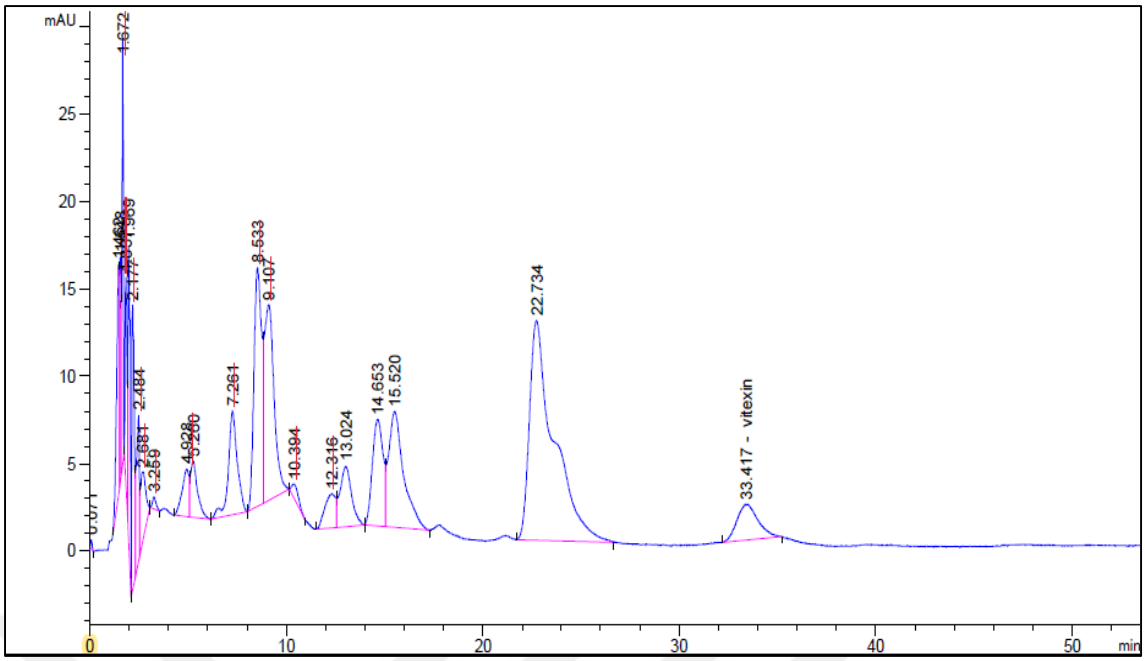

Figure 3.2. Chromatogram of *passiflora incarnata* extract containing vitexin one month later

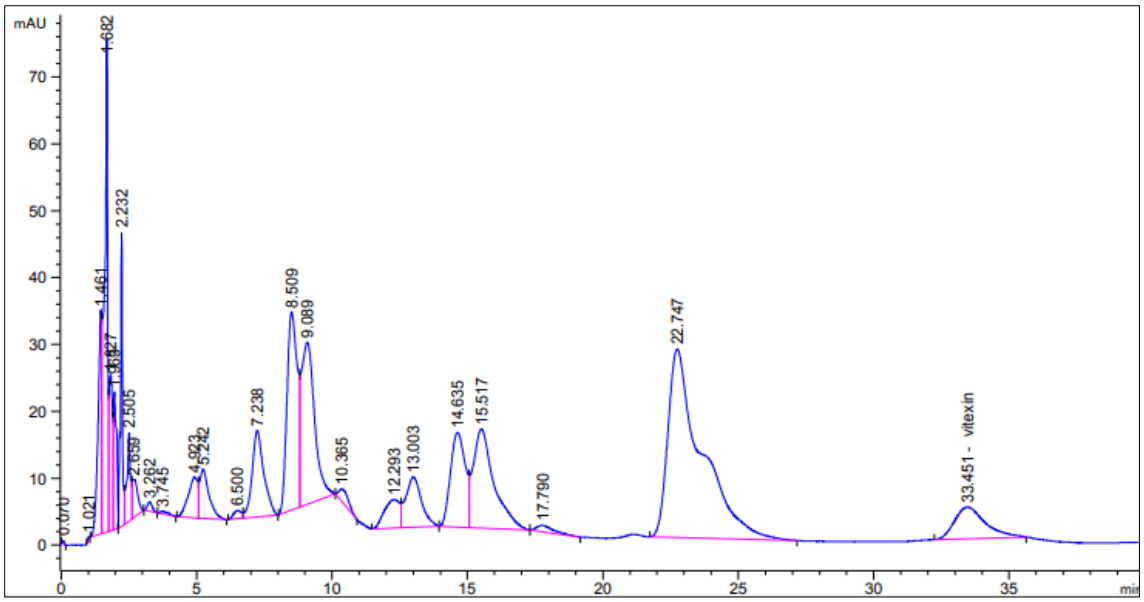

Figure 3.3. Chromatogram of *passiflora incarnata* extract containing vitexin

3.3. Results of pharmaceutical characteristics of P7 lozenge formulation

The obtained P7 formulation is characterized with vitexin amount in *passiflora incarnata* lozenge. The other pharmaceutical parameters; physical appearance of lozenge and disintegration time were evaluated.

The vitexin amount into the P7 *passiflora incarnata* lozange formulation was found 1.358 % (n=6). The standard deviation was calculated with initial amount of vitexin value. The standard deviation was found 0.1710. The obtained results were demonstrated in Table 3.2.

Table 3.2. Vitexin amount in *passiflora incarnata* lozenge (with relative standard deviation- RSD)

Initial vitexin amount (g/lozenge)	Average vitexin amount	RSD
1.68 1.28 1.35 1.38 1.19 1.27	1.3583	0.1710

The vitexin amount into the P7 *passiflora incarnata* lozenge formulation was found 1.301 % (n=6) after one month later. The standard deviation of this vitexin amount in lozenge was found to be 0.1285 demonstrated in Table 3.3.

Table 3.3. Vitexin amount in *passiflora incarnata* lozenge one month later (with relative standard deviation -RSD)

Vitexin amount (g/lozenge)1 month later	Average vitexin amount	RSD
1.346 1.450 1.124 1.384 1.165 1.342	1.3018	0.1285

According to the quality control results the optimum lozenge formulation was obtained as P7 formulation as seen in Table 3.4.

Table 3.4. Optimum formulation composition of P7 chewable lozenge and its components

	R.P (RECIPIE)	***Components***	***Amounts (w/w %)***	***Each Lozenge (1g)***
		Drug (*passiflora incarnata*)	10	0.1
		Gelatin	15	0.15
		Glycerin	40	0.4
		Simple Syrup	35	0.35

Each lozenge was 1g and containing 0.1 gram *passiflora incarnata*. P7 lozange formulation disintegration time was obtained 6-7 minutes. The obtained P7 formulation is characterizied with technological parameters which are represented in Table 3.5.

Table 3.5. All characteristics of P7 formulation were summarized

P7 formulation pharmaceutical characteristics	
Initial amount of vitexin	1.358 mg/g
A month later of vitexin	1.301 mg/g
Disintegration time (min)	6-7 min

The lozenge containing *passiflora incarnata* can demonstrate effective to treat sleep disorder. According to the obtained results P7 lozenge formulation is characterized with good physicochemical and pharmaceutical parameters which are presented in Table 3.4 and Table 3.5 respectively.

4. CONCLUSION

Nowadays, some diseases enormously arise which have been considered as CNS related disorders such as anxiety and insomnia [49]. The National Institute of Mental Health, Bethesda, the USA (NIMH) has been conducted researches about these diseases. The reports of this Institution demonstrated that 30% of people in the USA suffer from anxiety related disorders. In order to treat of anxiety, pharmaceutical drugs are available in market. Benzodiazepines, anti-depressants, azaspirones and some anti-convulsants are evaluated as the anxiety treatment drugs [50]. However, these products have a lots of side effects along with medication. Cognitive changes, addiction liabilities sedation are the primary ones. According to these serious problems of the pharmaceutical drugs, people turn onto researching herbal and nonsytnthetic products for their treatments. The herbal products are offered the same treatment with safe and cheap advantages [51].

Passiflora incarnata meet the requirements for medication of these prime anxiety disorders that affects the sleeping disorders.

In this study, it was formulated chewable lozange dosage form containing *Passiflora incarnata* extract for this sleeping disorder problem. The bioavailability of this herbal extract was highly effective when it was medicated in the lozenge formula than it was medicated in tablet dosage formulation for people who has suffered from this sleeping disorder problem according to investigated literatures for this study [37]. Lozenge dosage forms are utilized in oral dosage forms however this dosage forms can be also prepared in different dosage forms such as pastilles in community pharmacy.

Furthermore, the chewable lozenge formulation was developed for people who suffer from sleeping disorder problems and they do not prefer taking the capsule because of its taste or some people do not use this dosage form because of this administration. The developed chewable lozenge formulation do not require water for adminastration.

It is observed with several researches about the effect of GABA-benzodiazepine receptor in the brain. The sedative and anxiolytic effects are proved [37]. The GABA

receptors include the primary agonist binding site and other site of this receptor which is named allosteric sites include benzodiazepines, barbiturates etc [52].

In this study, it was evaluated that the *passiflora incarnata* has the potential of the sedative and anxioltic activity under favour of presence of flavonoids due to the fact that flavonoids acting like an agononist on the GABA-benzodiazepine receptor [53].

In this study the vitexin amount which is the flavanoid of the *passiflora incarnata* is analyzed. The vitexin amount is not less than 1.5% of total flavonoids according to European Pharmacopoeia, 2012 and the amount of vitexin which is analzyed in this study is found around % 1.36 so highly effective dosage form is managed to developed in the study.

Consequently, antidepresants, benzodiazepines which is used for the treatment of the insomnia, anxiety and depression etc. The commercial synthetic products have a potential of the various side effects so people seek out the the herbal products for their treatments. Hence, it is managed to obtain herbal, safe and an individual dosage form of the *passiflora incarnata* lozenge formulation with this study. Also developed lozenge formulation in this study is promise to use as an edible film formulation in advance.

5. REFERENCES

1. A.H. Shojaei, Buccal mucosa as a route for systemic drug delivery: a review, J Pharm. Pharmaceut. Sci. 1 (1998) 15–30.

2. R.B. Gandhi, J.R. Robinson, Oral cavity as a site for bioadhesive drug delivery, Adv. Drug Deliv. Rev. 13 (1994) 43–74.

3. N. Salamat-Miller, M. Chittchang, T.P. Johnston, The use of mucoadhesive polymers in buccal drug delivery, Adv. Drug Deliv. Rev. 57 (2005) 1666–1691.

4. M.E. Dowty, K.E. Knuth, B.K. Irons, J.R. Robinson, Transport of thyrotropin releasing hormone in rabbit buccal mucosa in vitro, Pharm. Res. 9 (1992) 1113–1122.

5. J.D. Smart, Lectin-mediated drug delivery in the oral cavity, Adv. Drug Deliv. Rev. 56 (2004) 481–489.

6. L.M.C. Collins, C. Dawes, The surface area of adult human mouth and thickness of salivary film covering the teeth and oralmucosa, J. Dent. Res. 66 (1987) 1300–1302.

7. Y. Sudhakar, K. Kuotsu, A.K. Bandyopadhyay, Buccal bioadhesive drug delivery – a promising option for orally less efficient drugs, J.Control.Release 114 (2006) 15–40.

8. Dodla S, Velmurugan S. Buccal Penetration Enhancer- An brief overview, Asian J Pharmaceut Clin Res. 2013; 6(3), 39-47.

9. Mitul P, Asif K, Pratik S, Ramana MV, Dubal A. Buccal Drug Delivery System: The Current Interest. Int Res J Pharm.2011; 2(12): 4-11.

10. Jaiswal, H. Oral Strip Technology. Ind J Pharmaceut Bio Res. 2014; 2(2): 130-114. Engel, R., S. Riggi and J. Fahrenbach, Nature 219 (1968) 856.

11. Satam MN, Bhuruk MD, Pawar YD. Fast Dissolving Oral Thin Films. Int J Uni Pharm Bio-Sci. 2013; 2(4), 27-39.

12. Waugh A, Grant A. Ross and Willson, Anatomy and Physiology in Health and Illness, tenth ed, Churchill Livingstone Elsvier. pp. 291.

13. D. Patel, A.W. Smith, N. Grist, P. Barnett, J.D. Smart, In-vitro mucosal model predictive of bioadhesive agents in the oral cavity, J. Control. Release 61 (1999) 175–183.

14. L. Martin, C.G. Wilson, F. Koosha, I.F. Uchegbu, Sustained buccal delivery of the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels, Eur. J. Pharm. Biopharm. 55 (2003) 35–45.

15. EMC School, "Drugs, Dosage Forms and Delivery Systems", Solid Dosage Forms, Tablets, 2019http://www.emcp.com/product_catalog/resourcefile.php?ID=1455.

16. Lozenges and Pastilles, Prolonged Medication From Palatable Preparations. Royal Pharmaceutical Society, Information sheet: 4.

17. Peters d. Medicated Lozenges. In: Lieberman HA, Lachman L, Schwartz JB, editors. Pharmaceutical Dosage Forms: Tablets. 2nd *ed.* New York: Marcel Dekker, Inc.; 2005. p.419-577.

18. Mendes RW, Bhargava H. Lozenges. In:Swarbick J, editor. Encyclopedia of Pharmaceutical Technology. 3rd ed. North California, USA: *Informa Healthcare Inc.*;2006. p. 2231-2235.

19. Batheja P, Thakur R, Michniak B. Basic Biopharmaceutics of Buccal & Sublingual Absorption. In: Touitou E, Barry BW, editors. Enhancement in drug delivery. London, New York: *CRC Press*, Taylor and Francis Group; 2006. p. 189.

20. James MD. Medicated Lozenges. Br Med J. 1880; 880.

21. H.A. Shojaei. Development of medicated Lozenges. J Pharm Sci. 1998; 1(1): 15-30.

22. Peters D. Medicated lozenges. In: Lieberman HA, Lachman L, Schwatz JB editors. Pharmaceutical Dosage Forms: Tablets, 2nd ed. New York: Marcel Dekker, Inc. 2005: 419-577.

23. Allen LV. Troches and Lozenges. Secundum Artem. Current & Practical Compounding Information for the Pharmacist. 4(2).

24. Lozenges and medication sticks. The Pharmaceutics and compounding Laboratory. UNC ESHEL MAN/school of pharmacy.

25. Phaemachud T, Tuntarawongsa S. Clotrimazol Soft Lozenges Fabricated with Melting and Mold Technique. Res J Pharm Biol Chem Sci. 2010; 1(4): 579-586.

26. M.L. Bruschi, O. de Freitas, Oral bioadhesive drug delivery systems, Drug Dev. Ind. Pharm. 31 (2005) 293–310.

27. Y. Kohda, H. Kobayashi, Y. Baba, H. Yuasa, T. Ozeki, Y. Kanaya, E. Sagara, Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion, Int. J. Pharm. 158 (1997) 147–155.

28. N.A. Nafee, F.A. Ismail, N.A. Boraie, L.M. Mortada, Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride, Acta Pharm. 53 (2003) 199–212.

29. N.A. Nafee, F.A. Ismail, N.A. Boraie, L.M. Mortada, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, Int. J. Pharm. 264 (2003) 1–14.

30. Narayana PR, Kumar MS, Reddy M, Ravishankar K. Formulation and Evaluation of Fast Dissolving Films of Loratidine by Solvent Casting method. Pharm Innova J. 2013; 2(2): 31-35.

31. Siddeshwar SS, Dattaprasad NV, Waghmare GA, Wadghule PB, Varpe PS. Fast Dissolving Oral Films: Easy way of Oral Delivery. Int J Curr Trends Pharmaceut. Res. 2014; 2(3): 483-490.

32. Satam MN, Bhuruk MD, Pawar YD. Fast Dissolving Oral Thin Films. Int J Uni Pharm Bio-Sci. 2013; 2(4), 27-39.
33. http://www.medicalnewstoday.com/articles/194180.php.
34. Aggarwal J, Singh G, Saini S, Rana AC. Fast Dissolving Films: A Novel Approach to Oral Drug Delivery. Int Res J Pharm. 2011; 2(12): 69-74.
35. Hickey, M., King, C., 1988. 100 Families of Flowering Plants. Cambridge University Press, Cambridge, pp. 130–133.
36. McGuire, C.M., 1999. *P. incarnata* (Passifloraceae): a new fruit crop. Economic Botany 53, 161–176.
37. Miroddi, M. et al., 2013. Passiflora incarnata L.;Ethnopharmacology, clinical application, safety and evaluation of clinical trials. Journal of Ethnopharmacology, 152(3), pp.791-804.
38. Prenner, G. (n.d.). Passion for Passion Flowers.

https://www.kew.org/read-and-watch/passion-for-passion-flowers

39. Gavasheli, N.M., Moniava, I.I., Eristavi, L.I., 1974. Flavonoids from *P. incarnata*. Khimiya Prirodnykh Soedinenii 10, 95–96.
40. Grandolini, G., Fardella, G., Mercati, V., Polenzani, P., Toja, E., 1997.New studies on the constituents of cultivated *P. incarnata L.* International Joint Symposium: Chemistry, Biological and Pharmacological Properties of Medicinal Plants from the Americas, Panama, Republic of Panama, B-27, 23–26 February 1997.
41. Lutomski, J., Segie, E., Szpunar, K., Grisse, K., 1981. Die Bedeutung der Passionsblume in der Heilkunde. Importance of Passion flower in the therapeutics. Pharmazie in Unserer Zeit 10, 45–49.
42. Chimichi, S., Mercati, V., Moneti, G., Raffaelli, A., Toja, E., 1998; Congora, C., Proliac, A., Raynaud, J., 1986; Geiger, H., Markham, K.R., 1986; Li, Q.,

Vanden, H.H., Delorenzo, O., Corthout, J., Pieters, L.A.C., Vlietinck, A.J., Claeys, M., 1991; Proliac, A., Raynaud, J., 1988. 2”-O-Glucosyl-6-C-glucosylapigenin from *P. incarnata L. (*Passifloraceae). Pharmaceutica ACTA Helvetica 63,174–175; Rahman, K., Krenn, L., Kopp, B., Schubert, Z.M., Mayer, K.K., Kubelka,W., 1997. Isoscoparin-2”-O-glucoside from *P. incarnata*. Phytochemistry 45, 1093–1094.

43. Menghini, A., Capuccella, M., Mercati, V., Mancini, L., Burata, M., 1993. Flavonoids contents in *Passiflora* spp. Pharmacology Research Communications 27, 13–14.

44. https://www.researchgate.net/figure/Chemical-structures-of vitexin_fig1_51786360.

45. European Pharmacopoeia,2012,“Committee for Herbal Medicinal Products (HMPC)”, 25 March 2014 EMA.

46. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep. 2005;28:1457–1464.

47. Byun JY, Lee JY, Chung SH. Menopause and sleep related breathing disorders. J Korean Soc Menopause. 2012;18:1–5.

48. Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (passion-flower) herbal tea on subjective sleep quality. Phytother Res. 2011;25:1153–1159.

49. Murray, C.J.L., Lopez, A.D., 2001. The Global Burden of Disease and Injury Series. Harvard University Press on behalf of the WHO and the World Bank, Cambridge, MA.

50. O’Brien, C.P., Woody, G.E., 1986. Sedative, hypnotic and anti-anxiety agents—review of diagnosis, treatment and prevention of sedative abuse. Based on a lecture give by Charles O’Brien, MD, PhD, to the medical students at the University of Pennsylvania on 22 September 1995. American Psychiatric Association Annual Review, APA Press, Washington, pp. 186–199.

51. Newell, C.A., Anderson, L.A., Phillipson, J.D., 1996. Herbal Medicine, A Guide for Health-Care Professionals. Pharmaceutical Press, London.

52. Wecker, L., Crespo, L.M. & Brody, T.M., 2010. Brody's human pharmacology: molecular to clinical/Lynn Wecker; with Lynn Crespo et al. 5th ed., Philadelphia, PA: Mosby/Elsevier.

53. Dhawan, Kumar & Sharma, 2001. Anxiolytic activity of *Passiflora incarnata* Linneaus. Journal of ethnopharmacology, 78(2-3), pp. 165-70.

54. C.A. Squier, M.J. Kremer, Biology of oral mucosa and esophagus, J. Natl Cancer Inst. Monogr. 29 (2001) 7–15.