

FORMULATION DEVELOPMENT AND EVALUATION OF ACYCLOVIR HARD CANDY LOZENGES

**Submitted in partial fulfillment of the requirements for the
award of**

BACHELOR OF PHARMACY

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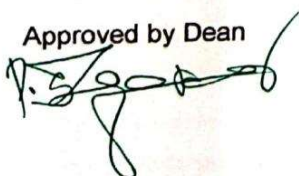
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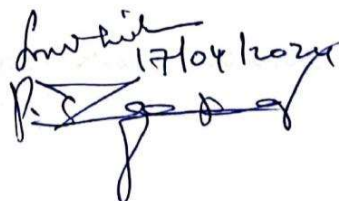
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DECLARATION

We hereby declare that the work presented in the thesis entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF ACYCLOVIR HARD CANDY LOZENGES"** submitted by us to the **Sathyabama Institute of Science and Technology (Deemed to be University), Chennai - 600119**, for the award of **Bachelor of Pharmacy (2020-2024)** by research is an original record of research work carried out by us under the supervision of **"Dr.S.Amudha, Associate Professor, School of Pharmacy"**. The contents of this dissertation, in full or in parts, have not been submitted to any other institute or university for the award of any degree, diploma, membership, fellowship, associate-ship etc. In keeping with the general practicing reporting scientific observation, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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ABSTRACT

Lozenges are dosage forms made of solid materials that are meant to dissolve or disintegrate gradually in the mouth. They are flavoured and sweetened to make them taste good, and they contain one or more active substances. Although its main purpose is topical, it may also contain substances with systemic effects. The results of the FTIR spectrophotometry study indicated that the drug and excipients employed in the formulation of the hard candy lozenges were compatible, as there were no interactions between the drug and the excipients. In this study, five formulations of Acyclovir Hard Candy Lozenges were prepared to investigate their hardness, thickness, disintegration, and in-vitro drug release. The formulated lozenges showed the uniformity in weight and thickness. The weight variation of the formulated lozenges was in the range of 3.283-3.295. The Hardness of the formulated lozenges was in the range of 10.5-15.5. The Drug content of the formulated lozenges was in the range of 98.61-99.62. The Moisture content of the formulated lozenges was in the range of 0.18-1.08. The Mouth dissolving time of the formulated lozenges was in the range of 10.16-32.67. The best formulation was found to be F5. The Acyclovir hard candy lozenges were shown to be a viable dosage form that could provide good therapeutic effect for antiviral treatment.

Keywords: Acyclovir; Fourier Transform Infrared Spectroscopy (FTIR); Hard Candy Lozenges; In-vitro Drug Release.

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredients
FT-IR	Fourier Transform Infrared
IP	Indian Pharmacopoeia
Ph.Eur	European Pharmacopoeia
NF	National Formulary
BP	British Pharmacopoeia
USP	United States Pharmacopoeia
BCS	Biopharmaceutical Classification System
PEG	Polyethyleneglycol
PG	Propyleneglycol
IR	Infrared
g	Gram
HCL	Hydrochloride
RH	Relative Humidity
Rpm	Revolution Per Minute
S.D	Standard Deviation
%	Percentage
°	Degree
°C	Degree Celsius
Cm	Centi Meter
Cum.	Cumulative
λ	Lambda

H	Hours
L	Litre
M.W	MolecularWeight
Mg	MilliGram
Min.	Minutes
Mm	MilliMeter
Sec.	Seconds
µg	Microgram
MC	MethylCellulose
HPMC	HydroxypropylMethylcellulose

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CHAPTER - 1

INTRODUCTION

CHAPTER:1

1.INTRODUCTION

The word "rhombus" comes from the French word "rhombus", which refers to a four-sided geometric diamond shape. Lozenges are single-dose solid preparations designed to be inhaled to produce topical effects, usually in the mouth and throat. Lozenges are used to relieve oropharyngeal symptoms caused by local infections and medications. These products may contain one or more drugs in a sweet or salty base, and are intended to treat local irritation or inflammation of the mouth or pharynx, and may also be used for drug delivery. Tablets are used in patients who cannot swallow oral solid forms, including drugs designed to be released slowly, creating a stable level of drug in the mouth, or washing the tissues of the throat with a medical solution. Medicines contained in the tablets include analgesics, anaesthetics, antibacterials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants and laxatives. They are easy to handle, the dosage is distributed and the throat is well delivered, as the ingredients are gently delivered and spread across the affected mucous membrane. There are many different types of candy, and they are classified by texture and composition: chewy candy, caramel candy, pressed candy, soft candy, and hard candy. Hardboiled Candy (HBL), also known as Hardboiled Candy (HBC), represents the most popular and popular product among consumers. A fully ripe candy weighs 2 to 3 grams and comes in many sizes, shapes, colors and flavors. These are usually made of water-soluble substances such as sucrose, glucose, liquid sugar, sugar-free or low-calorie substances such as isomalt, sorbitol or mannitol..

DEFINITION¹

Lozenges are available in different shapes. They contain a medicinal agent, sweetener and flavoring agents, proposed to be dissolved gently in a buccal cavity to not only have a localized effect but also a systemic effect. Are also known as pills, troches, lozenges and pastilles.

Losa (Spanish)

Lousa (Portuguese)

Lausialcopides (Late Latin) Lozenges

(Middle English)

ADVANTAGES²

- The sweeteners and flavours used in the formulation for taste masking.
- It can be used without the use of water.
- It can be given to those patients who have difficulty in swallowing.
- Has pleasant taste.
- Easy to administer to geriatric and paediatric population.
- Less production time.
- Less production cost.
- It can be prepared with minimal equipment.
- Reduces gastric irritation and bypasses first pass metabolism.
- It can improve onset of action.

DISADVANTAGES³

- Training of the medication from the mouth to the stomach and salivary glands is possible.
- High degree of preparation is required for hard lozenge sweets.
- Lozenges are not suitable for children under the age of six.
- Possible draining of drug from oral cavity to stomach along with saliva.
- Some drug may not be suitable with aldehyde candy bases e.g. Benzocaine.
- Mistakenly taken by children
- Hard lozenges become grainy
- The non-ubiquitous distribution of drug with saliva for local therapy.
- Drugs having minimum bitter taste are suitable.

CLASSIFICATION OF LOZENGES⁴

A) According to the site of action

- a) Local effects E.g. antiseptics, decongestants
- b) Systemic effects E.g. Vitamins, Nicotine

B) According to texture and composition

- a) Chewy or caramel based medicated lozenges
- b) Compressed tablet lozenges
- c) Soft lozenges
- d) Hard candy lozenges

CHEWY OR CARAMEL BASED MEDICATED LOZENGES



Fig1.1: Chewy or caramel based medicated lozenges

Chewy or caramel lozenges are a type of dose in which the medicine is mixed with a caramel base and chewed rather than swallowed. These lozenges are especially used for paediatric patients and are a very effective means of administering medications for gastrointestinal absorption and systemic use. They are prepared by using glycerinated gelatine suppository formula containing glycerine, gelatine and water.

INGREDIENTS

- Candy Base: A 50:50 to 75:25 ratio of sugar to corn syrup is used to make this mixture.
- Whipping agent: These give toffee-based confections the necessary amount of soft chew by adding air. Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin, and carrageenan are examples of these.
- Humectants: Glycerine, propylene glycol, and sorbitol are examples of substances that improve chew and mouthfeel.
- Lubricants: These are included to prevent confectionery from adhering to teeth when being chewed. Vegetable fats and oils are part of it.

- Medication: Medication can be included to a maximum of 35-40%.

- Seeding crystals: To expedite the crystallization process and enable the base to be moulded into tablets in a significantly shorter amount of time, 3-10% finely powdered sugar is added to warm candy mass.

MANUFACTURING PROCESS

The candy is cooked at 95-125°C and transferred to planetary/sigma blade mixer. Mass is allowed to cool to 120°C. This is followed by addition of whipping agent below 105°C. Then medicaments are added between 95- 105°C. Colour is dispersed in humectants and added below 85°C followed by lubricant addition above 80°C. Chewable or caramel lozenges are formed in the form of long rope of suitable thickness cut to a desired size and then packed by using wrappers. This process is called as rope forming.

COMPRESSED TABLET LOZENGES



Fig1.2: Compressed tablet lozenges

When the active ingredient is heat sensitive, it may be prepared by compression. The granulation is made same way that any compressed tablet is made. In terms of organoleptic and non-disintegrating characteristics and slightly soluble profiles. Lozenge pills differ from regular tablets. Lozenges are usually flat faced with size of 5/8- 3/4 inch, weight 1.5- 4 kg, hardness 30- 50 kg inch² and erosion time ranges between 5- 10 min.

INGREDIENTS

- Tablet base or vehicle.
- Sugar- Dextrose, sucrose.
- Sugar-Free vehicles: Mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000.
- Other fillers- Di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.
- Some commercially available sugar-based vehicles include- Emdex, Nu-tab, Sweetrex, Mola-tab, Hony-tab, Sugartab.
- Binders- These are used to hold the particles of mass as discrete granules and include acacia, corn syrup, sugar syrup, gelatin, polyvinyl-pyrrolidone, tragacanth and methylcellulose.
- Lubricants- These are used to improve flow of final troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG.
- Colours- Water soluble and alkaline dyes.

MANUFACTURING PROCESS

Direct compression

In this method all the ingredients are thoroughly mixed and directly compressed into lozenges tablets.

Wet granulation

Through sieve 40- 80 mesh size. Medicament is added to sugar mass and then mixed uniformly. Sufficient Wet granulation method involves grinding of sugar in to by mechanical agitation and passed amount of sugar syrup or corn syrup is added to homogeneously mixed mass for the granulation and then passed through 2- 8 mesh size to obtain wet granules. These wet granules are dried and once again passed through 10- 30 mesh size. Suitable flavor and lubricant are added before compression into required size of tablet lozenges.

SOFTLOZENGES



Fig1.3:Softlozenges

Soft lozenges have become popular because of the ease of extemporaneous preparation and applicability to a wide variety of drugs. They can be chewable or have a delayed release of the medicine in the mouth. Polyethylene glycol 1000 or 1450, chocolate or sugar acacia base are used as base in the soft lozenges formulation and they give soft texture to the lozenges. Some soft lozenges contain acacia and silica gel. To prevent material from settling to the base of the mold cavity during cooling, use a suspending agent. Only heat-resistant materials are appropriate for formulation, which necessitates a heating process of around 50°C. Only heat-resistant materials are appropriate for formulation, which necessitates a heating process of around 50°C. These are an amorphous mixture of sugar and other carbohydrates (non-crystalline) or a condition of glass. They're also known as solid sugar syrups.

MANUFACTURING PROCESS

Soft lozenges are manufactured by hand rolled and then cut in to pieces by maintaining desired size and thickness. Another method involves heating of all ingredients along with medicament at about 5°C and poured into a plastic mould. Mould cavity should be overfilled if polyethyleneglycol is used, as polyethyleneglycol contracts as they cool. This is not required in case of chocolate as it does not shrink.

Soft lozenges containing Clotrimazole is made by moulding method in which the increasing amount of polyethylene glycol, xanthan gum or xylitol. This agent increases the hardness of the lozenges and hence the disintegration time care must be taken in the quantity of these agents.

HARD CANDY LOZENGES



Fig1.4: Hard candy lozenges

Hard candy lozenge is an amorphous (nanocrystalline) or glassy mixture of sugar and other carbohydrates. They can also be considered solid sugar syrups. The moisture content and weight of hard candy lozenge should be between 0.5 to 1.5% and 1.5-4.5g respectively. These should undergo a slow and uniform dissolution or erosion over 5-10min and should not disintegrate. High temperature is required for the preparation of hard lozenges so heat sensitive ingredients are not suitable for this formulation. Sweeteners such as dextrose, sucrose, lactose and maltose are added. Acidulants are added to the candy base to enhance the flavor properties of the finished product. The most widely used acids are tartaric, citric, malic and fumaric acid. Colors include FD & C colors, orange paste, red cubes etc. while the flavors used include cherry flavor, eucalyptus oil, spearmint, menthol, etc. Up to 2-4% of medicines can be added to hard candy lozenges. Salvage solution can be in the form of liquid or solid

INGREDIENTS

- Bodying agent or base- This includes Corn syrup which is available on Baume basis. A430 Baume corn syrup is preferred in hard candy lozenge.
- Sweetening agent- It includes sucrose, dextrose, maltose, lactose.
- Acidulants- These are added to candy base to strengthen the flavour characteristics of the finished product. Commonly used acids are citric, tartaric, fumaric and malic acid.
- Colours- FD&C colours, orange colour paste, red colour cubes, etc.
- Flavors- It includes menthol, eucalyptus oil, spearmint, cherry flavour, etc.
- Medicaments- Medicaments upto 2-4% can be incorporated in the hard candy lozenges.
- Salvage- Salvage can be liquid or solid.

MANUFACTURING PROCESS

Hard candy lozenges are manufactured by cooking process by dissolving desired quantity of sugar to prepare the candy base and other carbohydrates in one third amount of water in the candy cooker at temperature about 110°C. If corn syrup is used for the manufacturing of hard candy lozenges, the temperature should be kept in between 145- 156°C. 2-4% medicaments are incorporated in hard candy lozenges. Other ingredients are added like sweetener acidulants to strengthen the candy base, colors, flavoring agents. Color is added in to it in the form of solution or paste and mixed uniformly. The weight of candy mass is checked by mounting the lubricated vessel containing candy mass. This mass is then transferred to a water- jacketed stainless-steel cooling table for mixing of drug and flavor. The mixed mass is poured into mold to get desired and uniform lozenge as well as

mass may also be pulled into a ribbon and after cooling it is cut into desired length to obtain lozenges which are packed as single unit wrappers.

1.5.DIFFERENT TYPES OF LOZENGE MOLD

1. Flat mold.



Fig 1.5: Flat mold

2. Cylindrical mold



Fig 1.6: Cylindrical mold

3. Octagonal mold



Fig1.7:Octagonal mold

4. Biconvex mold

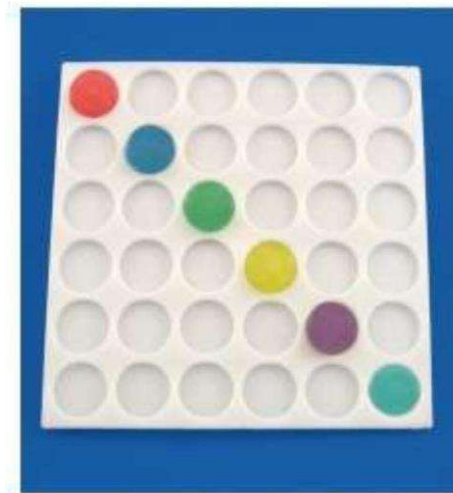


Fig1.8:Biconvexmold

5. Circularmold



Fig1.9: Circularmold

FORMULATION OF FLOZENGES⁶

Table 1.1: Formulation of flozenges

S. No	INGREDIENTS	EXAMPLE	ROLE
1.	Candy base Sugar free	Dextrose, sucrose, maltose, lactose. Mannitol, sorbitol, PEG 600 & 800.	These are used as sweetening agent and impart the taste masking properties
2.	Fillers	Di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.	These are used to improve the flowability
3.	Lubricants	Magnesium stearate, calcium stearate, stearic acid and PEG, vegetable oils and fats.	These are used to avoid sticking of candy to the teeth
4.	Binders	Acacia, corn syrup, sugar syrup, polyvinylpyrrolidone, gelatin, tragacanth, and methylcellulose	These are used to hold the particles.
5.	Colouring agent	Water soluble and Lakolene dyes, FD & C colors, orange color paste, red color cubes, etc.,	These are used to enhance appearance and organoleptic properties of dosage form

6.	Flavoring agent	Menthol, eucalyptus oil, spearmint, cherry flavor, etc.	These are used to give a taste
7.	Whipping agent	Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carrageenan.	These are used in coffee-based confection

POLYHERBAL FORMULATION⁷

Table 1.2: Polyherbal formulation

S. No	COMMON NAME	BOTANICAL NAME	PLANT PART USED	ETHNOBOTANICAL USES
1.	Prickly pear	Opuntia basilaris	Fruit Powder	Antidiabetics, Improve haemoglobin, reduces inflammation, Anti-aging properties, protects gut.
2.	Guduchi	Tinospora cordifolia	Leaves	Anti-pyretic, Anti-spasmodic, Anti-diabetic, Antioxidant.
3.	Mint Tulsi	Ocimum tenuiflorum	Leaves	Antidepressant Anti-anxiety Antiasthmatic Antifatigue, Antithyroid Anthelmintic. Etc.,
4.	Ginger	Zingiber officinale	Rhizome	Colds, nausea, arthritis, migraines, and hypertension.
5.	Honey	Apis		Anti-inflammatory, antibacterial, antimicrobial, treat burn topically, treat cold, cough

6.	Jaggery	Saccharumofficinarum L		Digestion,immunitybooster, infection and beauty treatment,water retention. Etc.
7.	Sugar	SaccharumofficinarumL		Glucosesyrupisusedtobind the mixture together and solidify the finalproduct
8.	Cinnamon	Cinnamomum zeylanicum	BarkPowder	Anti-bacterial,Maysupportgut health,Lower Blood sugar,Anti-Inflammatory.
9.	Crystal Menthol	Menthaarvensis	Natural mentholflakes	UseinAromatherapy,Promote easierbreathing,Relievenasal congestion,soothe sore throats,coughs,headaches.Su pport immunity and stabilize theemotions.

PATENTED TECHNOLOGY ON LOZENGES

Table 1.3: Patented technology on lozenges

S. NO	TITLE	PATENT NO	ACTIVE INGREDIENT	THERAPEUTIC INDICATION
1.	An anti-motion sickness throat lozenge	CN105412876 A20160323	Ginger extract	Anti-motion sickness
2.	A throat lozenge for treating acute pharyngitis, and its preparation method	CN104840566 A20150819	Nepalese polygonum, Auricle, Hedyotis, Bulleyanachang	Acute pharyngitis

3.	Herb extract- containing lozenge composition for treating inflammatory diseases of the mouth and pharynx	WO 2010003472A2 20100114	Herbal extracts	Inflammation in mouth and pharynx, cough, and upper respiratory tract infection
4.	Herbal formulations comprising cineole, eugenol, and vasicine as a cough lozenge	WO 2010003472A2 20100114	Clove, Adhatoda vasaka, Eucalyptus oil	Coughs and sore throat.
5.	Process for addition and stabilization of vitamin-C in a hard candy-like comestible	USP4692339	Sodium ascorbate and ascorbic acid	Antimicrobial and nutritional supplement
6.	Herbal cough candy and process for the preparation of the same	Indian Pat. Appl. (2014), IN2012D E03038 A 20140425	Vitis vinifera, Terminalia chebula, Piper longum, Glycyrrhiza glabra, Cinnamomum zeylanicum, Melaleuca leucodendron, Eucalyptus oil, sugar and liquid glucose base	Minor throat infections and laryngitis

7.	Synergistic herbal blood detoxifier formulation	Indian Pat. Appl. (2012), IN 2010DE02545A 20120427	Echinacea purpurea leaves, Andrographis paniculata leaves, Boerhaavia diffusa whole plant, Arctium lappa root, Rubia cordifolia root, Pothos aureus, leaves of Ixoracoccinea, stems of Jacaranda mimosifolia,	Blood purification
8.	Therapeutic herbal lozenge composition	U.S. Pat. Appl. Publ. (2006), US 20060251731 A1 20061109	Osha root, lobelia herb. licorice root, yerba santa leaf, eyebright herb, cat's claw, rosemary, ginger, green tea leaf, grape seed, and peppermint	Enhances respiration
9.	Development of anti-cough, antitussive and throat soothing herbal formulation	U.S. Pat. Appl. Publ. (2006), US 20060251731 A1 20061109	Extract of Piper cubeba, Glycyrrhiza glabra, Acorus calamus, Alpinia galanga, Zingiber officinale	Anti-cough, antitussive
10.	Herbal formulation of Gymnema sylvestre as a dietary aid	U.S. Pat. Appl. Publ. (2004), US 20040071801 A1 20040415	Gymnemic acid	Dietary aid for controlling sweet intake

11.	Candy for larynx	CN 200510024625	licorice, dried tangerine peel, boat fruited sterculia seed	Cough relief
12.	Process for making a hard-candy based oral pharmaceutical lozenge containing an antacid.	US5616340 (1997) US5399354 (1995)	calcium carbonate or magnesium carbonate	Antacid
13.	Production process for NSAID containing lozenges	US1032803 9 (2019)	NSAIDs	Sore throat
14.	Medical cannabis lozenges and composition thereof	US9504723 (2016)	Cannabidiol and tetrahydrocannabinol	Psychoactive drug
15.	Suckable-flurbiprofen lozenges for treatment of sore throat	US 6166083 (2020)	Flurbiprofen	Sore throat

LIST OF SOME MARKETED LOZENGES⁹

Table 1.4: List of some marketed lozenges

S.NO	TRADE NAME	ACTIVE INGREDIENT	DEVELOPER	INDICATION
1.	Drill	Chlorhexidine-digluconate, tetracaine hydrochloride	Pierre Fabre-France	Cough relief antimicrobial and antiviral
2.	Horehound lozenges	Marrubium vulgare		Cough relief
3.	Halls	Menthol, eucalyptus oil, hexylresorcinol	Mondelez International, Cadbury-USA	Antitussive, natural cough suppressant
4.	VICKS cough drops	Menthol	Procter and Gamble USA	Antitussive: Throat lozenge for cough and sore throat- cough suppressant and oral.

5.	ZICAMcold remedy	Zinc acetate, zinc gluconateandmenthol		Cold,fluand allergies, to treatorreduce symptomsofthe cold virus
6.	Strepsils	2,4-dichlorobenzyl alcohol,amylmetacresol, hexylresorcinol, flurbiprofen	ReckittBenckiser-UK	Sore throat, viral infection, antiinflammatory actions,antiseptic, upper respiratory tract infection, analgesic
7.	Dorithricin	Tyrothricin,benzalconium chloride, and banzocaine	MEDICE ArzneimittelPütter GmbH and Co. KG, Germany	Throatpain, acute pharyngitis and sore throat,antiviral.
8.	Koflet	Ginger,pepper, clove, licorice	HimalayaDrug company-India	Pharyngitis, Laryngitis, respiratorytract disease
9.	Hajmola	Combinationof digestive herbalsextractsand powder	Dabur-India	Digestive
10.	Bronchipret	Thymus vulgaris), ivy (Hederahelix)orcowslip (Primula veris)	Bionorica-Germany	Commoncold, respiratory inflammati onand bronchitis
11.	NTtuss	Holy basil, turmeric, licorice,galangal,Vasaka	CadilaPharma	Sorethroatand cough

12.	Golden Throat Lozenge	HoneySuckleFlower(jin yinhua),PeppermintOil, Eucalyptus Oil, Luo-HanGuoFruit, Tangerine Peel (juhong),Star Anise Oil,Sucrose	Solstice medicine company	Sore throat, halitosisandupper respiratory tract discomfort
13.	Devilion	Caffeineand taurine	DevilionEnergy	Energyandsports
14.	ViraBLOC®	Elderberryextract	GNC	Upperrespiratory tract infections.
15.	Sambucus Immune Lozenge	Elder berry extract, VitamicC,Zincgluconate	Nature's Way	Immunesupport
16.	Benadryl-DR cough lozenges	Dextromethorphan Hydrobromide	Johnson and Johnson	Drycough andthroat irritation
17.	Strepsils Intensive	Flurbiprofen	ReckittBenckiser	Painrelieffromsore throat
18.	Andolex-C	Benzydamine-hydrochloride, Cetylpyridiniumchloride	iNOVA Pharmaceuticals	Pain and inflammationin the throat
19.	Cepacol	Mentholand Benzocaine	AdcockIngram	Sorethroatand throat pain
20.	Medi-KeelA	cetylpyridiniumchloride, benzocaine	AdcockIngram	Sorethroat
21.	Goldex throatlollies	CetylpyridiniumChloride	Goldexhealthcare	Sorethroat, tonsilitis, laryngitis
22.	EpiCor® Throat Lozenges	Saccharomyces cerevisiaeextract, menthol,manukahoney	Embria Health Sciences, LLC	Immunesupport

23.	AllergEase	Nettle, eyebright, elderflower, plantain, vitaminC,andmenthol	AllergEaseLLC	Seasonal allergies, immune supports
24.	PhytoRelief-CC	Contains Turmeric, PomegranateandGinger	Alchemlife	Cold,Fluand immune health.

DISEASEPROFILE¹⁰

HERPESIMPLEXVIRUS

Herpes, also known as herpes simplex virus (HSV), is a common illness that can result in excruciating blisters or ulcers. The main way it spreads is through skin-to-skin contact. Although treated, it cannot be cured. The herpes simplex virus comes in two varieties. Oral herpes and cold sores are two common illnesses caused by Type 1 (HSV-1) that are primarily transmitted through oral contact. Herpes genitalia can also result from it. The majority of adults have HSV-1 infection. Genital herpes is caused by type 2 (HSV-2) and is transmitted during intercourse. Most people only have minor symptoms or no symptoms at all. Blisters or ulcers may be unpleasant and may return as a result of the infection. Drugs can lessen symptoms, but they cannot eliminate the infection.

PATHOPHYSIOLOGY

The following distinct biological characteristics of HSV-1 and HSV-2

- i. Neurovirulence (system and the ability to enter the neurological spread).
- ii. Latency (the development and upkeep of latent infection in nerve cells ganglia close to the infection location): The trigeminal ganglia are typically affected in

orofacial HSV infections, whereas the sacral nerve root ganglia (S2-S5) are affected in genital HSV infections.

- iii. **Reactivation:** Numerous stimuli can cause latent HSV to reactivate and replicate, always in the region supplied by the ganglia where latency was created. (Eg: fever, trauma, emotional stress, sunlight, menstruation), leading to HSV shedding and recurring infection, whether overt or covert. When HSV-1 and HSV-2 are acquired orally and genitally in immunocompetent individuals, the oral cavity is the site of HSV-1 reactivation more often than the genital area. However, compared to the orolabial areas, the vaginal region experiences 8-10 times more HSV-2 reactivations. Reactivation is more frequent and severe in people with impaired immune systems.

An essential line of defence against herpes simplex is cellular immunity. Those with AIDS and organ transplant recipients, for example, who have compromised T-cell immunity, are susceptible to the spread of herpes simplex infection. Additionally, burn wounds and skin damage from atopic dermatitis or other allergic dermatoses may become worse due to herpes simplex infection.

HSV is available everywhere. There are no vectors involved in the transmission process; humans are the only natural reservoirs. In most human societies, endemicity is easily maintained due to latent infection, reactivation on a recurrent basis, and asymptomatic virus shedding.

HSV is spread through intimate physical contact, and infection results from the virus being injected into tiny skin fissures or into mucosal sites that are vulnerable to it, such as the oropharynx, cervix, or conjunctiva. Aerosol and fomite dissemination are uncommon since the virus is easily rendered inactive at room temperature and through drying.

PATHOGENESIS

Herpes simplex virus (HSV) infection can only spread when a vulnerable seronegative person comes into close, personal contact with an HSV-excreting individual. For an infection to begin, the virus needs to come into touch with mucosal surfaces or abraded skin. After a second round of viral replication at the site of original infection, neurons carry either an intact virion or, more simply, the capsid retrogradely to the dorsal root ganglia, where latency is formed. Recurrences are likely to occur more frequently in cases where the first infection was more severe, as evidenced by the size, number, and extent of lesions. Replication can occasionally cause illness and, rarely, culminate in a potentially fatal infection (such as encephalitis), but it is mostly the host-virus interaction that causes latency. Once latency has been established, the virus reactivates in response to the right stimuli, making itself visible at mucocutaneous sites as skin vesicles or mucosal ulcers.

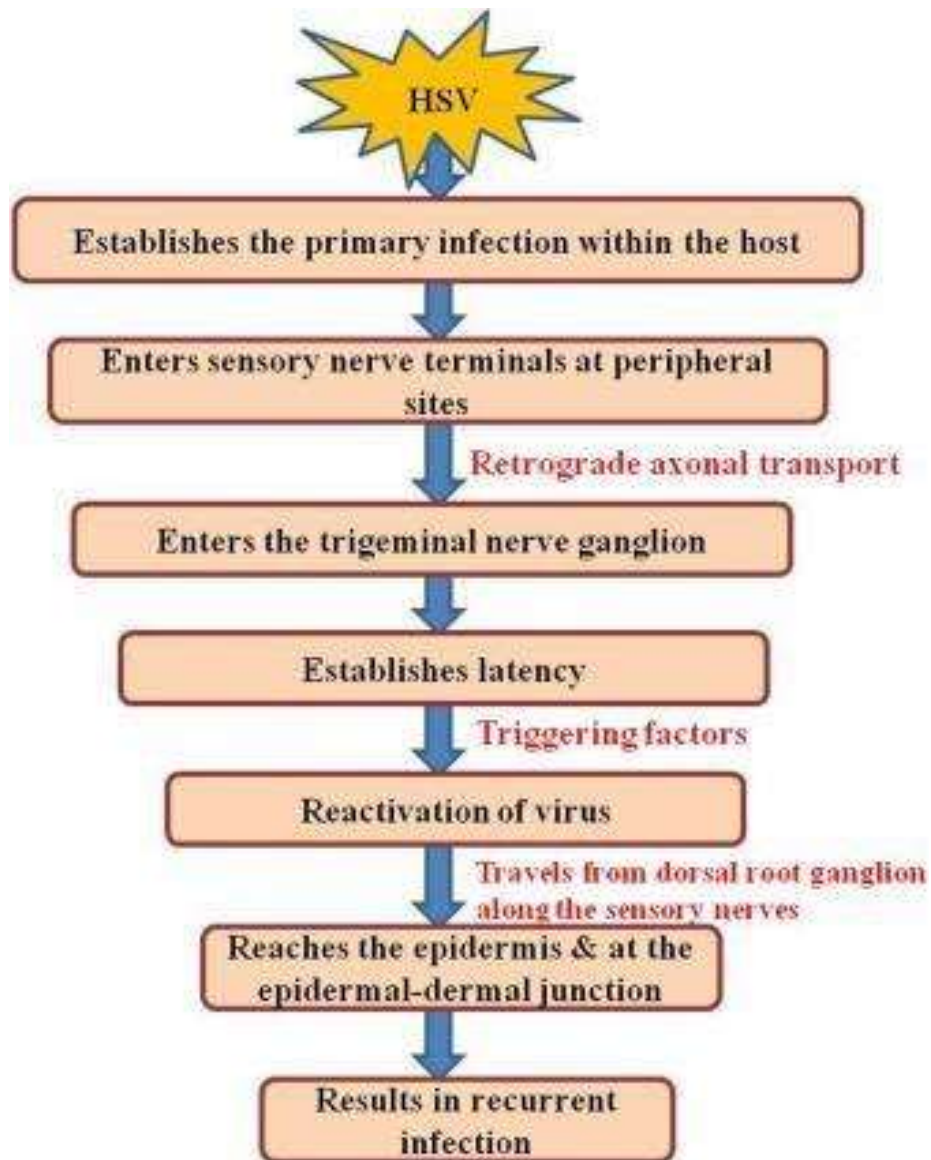
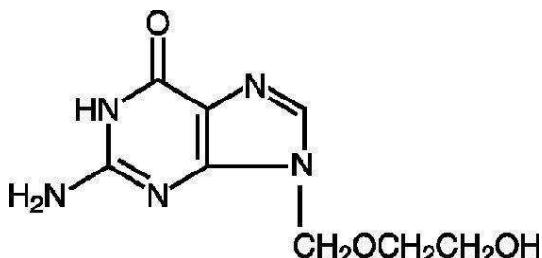


Fig1.10:Pathogenesis of HSV

DRUG PROFILE¹¹

Chemical structure:



Molecular formula: C₈H₁₁N₅O₃

Description: Acyclovir is an antiviral prescription medicine approved by the U.S. Food and Drug Administration (FDA) to treat and/or prevent the recurrence of certain types of herpes simplex virus (HSV) infections, including genital herpes. It also treats varicella-zoster virus (VZV) infections, including chicken pox (primary varicella infection) and shingles (herpes zoster). Acyclovir is approved in different formulations and strengths for use in specific populations, including in people who are immunocompromised. HSV and VZV infections can be opportunistic infections (OIs) of HIV. An OI is an infection that occurs more frequently or is more severe in people with weakened immune systems—such as people with HIV—than in people with healthy immune systems.

Chemical name: 2-amino-9-(2-hydroxyethoxymethyl)-1H-purin-6-one.

Category: Acyclovir is in a class of antiviral medications called synthetic nucleoside analogues. It works by stopping the spread of the herpes virus in the body.

pH: 7 to 7.4

Molecular weight: 225.20 g/mol.

CAS Number: 59277-89-3

Solubility: White crystalline powder. Maximum solubility in water (25°C): >100 mg/mL / Acyclovir sodium salt, slightly soluble in water; insoluble in alcohol.

Melting point: 256.5–257°C

BCSClass:Class-III

Logp:-1.76

pKa:2.52 (strongacidic)

Mechanism of action: Acyclovir is converted to its triphosphate form, acyclovir triphosphate (ACV-TP), which competitively inhibits viral DNA polymerase, incorporates into and terminates the growing viral DNA chain, and inactivates the viral DNA polymerase.

Absorption: Acyclovir is slowly and poorly absorbed from the gastrointestinal tract and bioavailability decreases with increasing dose. Acyclovir is widely distributed into tissues and body fluids. Plasma protein binding is relatively low at 9 to 24%. Renal excretion is the major route of elimination of acyclovir.

Distribution: Plasma protein binding is relatively low at 9 to 24%. Renal excretion is the major route of elimination of acyclovir.

Elimination: The majority of acyclovir is excreted in the urine as unchanged drug. 90-92% of the drug can be excreted unchanged through glomerular filtration and tubular secretion.

Half-life:2.9 hours

Dose:200mg,400mg,800mg for tablet, 5mg/kg for cream.

Dosage forms: Injectable solution, cream, ointment, injection, lyophilized powder for reconstitution, suspension, tablet, capsule.

Drug interaction: Some products that may interact with this drug include: other drugs that may cause kidney problems (including non-steroidal anti-inflammatory drugs NSAIDs such as ibuprofen, naproxen). Acyclovir is very similar to valacyclovir. Do not use medications containing valacyclovir while using acyclovir.

Marketed products: s Parenteral: For injection, concentrate, for IV infusion only: 25 mg (of acyclovir) per mL (500 mg, 1 g) Acyclovir Sodium Injection (Mayne), 50 mg (of acyclovir) per mL (500 mg, 1 g) Acyclovir Sodium Injection (American Pharmaceutical

Partners), For Injection, for IV infusion only: 500 mg (of acyclovir) Acyclovir Sodium for Injection (Abbott, American Pharmaceutical Partners, Bedford), Zovirax (GlaxoSmithKline), 1 g (of acyclovir) Acyclovir Sodium for Injection (Abbott, Bedford), Zovirax (GlaxoSmithKline).

EXCIPIENT PROFILE¹²

SUCROSE

Non-proprietary names:

BP: Sucrose

JP: Sucrose

Ph Eur: Sucrose

USP-NF: Sucrose

Synonyms:

Beet sugar; cane sugar; refined sugar; saccharose; saccharum, sugar.

Chemical name: β -D-fructofuranosyl- α -D-glucopyranoside

Molecular weight: 342.30 g/mol

Melting point : 160-186°C

Functional category:

Confectionary base; coating agent; granulation aid; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; therapeutic agent; viscosity-increasing agent.

Description:

Sucrose occurs as colourless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odourless and has a sweet taste

Solubility:

- i. Soluble in ethanol 1 in 400 at 20°C
- ii. Soluble in water 1 in 0.5 at 20°C and 1 in 0.2 at 100°C.

Incompatibility:

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g., ascorbic acid. In the presence of dilute or concentrated acids, sucrose is hydrolysed or inverted to dextrose and fructose (invert sugar).

Applications:

It is used for oral liquid formulations in the concentration of 67% w/w as syrup and sweetening agent.

DEXTROSE**Non-proprietary Names:**

BP: Glucose

JP: Glucose

PhEur: Glucose Monohydrate

USP: Dextrose

Synonyms:

Blood sugar; Caridex; corn sugar; C PharmDex; Dextrofin; D-(p)-glucopyranose monohydrate; glucosum monohydricum; grape sugar; Lycadex PF; Roferose; starch sugar; Tabfine D-100.

Chemical Name:

D-(p)-Glucose monohydrate

CAS Registry Number:

[5996-10-1]

Empirical Formula:

$C_6H_{12}O_6 \cdot H_2O$

Molecular weight: 198.17g/mol (formonohydrate)

Melting point: 146°C

Description:

Dextrose occurs as odourless, sweet-tasting, colourless crystals or as a white crystalline or granular powder.

Solubility:

- i. Soluble in water 1 in 1 at 20°C
- ii. Soluble in 95(%) ethanol 1 in 60 at 20°C
- iii. Practically insoluble in chloroform and ether.

Functional Category

Diluent, therapeutic agent, tonic agent, sweetening agent.

Applications

- i. Dextrose is widely used in solution to adjust tonicity and as a sweetening agent.
- ii. Dextrose is also used as a wet granulation diluent and binder, and as a direct-compression tablet diluent and binder.

ISOMALT

Non-proprietary Names:

BP: Isomalt

PhEur: Isomalt

USP-NF: Isomalt

Synonyms:

CPharm Isomaltidex, E953; galenIQ; hydrogenated isomaltulose; hydrogenated palatinose; Isomaltidex 16500; isomaltum; Palatinit.

ChemicalName:

Isomalt

CASRegistryNumber:

[64519-82-0]

EmpiricalFormulaandMolecularWeight:

C₁₂H₂₄O₁₁- 344.32 (for anhydrous)

C₁₂H₂₄O₁₁·2H₂O-380.32(for dihydrate) **Melting**

point: 168-171°C

Solubility:

Soluble in water.

Description:

Isomalt is a sugar alcohol (polyol) that occurs as a white or almost white powder or granular or crystalline substance. It has a pleasant sugar like taste with a mild sweetness approximately 50-60% of that of sucrose.

FunctionalCategory:

Coating agent, granulation aid, sweetening agent, tablet and capsule diluent, medicated base.

Applications:

In buccal applications such as chewable tablets it is commonly used because of its negligible negative heat of solution, mild sweetness, and 'mouth feel'.

It is also used widely in lozenges, sugar-free chewing gum, and hard-boiled candies, and as a sweetening agent in confectionery for diabetics.

LIQUIDGLUCOSE

Non-proprietaryNames:

BP:LiquidGlucose

PhEur: Glucose, Liquid

USP-NF:LiquidGlucose

Synonyms:

Corn syrup, Pharm Sweet, Flolys, Glucomalt, glucosesyrup, glucosum liquidum, Glucosweet, Mylose, Roclys, starch syrup.

ChemicalName:

Liquid glucose

CASRegistryNumber:

8027-56-3

EmpiricalFormula:

$C_6H_{14}O_7$

MolecularWeight: 198.17g/mol

FunctionalCategory:

Coating agent, sweetening agent, tablet binder.

Description:

Liquid glucose is an aqueous solution of several compounds, principally dextrose, dextrin, fructose, and maltose, with other oligosaccharides and polysaccharides. It is a colourless, odourless, and viscous sweet-tasting liquid, ranging in colour from colourless to straw-colour.

Solubility:

Solubility miscible with water, partially miscible with ethanol (90%).

Applications

- i. Liquid glucose is used as a base in oral solutions and syrups and also as a granulating and coating agent in tablet manufacture.
- ii. In sugar solutions for tablet coating, liquid glucose is used to retard the crystallization of the sucrose.
- iii. Liquid glucose is also used in confectionery products.

1.12.5 METHYLCELLULOSE

Non-proprietary Names

BP: Methylcellulose

JP: Methylcellulose

PhEur: Methylcellulose

USP: Methylcellulose

Synonyms:

Benecel; Cellacol; Culminal MC; E461; Mapolose; Methocel; methylcellulosum; Metolose; Tylose; Viscol.

Chemical Name:

Cellulose methylether

CAS Registry Number:

[9004-67-5]

Molecular Weight: 10,000-22000 Da.

Melting point: 190-200°C

Functional Category:

Coating agent, emulsifying agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity-increasing agent.

Description:

Methylcellulose occurs as a white, fibrous powder or granules. It is practically odourless and tasteless. It should be labelled to indicate its viscosity type (viscosity of a 1 in 50 solution).

Applications

- i. Methylcellulose may be added to a tablet formulation to produce sustained release preparations.
- ii. Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach

1.12.6. HYDROXYPROPYLMETHYLCELLULOSE**Non-proprietary names:**

BP: Hypromellose

JP: Hydroxypropyl Methylcellulose

PhEur: Hypromellose

USP-NF: Hypromellose

Synonyms:

Cellulose hydroxypropyl methyl ether, Hypromellose, Hydroxypropyl Methylcellulose 2208, Hydroxypropyl Methylcellulose 2910, Hydroxypropyl Methylcellulose 4000, Hypromellose, Cellulose 2-hydroxypropyl methyl ether.

Chemical name:

Cellulose 2-hydroxypropyl methyl ether

CAS Registry Number:

[9004-65-3]

Empirical Formula:

$C_{56}H_{108}O_{30}$

Molecular weight: 1261.4g/mol

Melting point: 225-254°C

Description:

Hydroxy propyl methyl cellulose is a semisynthetic, inert, and viscoelastic polymer that forms a colloid solution when dissolved in water. It acts as a thickening agent, coating polymer, bio-adhesive, solubility enhancer in solid dispersions, and binder in the process of granulation and in modified release formulations.

Solubility:

Soluble in hot water at 70°C

Applications:

- i. HPMC is commonly used as a binder and film coating material for tablets.
- ii. HPMC with high viscosity is used as a matrix for sustained-release preparations.
- iii. It is extensively used in the food industry as a stabilizer, as an emulsifier, as a protective colloid, and as a thickener.

1.12.7. SORBITOL

Non-proprietary Names:

BP: Sorbitol

JP: Sorbitol

Ph Eur: Sorbitol

USP-NF: Sorbitol

Synonyms:

D-Sorbitol, D-Glucitol

Chemical name:

D-Glucitol

CAS Registry Number:

[50-70-4]

Empirical Formula:

C₆H₁₄O₆

Molecular weight: 182.17g/mol

Functional Category:

Humectant; plasticizer; stabilizing agent; sweetening agent; tablet and capsule diluent.

Description:

Sorbitol is an odourless, colorless solid. Sinks and mixes with water.

Solubility:

- i. Soluble in water.
- ii. Slightly soluble in ethanol.

Application:

- i. Sorbitol is used as a diluent in tablet formulations prepared by either wet granulation or direct compression.
- ii. It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation.
- iii. In capsule formulations it is used as a plasticizer for gelatin.
- iv. Sorbitol has been used as a plasticizer in film formulations.

CHAPTER - 2

LITERATUREREVIEW

CHAPTER:2

2. REVIEW OF LITERATURE

LITERATURE REVIEW ON LOZENGES

13. Chui Chong et al., (2009) prepared ketamine lozenge formulation for usage in patients with neuropathic pain, as well as to explore its storage stability and bioavailability following oral or sublingual administration. In a hospital pharmacy, a lozenge containing 25 mg of ketamine was developed and made. High-performance liquid chromatography (HPLC) was used to determine stability during storage at 25°C or 28°C for up to 14 weeks. In six individuals with chronic neuropathic pain, bioavailability was assessed following both oral and sublingual administration. For at least 14 weeks, the lozenge composition was chemically stable. The median (interquartile range) oral and sublingual bio-availabilities were 24% (17-27%) and 24% (19-49%), respectively. The ketamine lozenge exhibited adequate storage stability and bio-availability was sufficient.

14. Dandagi Panchaxari Mallappa et al., (2020) studied Promethazine hydrochloride as a lozenge to address shortcomings in traditional dosing form. Lozenge were made by boiling and congealing isomalt and sucrose as a basis, with various quantities of HPMC E5. Preformulation demonstrated drug-excipient compatibility using FT-IR and DSC. General appearance, thickness, hardness, friability, cooling check, drug content, moisture content, in vitro dissolution, and microbiological test were among the post-compression parameters investigated. To optimize the formulation, factorial design 32 was chosen. The microbiological test revealed a broad inhibition zone, implying that it exhibited good resistance and thus regarded a suitable choice.

15. Ali Ali et al., (2022) formulated chewable lozenges containing natural extracts and evaluated their physiochemical qualities as well as their local positive effect on oral health. An ethanolic extract including myrtle berries, cinnamon, and cloves was macerated for 60 days before being employed in the production of chewable lozenges batches employing moulding technology and gelling agents such as gelatine, salep, and pectin. Batches containing 1.5 g of gelatine and 0.2 g of salep

with or without sugar had the best physicochemical qualities, the highest polyphenols release rate in both saliva and stomach simulated media, and were stable for three months at storage temperature (4°C). The chewable lozenges likewise had a 14 mm inhibition zone diameter.

16. Dalya Badry Khudhair et al., (2020) prepared nine formulations of acyclovir compressed tablet lozenges and examined the effects of binder type and concentration (gelatine, acacia, and tragacanth) on physical appearance, weight variation, hardness, thickness, friability, dissolving, drug content, and in-vitro drug release. Compressed tablet lozenges formula F4 using (Acacia 10%) as a binder were successfully manufactured and chosen as the best recipe since it released 98% of the medicine after 45 minutes, compared to other formulas.

17. Amra Althaf et al., (2022) developed herbal lozenges with anti-emetic properties using *Kaempferia galanga* L. and *Zingiber officinalis*. Sugar was dissolved in water, and the drug extracts were blended and heated until a proper consistency was reached, then poured into a lozenge mould and cooled to make a lozenge. To meet with GMP criteria, the lozenge was examined for different quality factors such as hardness, friability, thickness, weight uniformity, and disintegration. Lozenges are 100% herbal, contain no synthetic ingredients, and are a cost-effective way to treat emesis.

18. Rupali Chanda et al., (2020) formulated and evaluated medicated lozenges for sore throat. Solid dispersion of Loratadine was prepared using β -cyclodextrin in the ratios of 1:1, 1:2, and 1:3 to enhance the solubility of Loratadine. The prepared solid dispersion of Loratadine was analysed for solubility enhancement. Loratadine lozenges were then formulated with mannitol, sucrose, acacia, xanthan gum, liquid glucose by heat and congealing technique. The prepared lozenges were evaluated for drug-excipient incompatibility study, diameter, thickness, weight variation, hardness, friability, in vitro release study, and drug content. In this study, the possible interaction between the drug and excipient was determined by FTIR spectroscopy which indicated that there was no interaction between the chosen drug and excipients. Lozenges were successfully prepared by heat coagulating strategy utilizing sugar,

liquid glucose, acacia, xanthan gum, microcrystalline cellulose, β -cyclodextrin, flavor.

19. Anshul Kumar et al., (2019) developed and evaluated polyherbal lozenges for cold and flu. Polyherbal lozenge formulation was developed to eliminate all symptoms of cold and flu. Jaggery and sugar were dissolved in water and all the juices of drugs mixed and heated till suitable consistency and finally poured in lozenges mould and cooled to form lozenges. The lozenges are evaluated for various quality parameters like hardness, friability, thickness, weight uniformity and disintegration time which comply with the standard mentioned in GMP guidelines. Lozenge is completely herbal containing no synthetic ingredient and is economical to treat all the symptoms of cold and flu.

20. Manas R. Sahoo et al., (2022) developed and evaluated of talisapatradi and vyoshadi choorna lozenges. Physicochemical standardization of choorna was carried out as per the Pharmacopoeial Standards and can be used for quality control of the drug. TLC and FTIR fingerprint were found to be simple, unique, and rapid methods for each choorna and can be used as a diagnostic tool for the identification and authentication of the choorna. The HPTLC method developed for analysis can be used as a preliminary tool to ensure authenticity of lozenges formulation. In this study, lozenges formulation of well-known Ayurvedic choorna Talisapatradi and Vyoshadi choorna was developed.

21. Rajesh Kini et al., (2011) investigated the suitability of isomalt and liquid glucose as sugar substitute in the formulation of Salbutamol sulphate hard candy lozenges. The candy based lozenges were prepared by heating and congealing method in a candy based industry on request with sugar base, glycerine, citric acid, artificial flavours and colours and other essential excipients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability, moisture content, in vitro disintegration and dissolution by pharmaceutical standard methods. From this study, it can be concluded that the Isomalt can be successfully used as the tooth friendly sugar substitute in the formulation of medicated lozenges and owing to its low caloric value and its ability to

withstand formation of plaques, it could be used safely for paediatric patient concerns.

22. Rukiye Sevincozakaret al., (2021) formulated lozenges containing bentonite and characterization studies were carried out. Lozenges were prepared by moulding and hand-rolling techniques. The chewable lozenges were subjected to evaluation viz., Weight variation, Diameter and thickness, Friability, Disintegration time. Bentonite included lozenges in 4 different doses and were successfully prepared with the blank ones by using moulding and hand-rolling techniques. All the formulations showed good physical appearance. The gelatine used in the moulding method as binder enabled the lozenges containing low-dose bentonite to keep their shape due to its gelling feature. The radiation absorption study was conducted and the effectiveness of bentonite in this formulation was evaluated. Radiation absorption increased significantly with the increase of the bentonite dose.

23. Prashanth Kumawat et al., (2013) formulated clotrimazole lozenges by HPLC method. The mobile phase was 0.1% Tri-ethylamine in water (pH 3.000.05 adjusted with Ortho-phosphoric acid) and Methanol in a ratio of (25:75 v/v%) with isocratic programming, with a Grace mart C18 (250mm4.6mm, 5) column used as stationary phase with a flow rate of 1.0 mL/minute. 215 nm was chosen as the detecting wavelength. Clotrimazole retention time was reported to be 5.5-0.008 min. Clotrimazole was put through a series of stress tests. Under the tested conditions, degradation products were well resolved from the medication. At a concentration range of, the technique was linear ($r = 0.9998$). 0.5 to 60 µg/ml. According to the precision investigation, the percentage relative standard deviation was within acceptable limits and the mean recovery was Clotrimazole assay yielded a result of 100.75% 1.51.

24. Janet E. Codd et al., (1998) created two new bio-adhesive antifungal lozenges. To facilitate application to the oral mucosa, both were two-layered, with an upper modified- release drug-containing layer and a lower bio-adhesive layer consisting of drum-dried waxy maize starch and Carbopol 980. The first type of lozenge contain spray-dried miconazole nitrate. Acacia and Cremophor RH40 were added to improve

the dissolution of the weakly solubleazole as well as flavour. These second version also included chlorhexidine acetate in the medication layer, as both medicines had been shown to have antibacterial properties synergistically. The lozenges were used to test the in vivo release of drug(s) into saliva in a group of healthy participants. Located in the oral cavity's upper posterior region. Therapeutic levels were maintained for long periods of time using both formulations are acceptable.

26. Jean-francois et al., (2014) Compared ambroxol lozenges at various dosage (5- 30 mg) with lozenges flavoured with mint the primary result was a ratio of pain reduction measured repeatedly over a period of 3 hours in comparison to the initial 6- item verbal rating scale. The studies involved 1,772 adult patients in total. In all study arms, pain severity decreased. There was a meta-analysis of the 5 controlled trials in favour of ambroxol, with a difference in pain reduction of 0.11 (95% CI [0.15, 0.07]; p 0.0001) 20 mg. The studies' reporting was of poor quality. Ambroxol was somewhat more efficient at reducing pain in open sores than mint-flavoured lozenges during a three-hour period. However, there were more advantages to ambroxol than just these three given that more than 50% of patients utilizing mint-flavored lozenges for pain treatment claimed that their symptoms lasted longer than eight hours or Compared to 69% with ambroxol, The effectiveness after 1 day was good or very good. Individual patients seeking treatment for mostly local symptoms might choose the safe alternative of ambroxol.

27. Divya Gupta et al., (2014) experimented Strepsils lozenges to reducing POST in smokers who were undergoing surgery, endotracheal intubation combined with general anaesthesia. 100 individuals, Ages 20 to 65, physical status II according to the American Society of Anaesthesiologists (ASA) either sex, smoking history, or posting for more than one elective surgery procedure 1 hour, necessitating endotracheal intubation and general anaesthesia, were included. Strepsils (Group A) and sugar sweets (Group B) were distributed to 50 groups that were randomly assigned. (B Group). The patients' cough, painful throat, and hoarseness of voice were evaluated. 30 minutes, 12 hours, and 24 hours following extubation are included. At extubation, mild cough was present in 22% (Group A) and 52% (Group B),

respectively, in 39 (78%) patients (Group A) and 23 (46%) patients (Group B). frequency of sores Group A had a lower throat at extubation than Group B ($P = 0.04$). the other Observation periods (30min, 12 hrs, and 24hrs) there was a notable decline in Group A experienced a higher incidence of sore throats than Group B ($P = 0.000$). a hoarse voice. Utilizing preoperative Strepsils lozenges reduced the occurrence of POST and could be used as a quick and easy inexpensive method to lessen the symptoms of post and increasing the satisfaction of patients.

25. Vennela Srujan et al., (2019) designed montelukast sodium lozenges to give a delayed release of medication for the treatment of chronic asthma and allergic rhinitis. The advantages of prepared lozenges were increased bioavailability, decreased gastrointestinal discomfort, bypassing of the first metabolism, and Increased action onset. Sucrose, liquid glucose, and hydroxy propyl alcohol were used to make the lozenges. K4M methyl cellulose (HPMC K4M). To cover the odor, sodium saccharine and flavors were utilized. The medication has a nasty flavor. Weight variation, hardness, thickness, friability, content consistency, and wetness were all factors to consider content, and so forth. The hardness of the produced formulations ranges from 8 to 11 kg/cm², non-scary, and enjoyable. In vitro release rate investigations revealed that the drug release for lozenges was greatest in formulation F6 (99.30.52%) at 30 minutes when tested for drug excipient interactions using IR Spectral analysis.

28. B. Moulika Lakshmi et al., (2017) prepared and evaluated domperidone candy lozenges. The preparation process involves mixing of domperidone with all excipients, used in the formulation in different ratios by using heat congealing technique in which sucrose and dextrose heated separately upto 600C fusion together and reheated upto 1600C after which polymer HPMC K 100M, HPMC E5 and all other excipients are added and molded. The lozenges were subjected to evaluation viz., weight variation test, hardness, friability, drug content and in vitro release studies. Formulation showed that candy lozenges can be used as efficient means of formulation to enhance solubility and bioavailability of the drug as carried through oral cavity.

2.Avalaskaramruta et al., (2019) formulated and evaluated sweet hard candy lozenges using medicinal plant extract for pediatric patients to show better patient compliance using juice of vasaka leaves. Melting and molding technique was used for the preparation of lozenges. The sweet hard candy lozenges were subjected to evaluation viz., weight variation test, hardness, friability. Thus, herbal lozenges are formulated from aqueous extract of vasaka with bitter taste masked with sugar and flavored with ginger extract, easy for paediatric patients to administer. It can also be an ideal choice for travelling patients as it eliminates the need of water for its administration.

7.Sasikumarmenon et al., (2018) formulated the low bioavailability of curcumin from therapeutic formulations. A novel lozenge of 100mg turmeric extract in mouth dissolving formulation is evaluated for bioavailability of curcumin as compared with the conventional hard gelatin capsule containing 475mg curcumin. Fourteen healthy male subjects of Indian origin are dosed in a two way, two treatments, two sequence cross-over balanced, randomized design. Blood samples were collected sequentially to cover the plasma concentration-time curve to obtain a reliable estimate of the extent of absorption. Blood plasma was processed and analyzed using a validated isocratic hplc-ms/ms method to estimate the concentration of curcumin. The current study demonstrates the buccal absorption of curcumin with an innovative delivery system of lozenge which results in higher level of plasma curcumin level with 100mg dose compared to the 475mg of curcumin dosed through hard gelatin capsules.

30.Harrihemila et al., (2017) compared the efficacy of zinc acetate lozenges with zinc gluconate lozenges in common cold treatment and to examine the dose-dependency of the effect. Placebo-controlled zinc lozenge trials, in which the zinc dose was > 75 mg/day. The pooled effect of zinc lozenges on common cold duration was calculated by using inverse-variance random-effects method. The current evidence of efficacy for zinc lozenges, in particular zinc acetate lozenges, was so strong that common cold patients may be encouraged to try them for treating their colds.

10. Juliana Jabur Polete Witzler et al., (2016) developed potential probiotic lozenges containing *enterococcus faecium* crl 183. Lozenges were produced through three treatments: pcecontrol formulation; ppp1eprobiotic formulation; ppp2eprobiotic formulation with inulin. The probiotic strain had the viability decreased after lozenges production and during the storage from 5.53 to 4.83 log cfu/g at the beginning to 1.05e1.86 log cfu/g after 28 days, for both ppp1 and ppp2. Formulations were different concerning water activity, moisture and color ($p < 0.05$). All formulations remained microbiologically safe during the storage period. The anticariogenic evaluation showed that the probiotic bacteria were able to survive in saliva and inhibit the growth of *streptococcus mutans* atcc 25175 in this study. The lozenge with *e. Faecium* crl183 and inulin represents an alternative to the diversification of the probiotic segment which aggregates anticariogenic potential.

LITERATURE REVIEW ON HERPES SIMPLEX

32. Paolo G Arduino et al., (2008) studied Herpes Simplex Virus Type 1 (HSV-1) is an enveloped virus that reproduces nuclearily. It is primarily contracted via direct contact with lesions or bodily fluids (mainly saliva). HSV-1 infection is more common starting in childhood, with a negative correlation between seroprevalence and socioeconomic status. Children with primary HSV-1 infections might either show no symptoms at all or develop mucocutaneous vesicular eruptions after an approximate one-week incubation period. Typically, the tongue, lips, gingival, buccal mucosa, and hard and soft palate are affected by herpetic gingivostomatitis. HSV-1 is the primary cause of most orofacial HSV infections, whereas HSV-2 infection is becoming more prevalent. Herpes labialis, or vesiculo-ulcerative lesions at mucocutaneous junctions, are commonly the result of recurrent infections that happen at varying intervals. In generally healthy individuals, recurrent HSV-1 infection in the mouth is rare; nevertheless, in immunocompromised patients, recurrent infection may be more severe and/or aggressive. The clinical history and presenting symptoms are typically sufficient to make the diagnosis of common herpetic infection. However, in individuals

who are or may become immunocompromised, a confirmatory test diagnosis is necessary.

33. Nancy M. Sawtell et al., (2021) studied alpha herpesvirus reactivation and latency and its relationship to human disease is developing at an intriguing moment. Both animal models and neural culture models have contributed to conceptual advancements. The idea that the tegument protein and viral transactivator VP16 are important in the change from latency to the lytic cycle is the main topic of this review. The neurological system's modulation of VP16 transactivation balances the development of latent infections, pathogenicity, and acute infection. This transactivator is necessary for reactivation in order to promote entrance into the lytic cycle. Sequences granting pre-immediate early transcription contained in the typically leaky late promoter induce in vivo de novo production of VP16 protein. The SCG neuron culture model has provided alternative mechanisms for controlling VP16 expression in vitro. These mechanisms include the ideas that (i) VP16-dependent reactivation (Phase II) requires and precedes generalized transcriptional derepression of the viral genome and sequestration of VP16 in the cytoplasm for approximately 48 hours (Phase I); and (ii) Phase II reactivation requires a histone methyl/phospho transition made during Phase I. The field's goal is to reconcile various facts into a united Virus reactivation model.

34. Shuyong Zhu et al., (2021) investigated Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2, respectively) are two of the most common human viruses in the world. They can cause a number of illnesses, such as encephalitis, meningitis, cold sores, vaginal herpes, and herpes stromal keratitis. HSV has evolved defence mechanisms to elude the intrinsic, innate, and adaptive immune responses, which are essential for maintaining control over the virus. Pathogenesis can also be aided by the immune system, as evidenced by encephalitis and stromal keratitis. Human genetic polymorphisms contribute to the explanation of why some people are more likely than others to experience severe illness following HSV infection. HSV has two replication

cycles: lytic and latent, just as all other herpesviruses. While there is little gene expression and no infectious virus particles during latency, HSV generates infectious viral particles during lytic replication in order to infect other cells and species. HSV causes disease during primary infection and upon reactivation. It establishes latency in neurons. It is unclear exactly which host and viral variables regulate latency and reactivation, as well as the mechanisms underlying these processes. The HSV life cycle, HSV's relationship to the immune system, and three of the most well-researched pathologies—genital herpes, herpes simplex encephalitis, and herpes stromal keratitis—are all reviewed here. We also talk about the possible link between Alzheimer's disease and HSV-1 infection.

35. K J Looker et al., (2004) investigated the epidemiological data about the interplay between HSV-1 and HSV-2 infections. A comprehensive analysis of published epidemiological research detailing the age-specific distribution of HSV-1 or HSV-2 and the co-occurrence of the two viral illnesses was conducted. According to cross-sectional research, individuals with HSV-1 infection in study populations classified as "low risk" ($p = 0.06$) and across European populations ($p = 0.001$) have higher unadjusted odds of having HSV-2. Neither in the US nor in "high risk" groups was this apparent. The results of prospective studies, which show a nonsignificant tendency towards a decreased risk of HSV-2 infection linked with prior HSV-1 infection, are not consistent with the higher risk of HSV-2 in individuals with HSV-1 infection. "Low risk" and European populations have a comparatively low seroprevalence of HSV-2, and the majority of infections are found in individuals who have traits that make them highly susceptible to both HSV-1 and HSV-2. Any beneficial impact of HSV-1, which is suggested but not shown in prospective and adjusted studies, may be obscured by this confounding.

36. Mahnaz Fatahzadeh et al., (2007) determined over 80 herpesviruses known to science, eight are human diseases. The human herpes simplex virus (HSV) is a communicable infection that is widely distributed in the general public. Significant difficulties could arise in the immunocompromised host. It is also a difficult clinical

conundrum because of the psychological pain brought on by the stigma attached to genital herpes and prominent facial sores in individuals who have outbreaks frequently. This article gives the doctor a current overview of the various management techniques for mucocutaneous HSV-induced disease by reviewing the epidemiology, pathophysiology, and diagnostic aspects of HSV infections.

37. Anthony L. Cunningham et al., (2006) determined Herpes simplex virus reaches sensory nerve endings after infecting the skin or mucosa. It then travels by retrograde axonal transport to the dorsal root ganglion, where it enters a state of permanent latency. Human experiences spontaneous intermittent reactivation, which results in the anterograde transfer of viral particles and proteins to the skin or mucosa, where the virus sheds and/or causes illness. During an initial or recurring infection, the skin or mucosa is the site of immune control over viral infection and replication. Immune processes also regulate latency and reactivation inside the dorsal root ganglion. The mechanisms of innate and adaptive immunity that regulate infection in the skin or mucosa and in the dorsal root ganglion are also examined in this article. Of particular interest are the roles played by interferons, myeloid and plasmacytoid dendritic cells, CD4+ and CD8+ T cells, interferon-g, and other cytokines, as well as their potential relevance in the development of genital herpes vaccines.

LITERATURE REVIEW ON ACYCLOVIR

38. Dalya Badry Khudhair et al., (2020) formulated lozenges are that have a tendency to melt in the mouth or throat. They might be made up of one or more medications in a base that has been sweetened and flavored. They are advised for the treatment of localized irritation or infection of the mouth or throat, but they can also be used systemically to combine Acyclovir with Lidocaine in the form of pressed-coated tablet lozenges. Since of this, the lozenges are appropriate for treating viruses that cause oral cavities since they have both local anaesthetic and antiviral properties. The purpose of this study was to examine the effects of different types and concentrations

of binders (gelatine, acacia, and tragacanth) on the physical appearance, weight variation, hardness, thickness, friability, dissolving, drug content, and in vitro drug release of acyclovir compressed tablet lozenges. recipe F4, which contains 10% Acacia as the binder in compressed tablet lozenges, was developed effectively and chosen as the best recipe since, in comparison to other formulas, it released 98% of the medicine after 45 minutes.

39.V.R. Sinha et al., (2007) treated many forms of herpes virus infections, such as genital herpes simplex infections, herpetic conjunctivitis, herpes simplex encephalitis, etc., acyclovir is the preferred antiviral medication. In order to establish a validated stability-indicating high-performance liquid chromatography method, the current study describes the degradation behaviour of acyclovir under various stress conditions (hydrolysis, oxidation, photolysis, and thermal decomposition) recommended by the International Conference on Harmonization. In acidic environments and under oxidative stress, acyclovir is observed to breakdown substantially. The medication degrades mildly in neutral and alkaline environments. The medication can withstand dry heat. When exposed to light in a solid state, the medication is shown to be sufficiently stable; nevertheless, when exposed as a solution in water, photolytic deterioration is noted. Guanine is found to be the primary breakdown product in both acidic hydrolysis and photolysis by comparison with the standard. Using a water- methanol ratio of 90:10, drug and degradation products can be successfully separated under a variety of circumstances on a C-18 column. The wavelength of detection is 252 nm, and the flow rate is 1 mL/min. In terms of linearity, precision, accuracy, selectivity, specificity, and robustness, the approach is validated. With relative standard deviation values less than 2%, the mean values of the slope and correlation coefficient are 39.307 and 0.9998, respectively. It is discovered that the drug's recovery falls between 97.34% and 102.35%. The previous study's findings suggest that the medicine can be analyzed in a variety of stability samples using the stability- indicating method created for acyclovir.

40.M.Tod et al., (2000) Acyclovir is authorized for the intravenous and oral treatment of paediatric varicella-zoster virus (VZV) and herpes simplex virus (HSV) infections. However, a lack of pharmacokinetic evidence limits the use of this medication orally in children under the age of two. In order to support the suggested dosing regimen (24 mg/kg of body weight three times a day for patients younger than one month of age, or four times a day otherwise), the present study set out to determine the typical pharmacokinetics of an oral suspension of acyclovir given to children younger than two years of age as well as the interindividual variabilities in the values of the pharmacokinetic parameters. A multicenter trial included children with HSV or VZV infections under the age of two. Children received oral acyclovir suspension treatment for a minimum of five days. Plasma samples were taken at steady state, before to the administration of acyclovir, and two, three, five, and eight hours after the drug was administered. Radioimmunoassay was used to measure the amounts of acyclovir. The population technique was used to analyze the data. The pharmacokinetic study took into account the data for 79 children (212 samples, 1 to 5 samples per patient). The estimated glomerular filtration rate, body surface area, and serum creatinine level were all correlated with acyclovir clearance. Body weight and distribution volume were correlated. In the first month following delivery, the elimination half-life dropped significantly, from 10 to 15 hours to 2.5 hours. There was 0.12 bioavailability. After the parameters were standardized to the body weight, the interindividual variability decreased. Therefore, it is advised that dosage be adjusted based on body weight for this demographic. According to simulations, acyclovir stays above the 50% inhibitory concentration for more than 12 hours for HSV but not for VZV during the course of a 24-hour period. For the treatment of HSV infections, the suggested dosage schedule is suitable; however, for the treatment of VZV infections, children older than three months may require a twofold dose increase.

41.Pradip Kumar Ghosh et al., (2006) created an oral microemulsion formulation to increase acyclovir's bioavailability was the primary goal of this investigation. For the oral administration of acyclovir, a Labrafac-based microemulsion formulation containing Plurol Oleique as a cosurfactant and Labrasol as a surfactant was created. Rats' in vivo oral absorption of acyclovir from the microemulsion was studied, and the

microemulsion system's phase behavior and solubilization capacity were described. The pseudoternary phase diagrams obtained at different Labrasol:Plurol Oleique:Labrafac ratios showed the presence of a single isotropic area, which was thought to be a bicontinuous microemulsion. The microemulsion region area, water solubility, and amount of Labrafac dissolved into the microemulsion system all rose with an increase in Labrasol concentration; on the other hand, a rise in Plurol Oleique % had the reverse effect. Other properties of the microemulsion system, including diffusion, bioavailability, pH, interfacial tension, viscosity, and refractive index, were also studied. The medication acyclovir, which is poorly soluble, showed excellent solubility when combined with Labrafac (10%), Labrasol (32%), Plurol Oleique (8%), and water (50%) in a microemulsion formulation. When the microemulsion formulation was administered orally instead of the commercially available tablets, the in vitro intraduodenal diffusion and in vivo testing showed a 12.78-fold improvement in bioavailability.

42. Manivannan Rangasamy et al., (2008) utilised hand shaking and ether injection, acyclovir-entrapped niosomes were created using varying ratios of Span-80 (a non-ionic surfactant) to cholesterol (CHOL) (1:1, 1:2, and 3:1). The generated niosomes ranged in size from 0.5 to 5 microns when shaken by hand and from 0.5 to 2.5 microns when injected with ether. An increase in span-80 concentration results in an increase in the order of encapsulation efficiency. An extended duration of one day and sixteen hours is required for the 76.64% release of formulation made with CHOL: Span-80 (1:1), according to an in-vitro release investigation on acyclovir niosomes.

43. Dalya B. Khudhair et al., (2021) studied an initial local anaesthetic effect of lidocaine during the treatment of viral infection by using acyclovir (ACV) lozenges in combination with a fast-dissolving lidocaine layer as a coat. The tablets were press-coated. The best ACV lozenge formulation was directly compressed to create the press-coated tablet, which was then placed in the tableting machine die with powdered

lidocaine that dissolves quickly both above and below the surface of the manufactured ACV lozenge. Next, everything is gently compacted. After making the pressed coated tablets, their hardness, thickness, disintegration, and in vitro release of lidocaine and ACV were assessed. The two medications that were contained in the pressed-coated tablets were identified using high-performance liquid chromatography-ultraviolet (HPLC-UV) detection. The results of FTIR spectrophotometry study indicated that the two medications and excipients employed in the formulation of the press-coated tablets were compatible, as there were no interactions between the pharmaceuticals or between the drugs and the excipients. The press-coated tablet was shown to be a viable dosage form that could provide continuous release of ACV and quick release of lidocaine without causing any issues with incompatibility.

CHAPTER-3

AIM AND OBJECTIVE OF THE WORK

CHAPTER:3

AIM AND OBJECTIVE OF WORK

AIM:

The aim of the current research is the Formulation Development and Evaluation of Acyclovir Hard Candy lozenges.

OBJECTIVE OF WORK:

1. To carry out the physicochemical characteristics of drug and excipients.
2. To perform FTIR studies for the formulations. (Drug-Excipient Compatibility study)
3. To study the physicochemical characteristics of Formulated Lozenges: Hardness, Weight variation. Thickness and Drug content.
4. To perform In vitro drug release studies of the Acyclovir Hard Candy Lozenges.
5. To perform the stability studies on the best formulation of Acyclovir Hard Candy Lozenges.

FUTURE SCOPE:

Continuous release formulation can be included in the lozenge to improve the therapeutic effect of the lozenge dosage form.

CHAPTER - 4

MATERIALS AND EXPERIMENTAL METHODS

CHAPTER:4

4.MATERIALSANDMETHODS

MATERIALS

INSTRUMENTS

Table4.1:Instrumentsusedfortheformulation

S.No	INSTRUMENTS	MANUFACTURER
1.	UVspectrophotometer	Shimadzu1800,Japan
2.	Weighingbalance	Asha Scientific Company
3.	Magneticstirrer	REMI
4.	pH meter	MCDalal,India
5.	DissolutionApparatus	CampbellElectronics
6.	FT-IR	Shimadzu,Japan
7.	Verniercaliper	Mitutoyo, Japan
8.	Monsantohardnesstester	CampbellElectronics

CHEMICALS

Table4.2:Chemicalsusedfortheformulation

S.No	Nameof the Chemical	Supplier
1	Acyclovir	AurobindoPharma
2	Isomalt	SDFineChemicals, Mumbai
3	Sucrose	SDFineChemicals, Mumbai
4	Liquidglucose	SDFineChemicals, Mumbai
5	Mannitol	SDFineChemicals, Mumbai
6	Dextrose	SD FineChemicals,Mumbai

7	Methylcellulose	SDFineChemicals, Mumbai
8	Aspartame	SDFineChemicals, Mumbai
9	Citricacid	SDFineChemicals, Mumbai
10	Propyleneglycol	SDFineChemicals, Mumbai
11	Polyethyleneglycol200	SDFineChemicals, Mumbai
12	Glycerine	SDFineChemicals, Mumbai
13	Menthol	SDFineChemicals, Mumbai

EXPERIMENTALMETHODS

PREFORMULATIONSTUDIES⁴⁴

The first logical step in the development of any formulation was preformulation research. It can be defined as “investigation of physical and chemical properties of the drug substance alone and combined with the excipients” These investigations focus on the physiochemical characteristics of the new compound that may have an impact on medication efficacy and formulation development. Preformulation testing's main goal is to produce data that formulators can use to create stable, bioavailable dosage forms that can be

- i. To determine physical characteristics.
- ii. To determine its compatibility with the excipient.

Determination of melting point of Acyclovir:⁴⁵

The electrical melting point apparatus using capillary method measured the melting point of Acyclovir.

Determination of λ max of Acyclovir:⁴⁵

Acyclovir solution in phosphate buffer 6.8 was prepared, then the solution was scanned by spectrophotometer from 200-400 nm, and λ max of the drug was determined.

Drug-Excipient compatibility studies⁴⁵

The proper design and formulation of a dosage form requires consideration for the physical and chemical characteristics of all drug substances and excipients used in fabricating the final product. The successful formulation of a stable and effective dosage form depends on the careful selection of the excipients that are added in the formulation.

The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and easy to administer and safe.

Compatibility study was carried out by recording the sample using Fourier Transform Infra-Red Spectrophotometer (FTIR) in the range of 4000 cm^{-1} to 400 cm^{-1} by Potassium Bromide pellet technique. The spectra was examined and analysed for the study.

PREPARATION OF PHOSPHATE BUFFER pH 6.8⁴⁶

13.609 g of potassium hydrogen orthophosphate dissolved in 500 ml of distilled water to give 0.2M of solution. 4g of sodium hydroxide is dissolved in 500 ml of water to give 0.2M of solution. 500 ml of 0.2M of solution potassium hydrogen orthophosphate and 224 ml of 0.2M sodium hydroxide solution are mixed together and made up to 2 litres concentration with distilled water.

PREPARATION OF CALIBRATION CURVE FOR ACYCLOVIR⁴⁷

Preparation of standard stock solution A Standard stock solution of Acyclovir was prepared by accurately weighing 50 mg Acyclovir in 50 ml of volumetric flask and dissolved in sufficient sulfuric acid (0.1 N) and volume make up with water to obtain a concentration 1 mg/ml or 1000 $\mu\text{g/ml}$ (standard Stock I). Further diluting 2.5 ml of stock I solution to 25 ml mixture of distilled water to get desired concentration of 100 $\mu\text{g/ml}$ (standard stock II).

Selection of wavelength for analysis of Acyclovir

The 10 µg/ml of Acyclovir solution is prepared by accurately measuring 1 ml of standard stock II solution, was transferred into a 10 ml volumetric flask and diluted to 10 ml with distilled water. This 10 µg/ml of Acyclovir solution was used for initial spectral scan in the UV range of 400-200 nm to detect wavelength at which maximum absorbance and this λ_{max} is used for development of method, and further dilutions for linearity were prepared from the stock II solution by alligation method.

Preparation of serial dilutions

The series of different dilutions were prepared by using the standard stock II solution to get a respective concentration of 2, 4, 6, 8 & 10 µg/ml. The results are tabulated in the results.

Table 4.3: Formulation of Acyclovir Hard Candy Lozenges

S. No	Ingredients	F1	F2	F3	F4	F5
1	Acyclovir	200	200	200	200	200
2	Sucrose	1500	2000	-	-	-
3	Dextrose	1500	1000	1500	2000	-
4	Liquid Glucose	-	-	1500	1000	-
5	Isomalt	-	-	-	-	3000
6	Aspartame	QS	QS	QS	QS	QS
7	HPMC	0.25%	0.50%	1%	-	2%
8	Methyl Cellulose	0.75%	0.50%	-	1%	-
9	Citric acid	60	60	60	60	60
10	Sodium Citrate	30	30	30	30	30

11	Colour	QS	QS	QS	QS	QS
12	Flavour	QS	QS	QS	QS	QS
13	MethylParaben	2	2	2	2	2

PREPARATION OF ACYCLOVIR HARD CANDY LOZENGES.⁴⁸

- The lozenges were prepared by heating and congealing technique.
- Syrupy base was prepared in a beaker by dissolving the required amounts of sugar in water and kept for heating on a hotplate.
- Temperature was maintained at 105-110°C till it became thick.
- The drug and other excipients (except plasticizer) were added manually and mixed thoroughly after 30 min with continue process of heating.
- The prepared mass was further heated for 45 min and then plasticizer was added into it.
- Then above syrupy base was poured into pre-cooled and pre-lubricated mould and the mould was kept aside for 10-15 min.
- Lozenges were removed from mould and were kept for air drying.

EVALUATION PARAMETERS

Physical parameters:⁴⁹

The medicated lozenges were examined in terms of clarity, texture and consistency. Texture of lozenges in terms of stickiness was evaluated by visual inspection of the product.

Weight variation test:⁴⁹

Ten lozenges from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviations are calculated. Individual weight of each lozenge is also calculated using the same and compared with average weight. If any weight variation is there, that should fall within the prescribed limits (generally 10% for lozenge weighing 120 mg or less, 7.5% for

lozenge weighing 120 mg to 300 mg and 5% for lozenge weighing more than 300 mg):

$$\% \text{Deviation} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} \times 100$$

Thickness test:⁴⁹

The thickness in millimetres (mm) was measured individually for 10 pre weighed lozenges by using a vernier caliper. The average thickness and standard deviation are reported. The thickness of a lozenge can vary without any change in its weight.

Hardness test:⁴⁹

The hardness of lozenges was measured using a Monsanto Hardness Tester. The crushing strength of the 10 lozenge with known weight and thickness of each batch was recorded in kg/cm² and the average hardness and the standard deviation is reported

Drug Content Uniformity:⁵⁰

The content uniformity was tested by measuring weight equivalent to one lozenge and dissolving the powder content in 100 ml volumetric flask containing 50 ml of 6.8 phosphate buffers and allowed to stand for 30 min. The mixture was made up to volume with buffer pH 6.8. The diluted sample absorption was recorded at 272 nm. Three replication of each test were analysed for mean and standard deviation. For most of the larger dose drugs in lozenge form, the official potency range permitted is not less than 90% and not more than 110% of the labelled amount.

Moisture Content:⁵¹

By Gravimetric method, one gram sample is weighed and placed in a desiccator at for 24 hrs. Final weight is subtracted from initial and the difference in moisture content is calculated:

$$\% \text{Moisture content} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

MouthDissolvingTime:⁴⁸

The mouth dissolving time was determined by in-house method. The time taken by the lozenge to dissolve completely was determined by placing each lozenge in separate beaker containing 100 ml phosphate buffer pH 6.8 at 50 rpm using mechanical stirrer and time was noted at 37°C.

In-vitro Drug Release:⁴⁹

The modified dissolution test apparatus USP type II (paddle) is used and 250 ml of the dissolution medium phosphate buffer pH 6.8 is placed in the beaker containing the lozenge and stirred at 100 rpm. Five ml aliquot samples are withdrawn at 5 min interval and replaced immediately with an equal volume of fresh medium i.e., phosphate buffer pH 6.8. Each aliquot is diluted and analyzed using blank, by UV-Visible spectrophotometer. The amount of drug release is determined from the standard calibration curve of pure drug.

Following parameters were used for the dissolution study

- 1 Apparatus : USP dissolution apparatus type II (paddle)
- 2 Speed of the paddle : 100 RPM.
- 3 Temperature : 37.5°C ± 0.5°C.
- 4 Dissolution medium : Phosphate buffer pH 6.8.
- 5 Volume of fluid : 250 ml

The samples were analysed at 272 nm using UV-Visible spectrophotometer

EVALUATION OF IN-VITRO RELEASE KINETICS OF OPTIMIZED FORMULATION⁵²

To study the kinetics, data obtained from in-vitro release were plotted in various kinetic models.

ZeroOrderReleaseKinetics:

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_0 t.$$

Where, Q is the fraction of drug released at time t and k_0 is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

FirstOrderReleaseKinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\text{Log } C = \text{Log } C_0 - kt/2.303$$

Where C is the amount of drug dissolved at time t,

C_0 is the amount of drug dissolved at t=0 and k is

the first order rate constant.

A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

Higuchi equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q = K_2 t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent:

Table 4.4 Drug Release Kinetics Mechanism.

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (Non-Fickian) diffusion
0.89	Casell transport
$n > 0.89$	SuperCasell transport

STABILITY STUDIES:⁵³

Stability studies were carried out according to ICH guidelines by exposing the Formulations F5 in their final packing mode to the temperature $40 \pm 2^\circ\text{C}$ and relative humidity $75 \pm 5\%$ in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content and in-vitro dissolution profile. Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing:

1. $21^\circ\text{C}/45\%\text{RH}$ analyzed every month for period of three months.
2. $25^\circ\text{C}/60\%\text{RH}$ analyzed every month for period of three months.
3. $30^\circ\text{C}/70\%\text{RH}$ analyzed every month for period of three months.

CHAPTER - 5

RESULTSANDDISCUSSION

CHAPTER-5

RESULT AND DISCUSSION

RESULTS OF PREFORMULATION STUDIES

Determination of melting point of Acyclovir:

Melting point was measured by the capillary method and it was found to be 255°C.

Determination of λ_{max} of Acyclovir:

a) Selection of wavelength

The spectra of Acyclovir in methanol showed absorption at 253.2 nm shown in figure which is complying with reported λ_{max} . Hence, it was selected as λ_{max} of Acyclovir in sulfuric acid distilled water for further use.

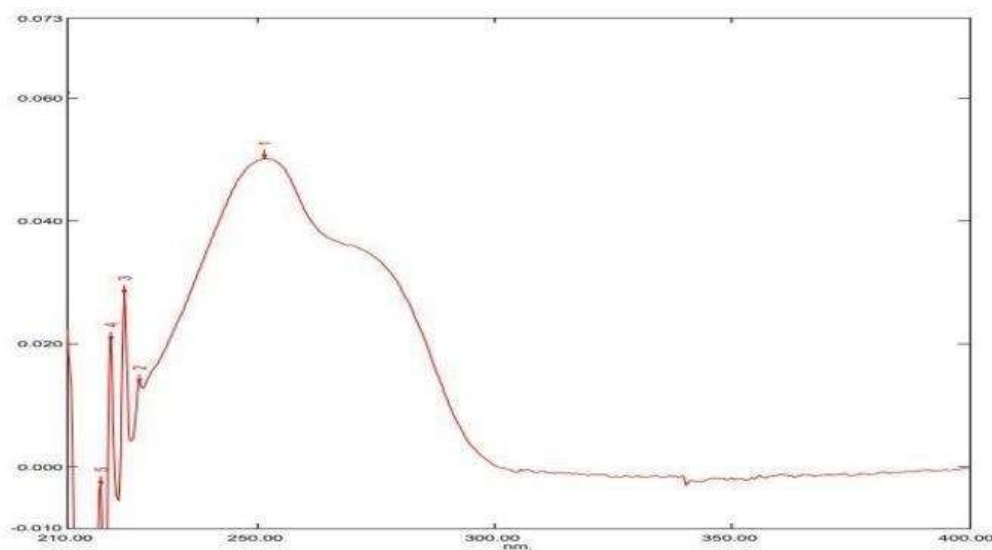


Fig 5.1: λ_{max} of Acyclovir

b) Preparation of calibration curve

Quantification of unknown samples by UV-Visible spectrophotometer or any other instrumental method of analysis needs a reproducible calibration curve and an equation stating correlation between concentration and the response. As compared to graphical method, above stated method is widely accepted and reproducible in nature. Considering the utility of quantitative analysis of Acyclovir,

calibration curve for Acyclovir was developed using seven different calibration standards. The absorbance of different calibration standards at 253.2 nm was recorded using fixed wavelength mode of UV-Visible spectrophotometer. Calibration curve was repeated five times and the mean values $\pm$ deviation was reported as shown in Table 5.1.

Calibration standard data of Acyclovir

Table 5.1: Calibration curve of Acyclovir

S.No	Concentration(mcg/ml)	Absorbance
1	0	0
2	2	0.421
3	4	0.472
4	6	0.520
5	8	0.562
6	10	0.612

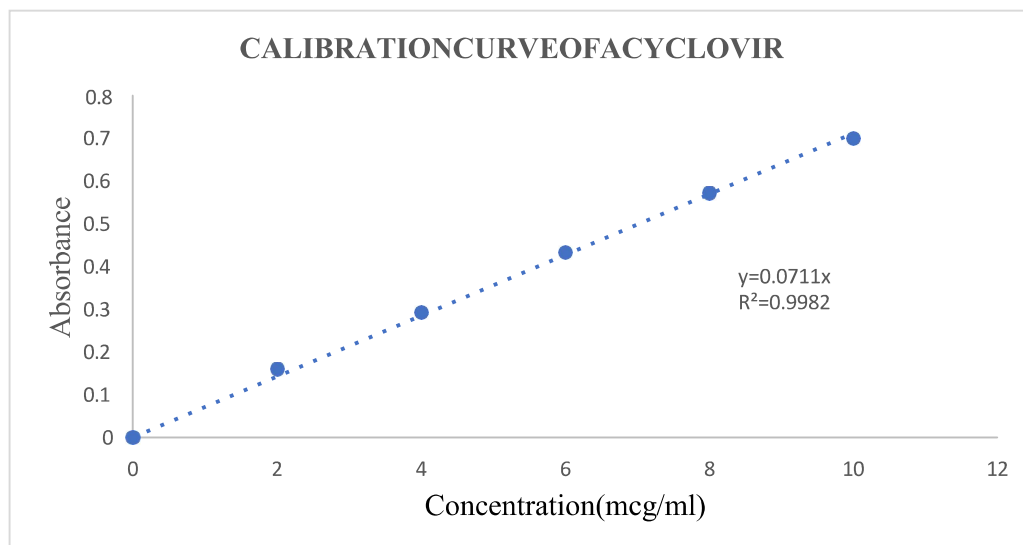


Fig 5.2: Calibration curve of Acyclovir

Drug-Excipient Compatibility Studies

The drug excipient study was conducted to reveal the excipient compatibility with the drug.

FTIR OF ACYCLOVIR

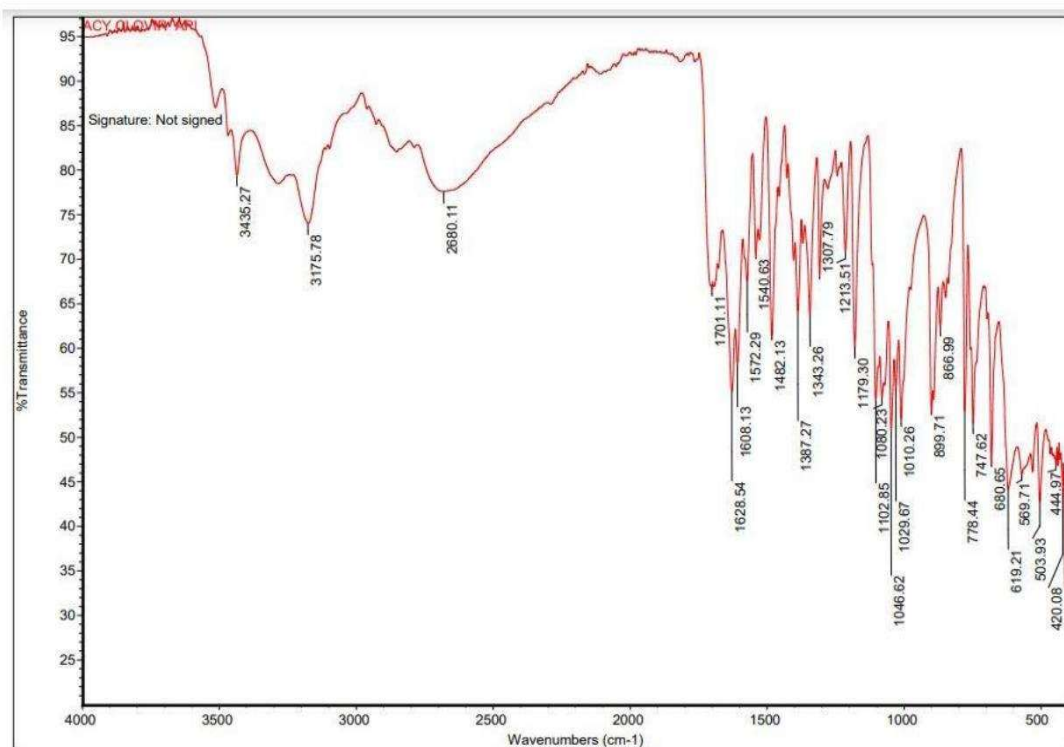


Fig5.3 FTIR of Acyclovir

Table 5.2: FTIR of Acyclovir

S.No	Wavenumber cm^{-1}	Assignment
1	3435.27	NH stretching
2	3175.78	OH stretching
3	2680.11	CH stretching
4	1213.51	C–O stretching
5	1701.11	C=O stretching
6	1628.54	C=N stretching

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

FTIRSPECTRAOFDRUG+SUCROSE

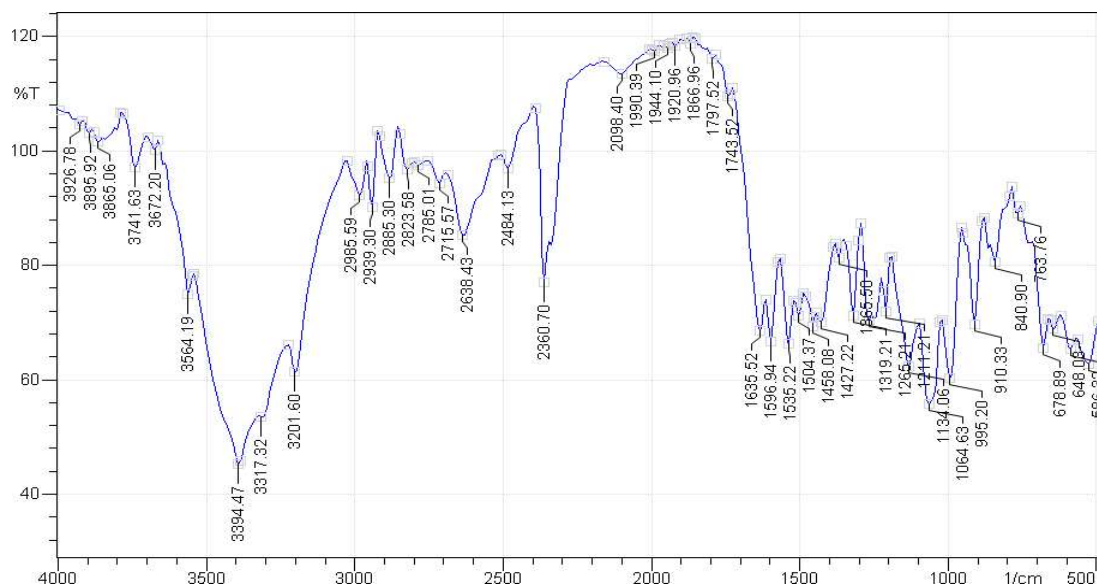


Fig 5.4: FTIR of Acyclovir + Sucrose

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

FTIRSPECTRAOFDRUG+DEXTROSE

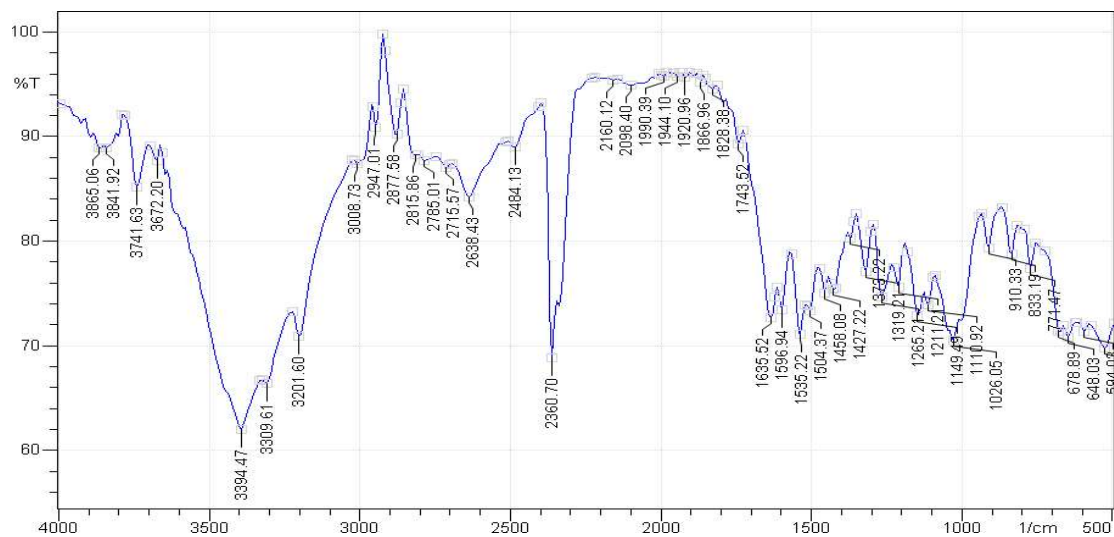


Fig 5.5: FTIR of Acyclovir + Dextrose

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

FTIR SPECTRA OF DRUG + MANNITOL

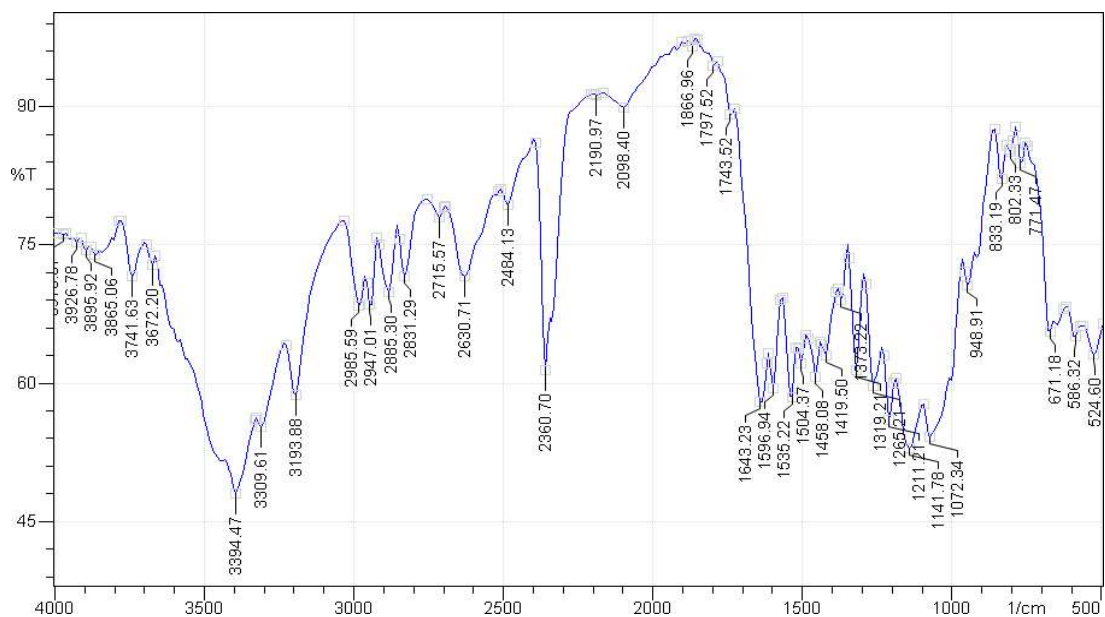


Fig5.6: FTIR of Acyclovir + Mannitol

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

FTIR OF DRUG + ISOMALT

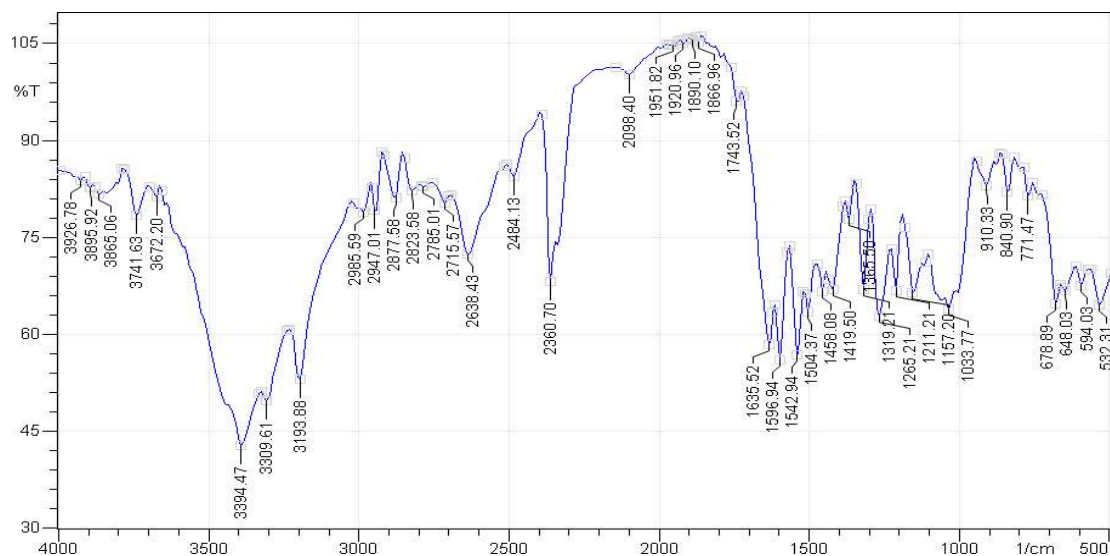


Fig5.7: FTIR of Acyclovir + Isomalt

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

FTIR SPECTRA OF DRUG + ASPARTAME

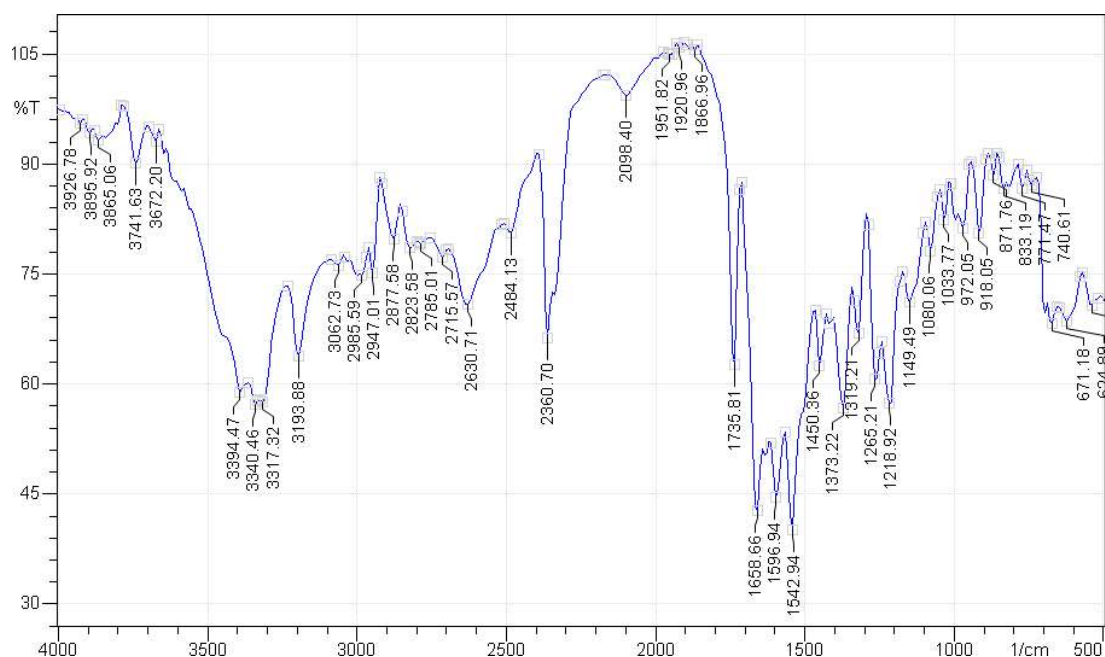


Fig 5.8: FTIR of Acyclovir + Aspartame

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

Evaluation of Physical Properties of Acyclovir Hard Candy

Table 5.3: Evaluation of Physical Properties of Acyclovir Hard Candy lozenges

S.No	Formulation Code	Clarity	Texture	Consistency	Stickiness
1	F1	Translucent	Smooth	Slightly Thick	Sticky
2	F2	Translucent	Smooth	Slightly Thick	Sticky
3	F3	Translucent	Smooth	Slightly Thick	Sticky
4	F4	Translucent	Smooth	Slightly Thick	Sticky
5	F5	Translucent	Smooth	Slightly Thick	Sticky

In physical appearance evaluation all the formulations were translucent smooth nature. All the formulations show slightly thick and sticky in nature. All

other formulations were good and acceptable.

EVALUATIONPARAMETERS

Weight Variation of Acyclovir Hard Candy Lozenges

Table5.4:WeightVariationofAcyclovirHardCandyLozenges

S.No	FormulationCode	WeightofLozenges
1	F1	3.292 ±0.032
2	F2	3.295 ±0.112
3	F3	3.283 ±0.103
4	F4	3.289 ±0.132
5	F5	3.295 ±0.197

The average weight of 20 lozenges was taken to determine weight variation from each formulated lozenges. There was no specified deviation in the weight of lozenges, comparing each formulation. This indicates the uniform weight of the prepared lozenges.

Hardness of Acyclovir Hard Candy Lozenges

Table5.5:HardnessofAcyclovirHardCandyLozenges

S.No	FormulationCode	Hardnessof lozenges (Kg/cm ²)
1	F1	10.5±0.57
2	F2	13.6±0.64
3	F3	15.25±0.63
4	F4	15.45±0.43
5	F5	15.50±0.74

The hardness of all formulated lozenges was found within the range up to 10.5 kg/cm² to 15.50 kg/cm². Among the five formulations of lozenges, the lowest value for hardness was noted for F1 (i.e., 10.5 kg/cm²) and F5 showed the highest i.e., 15.50 kg/cm². The hardness of the lozenges is due to the presence of methyl cellulose.

Thickness of Acyclovir Hard Candy Lozenges

Table 5.6: Thickness of Acyclovir Hard Candy Lozenges

S.No	Formulation Code	Thickness
1	F1	12.01
2	F2	12.06
3	F3	12.16
4	F4	12.22
5	F5	12.16

Drug Content Uniformity of Acyclovir Hard Candy Lozenges

Table 5.7: Drug Content Uniformity of Acyclovir Hard Candy Lozenges

S.No	Formulation Code	Drug content(%)
1	F1	98.61
2	F2	99.52
3	F3	99.67
4	F4	98.61
5	F5	99.62

Moisture Content of Acyclovir Hard Candy Lozenges

Table 5.8: Moisture Content of Acyclovir Hard Candy Lozenges

S.No	Formulation Code	Moisture content(%)
1	F1	0.67
2	F2	0.73
3	F3	0.46
4	F4	0.18
5	F5	1.08

Mouth Dissolving Time of Acyclovir Hard Candy Lozenges

Table 5.9: Mouth Dissolving Time of Acyclovir Hard Candy Lozenges

S.No	Formulation Code	Mouth Dissolving Time
1	F1	10.16
2	F2	12.26
3	F3	18.60
4	F4	26.77
5	F5	32.67

Mouth dissolving time of medicated lozenges was found to be within the range up to 10.16 to 32:67 minutes. The addition of plasticizer was increases the mouth dissolving time of the formulations. F5 formulation shows the highest mouth dissolving time.

In-vitro Drug Release of Acyclovir Hard Candy Lozenges

Table 5.10 In-vitro Drug Release of Acyclovir Hard Candy Lozenges

S.No	Time	PERCENTAGE DRUG RELEASE (%)				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	5	48.5	38.4	34.11	31.23	24.65
3	10	87.12	64.44	58.25	41.45	35.14
4	15	94.67	88.91	78.11	59.87	40.08
5	20	100.16	97.11	89.88	78.96	71
6	25		99.11	94.66	88.76	83.26
7	30			100.12	92.16	91.67
8	35				99.81	100.23

EVALUATION OF IN-VITRO RELEASE KINETICS OF OPTIMIZED FORMULATION

Cumulative Drug Release profile of Medicated Lozenges

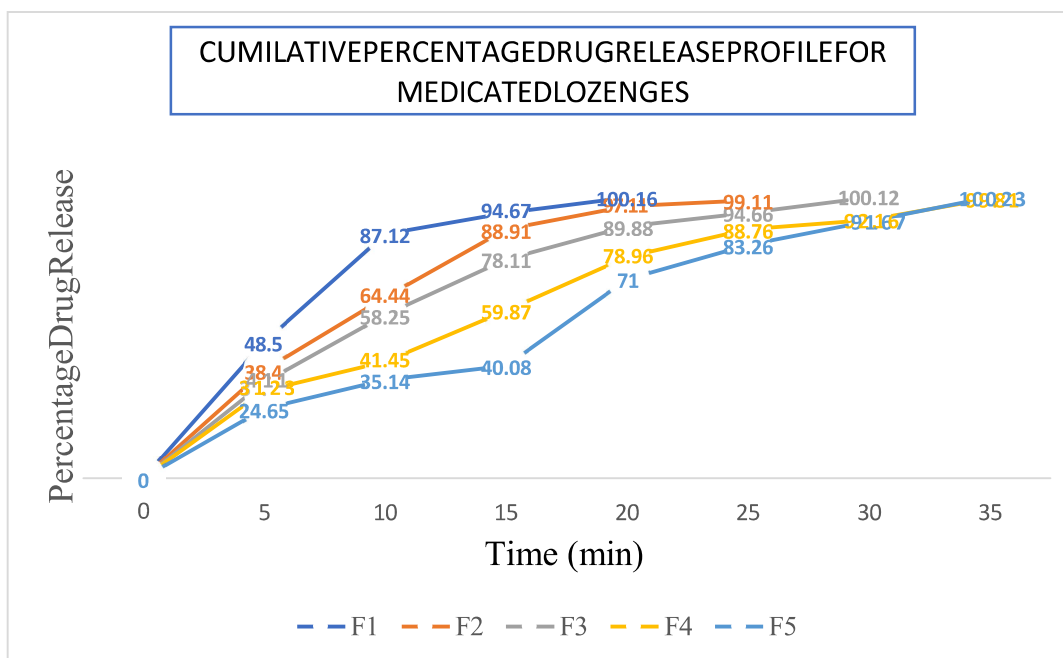


Fig5.9: Cumulative Drug Release profile of Acyclovir Hard Candy Lozenges

Zero Order Release Kinetics

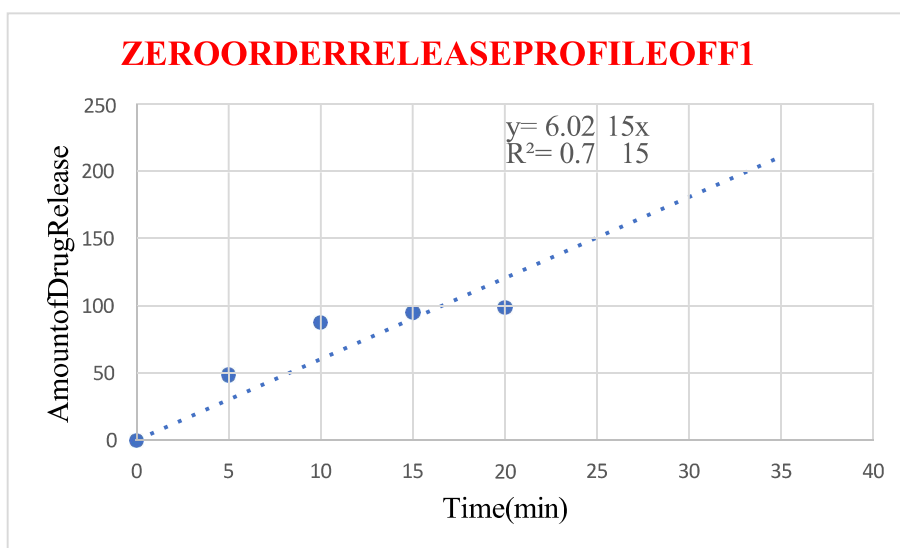


Fig5.10: Zero Order release profile of Acyclovir Hard Candy Lozenges (F1)

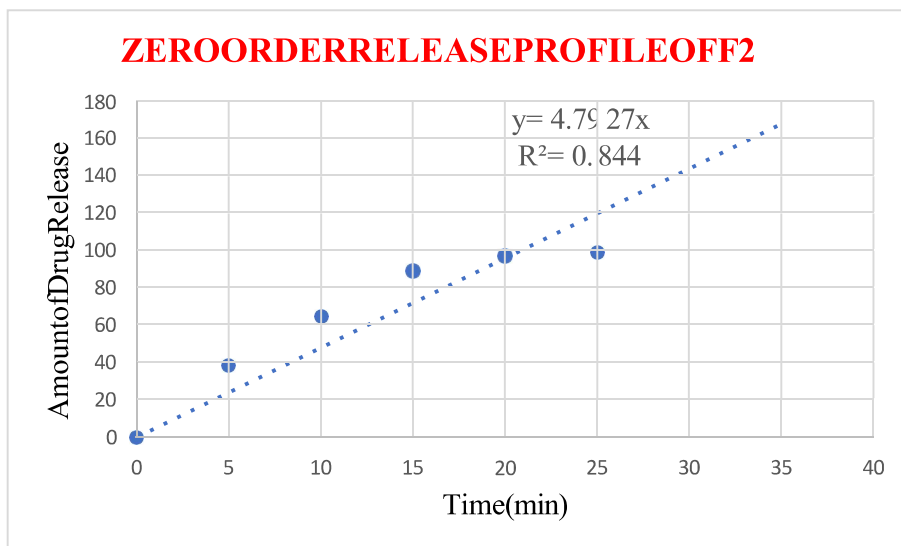


Fig5.11:Zero Order release profile of Acyclovir Hard Candy Lozenges (F2)

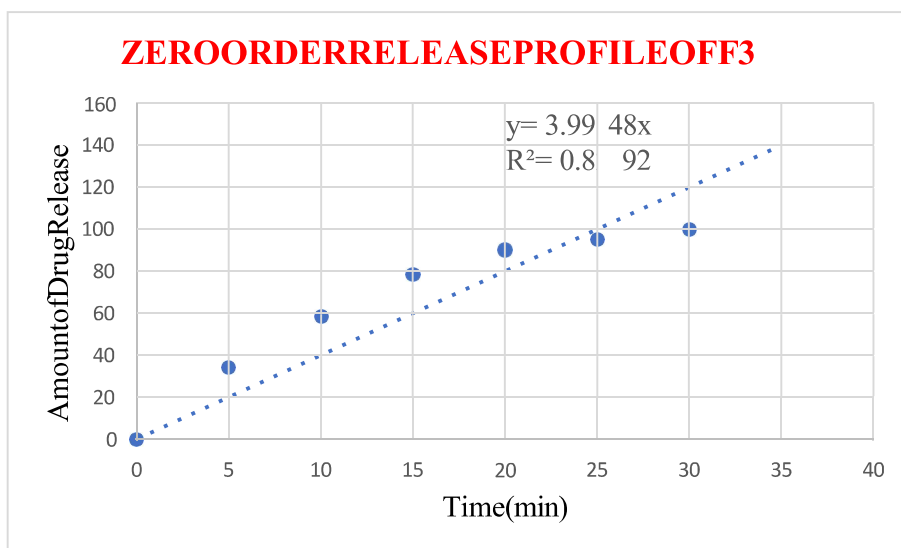


Fig5.12:Zero Order release profile of Acyclovir Hard Candy Lozenges (F3)

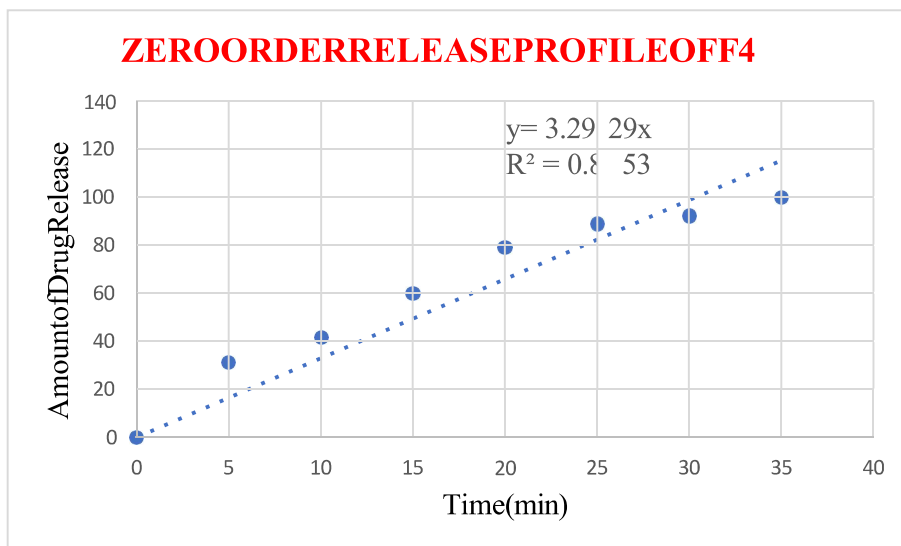


Fig5.13:ZeroOrderreleaseprofileofAcyclovirHardCandyLozenges(F4)

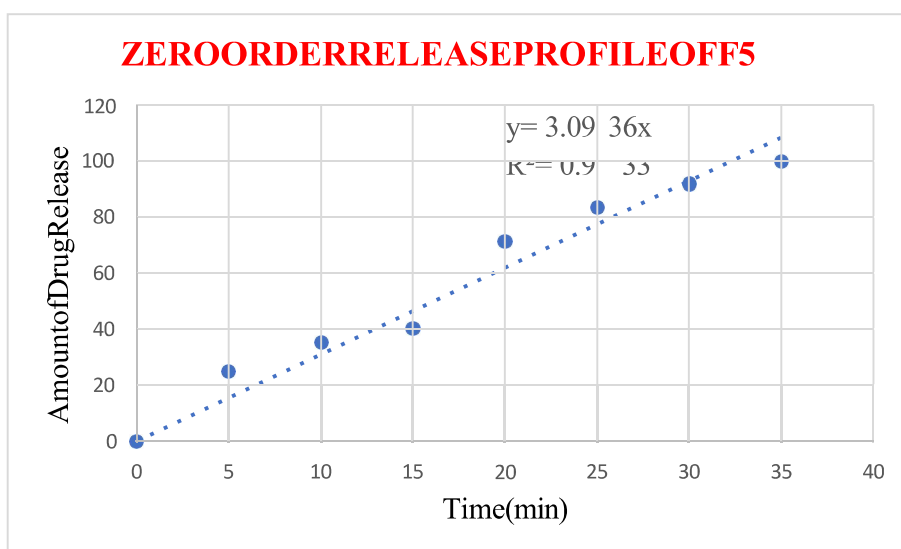


Fig5.14:ZeroOrderreleaseprofileofAcyclovirHardCandyLozenges(F5)

FirstOrderReleaseKinetics

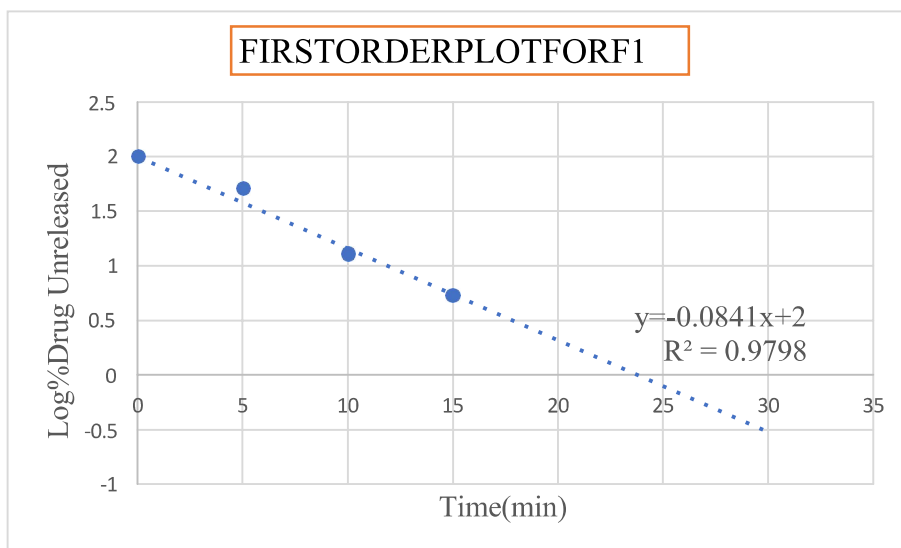


Fig 5.15: First Order release profile of Acyclovir Hard Candy Lozenges (F1)

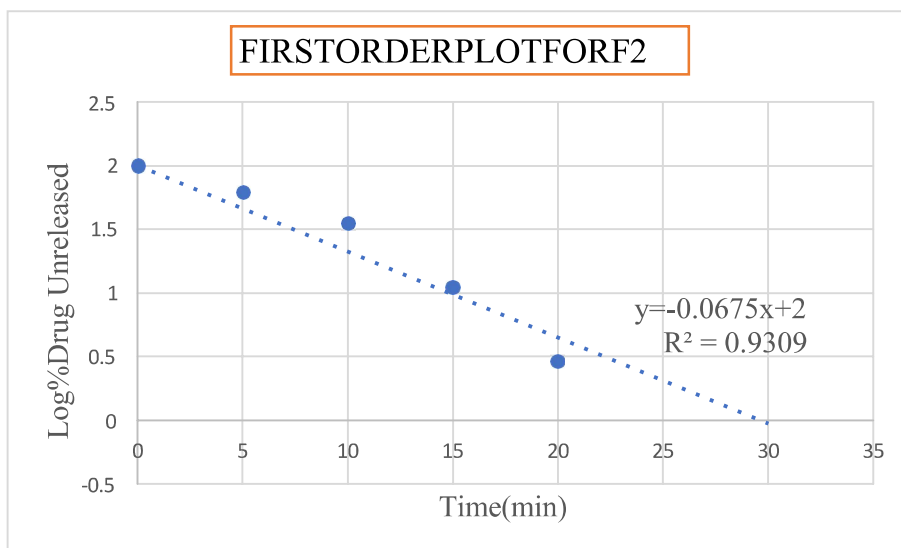


Fig 5.16: First Order release profile of Acyclovir Hard Candy Lozenges (F2)

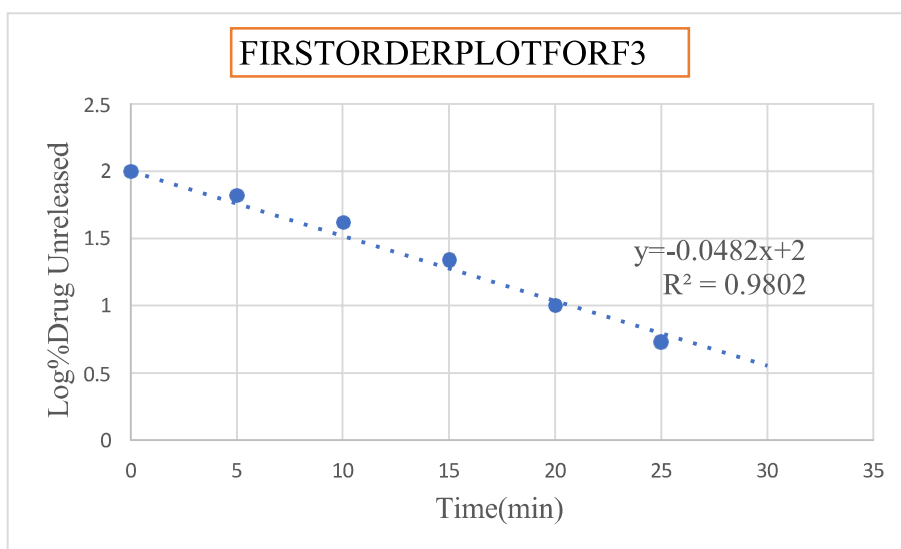


Fig 5.17: First Order release profile of Acyclovir Hard Candy Lozenges (F3)

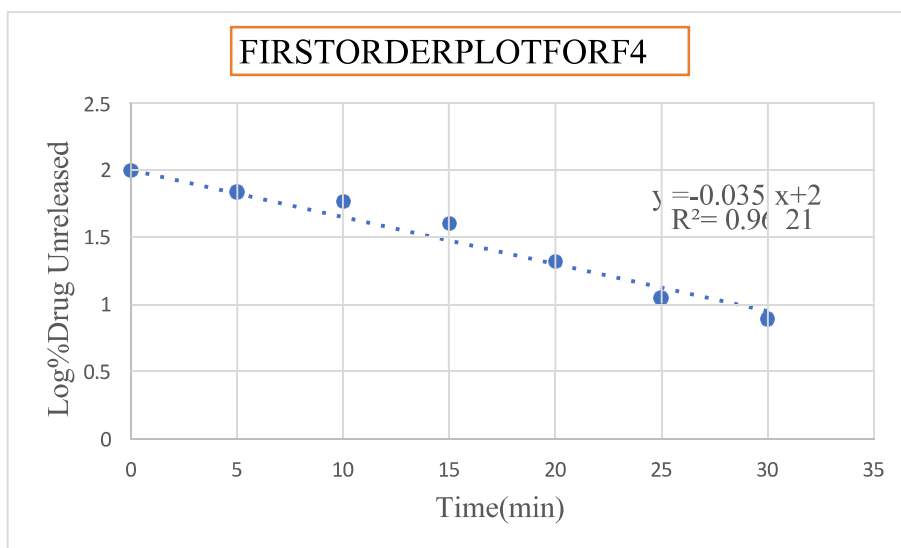


Fig 5.18: First Order release profile of Acyclovir Hard Candy Lozenges (F4)

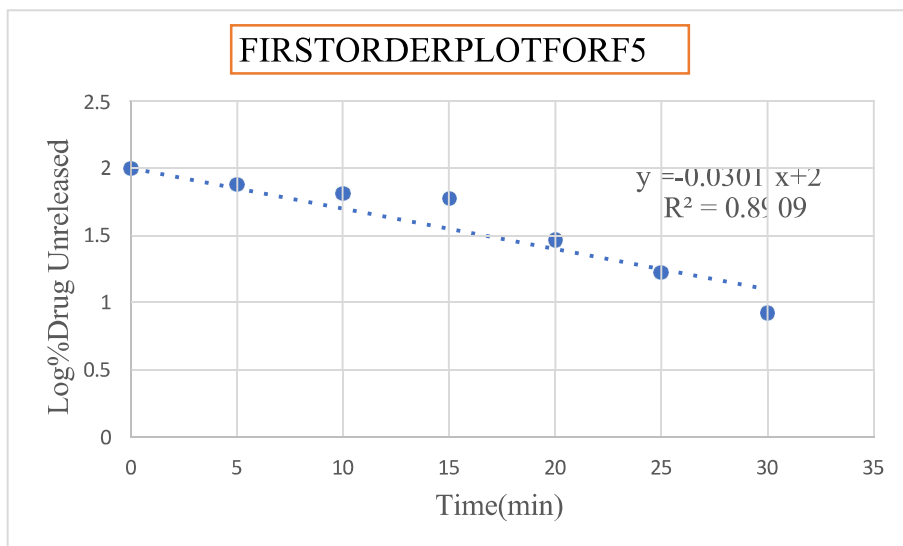


Fig 5.19: First Order release profile of Acyclovir Hard Candy Lozenges (F5)

The summarized data of the *In vitro* release kinetics

Table No 5.11: In-vitro drug release kinetics of Acyclovir Hard Candy lozenges

S.No	Formulation Code	Zero Order Profile	First Order Profile
1	F1	0.9466	0.9835
2	F2	0.9634	0.9503
3	F3	0.9632	0.9875
4	F4	0.9769	0.9717
5	F5	0.9902	0.917

BestFormulation(F5)ofAcyclovirHardCandyLozenges

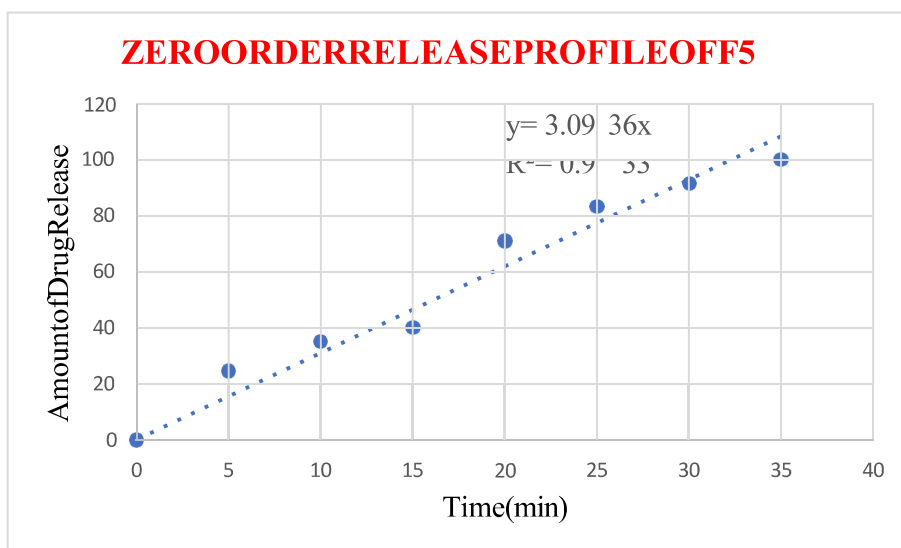


Fig5.20: BestFormulation(F5)ofAcyclovirHardCandyLozenges

Table5.12:BestFormulation(F5)ofAcyclovirHardCandyLozenges

Sl.No	FormulationCode	ZeroOrder
1	F5	0.9902

From the *in-vitro* drug release study, it was found that the best formulation (F5) showed the maximum drug release 100.23% at 35 minutes.

STABILITY STUDIES

Table No 5.13: Stability study of Acyclovir Hard Candy Lozenges

EVALUATION PARAMETER	OPTIMIZED FORMULATION(F5)	AFTER STABILITY STUDY OF 1 MONTH
Weight variation	3.295	3.29
Hardness	15.50 kg/cm ³	15.10 kg/cm ³
Moisture Content	1.08%	1.02%
Mouth dissolving Time	32.67 min	31.07 min
Content uniformity	99.62%	99.02%
Drug release	100.23%	99.83%

CHAPTER - 6

SUMMARYANDCONCLUSION

CHAPTER – 6

CONCLUSION

The present study was aimed to formulate and evaluate Acyclovir medicated lozenges to provide the anti-viral activity through the buccal absorption by the addition of polymer

- Physical compatibility study showed that both the API and excipients used in the formulations are physically compatible with each other.
- Chemical compatibility study was performed using FT-IR spectroscopy and FT-IR studies revealed that there was no change in major peaks, thus confirming no interaction between the drug and excipients.
- All formulations were prepared and evaluated for in-vitro drug release, physical appearance, weight variation, thickness, hardness, moisture content, mouth dissolving time and drug content.
- The formulated lozenges showed the uniformity in weight and thickness.
 - ✓ The weight variation of the formulated lozenges is in the range of 3.283-3.295
 - ✓ The Hardness of the formulated lozenges is in the range of 10.5-15.5
 - ✓ The Drug content of the formulated lozenges is in the range of 98.61-99.62
 - ✓ The Moisture content of the formulated lozenges is in the range of 0.18-1.08
 - ✓ The Mouth dissolving time of the formulated lozenges is in the range of 10.16-32.67.
- From the in-vitro drug release study, it was found that the formulations, Acyclovir lozenges containing showed the maximum drug release at 35 minutes. Among those formulations formulation F5 showed 100.23% of drug release.
- The in-vitro release kinetic study of the optimized formulation (F5) was found to be Zero order.

- Acyclovir lozenges by utilizing Isomalt as a vehicle which dissolve slowly in the mouth which prevail over the problem of dysphagia which is commonly associated with paediatric, geriatric patients suffering from nausea (in cancer patients) and other patients having a problem in swallowing tablets.
- From the present work, it can be concluded that Isomalt can be successfully used as the tooth friendly sugar substitute in the formulation of medicated lozenges and owing to its low caloric value and its ability to withstand formation of plaques, it could be used safely for diabetic and paediatric patient concerns.
- It is found that candy based medicated lozenges will be an alternative dosage form. These will have additional advantages of patient compliance, convenience and comfortness for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economy.

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