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Research Article

Design, Development and Evaluation of Cycloserine Lozenges by PEG Base Method

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ABSTRACT

Lozenges (from the French Lozenge which means a diamond shaped figure of four equal sides). Lozenges are one of the widely used solid dosage forms. Oral soft lozenges of Cycloserine were formulated. Many dosage forms like syrups, tablets and suppositories are available in the market but still there is need of a novel dosage form which acts effectively. Hence the present investigation is aimed towards design, development and evaluation of Cycloserine lozenges. Advantages of these lozenges are increased bioavailability, reduction in gastric irritation, by-passing first pass metabolism. All the formulations prepared were subjected to various physico-chemical parameters like hardness, content uniformity, weight variation, moisture content. The prepared formulations have a hardness of 4-5kg/cm2. The formulations were tested for drug excipients interactions subjecting to IR spectral analysis. IR spectroscopic studies indicated that there were no drug excipients interactions.

INTRODUCTION

Lozenges are especially useful for patients who have difficulty in swallowing oral solid dosage forms this includes some pediatric and geriatric patients. Lozenges dissolve slowly in the mouth that can give maximum benefit when in prolonged contact with local tissues. Lozenges contains variety of active ingredients like local anesthetics, antiseptics, antihistamines, antibiotics, antimicrobials, vitamins, decongestants, analgesics, cough suppressants, nicotine-like substances for smoking cessation. [1]

Advantages and Disadvantages of Lozenges-

Advantages of the lozenges as dosage forms include bypass of first pass metabolism, increase in bioavailability, reducing gastric irritation, and improves onset of action. The new design to this area always benefits for the patient, physician and drug industry. It is easy to administer to both

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pediatric and geriatric patients. It has a pleasant taste and will extend the time a quantity of drug remains in the oral cavity to elicit local activity. Systemic absorption of drugs can be possible through buccal cavity. It can be prepared with minimal equipment. Taste of the drugs can be masked by sweeteners and flavors used in the formulation. [2]

It could be mistaken as candy by children, hence should be kept out of the reach of children because of the non-ubiquitous distribution of drug within sativa for local therapy. [3]

Absorption of Drug Across the Oral Mucosa-

The oral cavity is point of entry for oral drug formulations but their contact with the oral mucosa is brief. So, in order to take advantages of these properties or to treat the mucosa locally, these delivery systems have been designed to prolong residence in this area. The total surface area available for drug absorption is quite limited being only approximately 100 cm^2.The oral cavity is rich in blood vessels and lymphatic, so rapid onset of action and high blood levels obtained quickly.

In many cases oral dosage form can result in the same availability as the same intravenous formulation, without need of aseptic preparation. Finally, they share with transdermal system the advantages that treatment can be rapidly stopped by removing dosage form. Ideally the plasma concentration versus time profile should resemble a square wave, similar to that seen after application of glycerol trinitrate patches, but this is not always achievable. [4,5]

Classification of Lozenges-

A. Medicated Lozenges-

1. Chewy lozenges
2. Hard Lozenges
3. Soft Lozenges
4. Compressed Lozenges

B. Non-medicated lozenges-

1. Sugar candies
2. Lollypops [6]

A. Medicated Lozenges-

1. Chewy or Caramel Based Medicated Lozenges-

Chewy or caramel based medicated lozenges are the dosage form in which medicament is incorporated into a caramel base which is chewed instead of being dissolved in mouth. Most formulations are based on the glycerinated gelatin suppository formula which consists of glycerin, gelatin, and water. These lozenges are often highly fruit flavored and may have a slightly acidic taste to cover the acrid taste of the glycerin Its constituent ingredients are the candy base, whipping agent, humectants, lubricants, flavor and of course medicaments incorporated into the lozenges.

Manufacturing of Chewy or Caramel Based Medicated Lozenges-

The candy base is cooked at 95-125℃ and transferred to planetary or sigma blade mixer. Mass is allowed to cool to 120℃. This is followed by the addition of whipping agent below 105℃. The medicaments are then added between 95-105℃. Color is dispersed in humectant and added to the above mass at a temperature above 90℃. Seeding crystals and flavor are then added below 85℃ followed by lubricant addition above 80℃. Candies are then formed by rope forming. [7]

2. Hard Candy Lozenges

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (non-crystalline) or glassy state. They can also be regarded as solid syrups of sugars. 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. The temperature requirements for their preparation is usually high hence heat labile materials cannot be incorporated in them.

Manufacturing of hard candy Lozenges-

The candy base is cooked by dissolving desired quantity of sugar in one third amount of water in a candy base cooker. This is continued till the temperature rises to 110℃. Corn syrup is added and cooked till the temperature reaches 145-156℃. The candy mass is removed from the cooker and transferred to a lubricated transfer container mounted onto a weight check scale where the weight of the mass is checked. This is followed by color addition in form of solutions, pastes or color cubes. The mass is then transferred to a water-jacketed stainless-steel cooling table for mixing and the flavor, drug and ground salvage is added. The mass is either poured in mold or pulled into a ribbon while cooling and then cut to desired length. The obtained lozenges are packaged. [8]

3. Soft Lozenges

They are either meant for chewing or for slow drug release in mouth. They can be made from PEG 1000, 1450 or 4000, chocolate or sugar-acacia base while some soft candy formulations can also contain acacia and silica gel. Acacia is used to provide texture and smoothness and silica gel is used as a suspending agent to avoid settling of materials to the bottom of the mold cavity during the cooling. The formulation requires heating process at about 50-55℃, hence is only suitable to heat resistant ingredients. These are mixtures of sugar and other carbohydrates in an amorphous (non-crystalline) or glassy state. They can also be regarded as solid syrups of sugars.

Manufacturing of Soft Lozenges

Soft lozenges are manufactured by following two methods

a. Hand-rolled lozenges

The binders used in these lozenges were acacia, gelatin and tragacanth at different concentrations. The powdered sugar and drug were sifted together and sufficient binder solution was gradually added to make a mass of the proper consistency. The mass was rolled into the shape of a cylinder and cut into 10 even sections (approximately twice the length of the diameter). Allowed to air dry.

b. PEG-Base Lozenges-

Blend the powders together until uniformly mixed. Melt PEG and add the powder mix to the molten base and blend thoroughly. Cool to less than 55ºc, add the flavor, color and mix well. Pour into troche molds and cool. They have to be stored under refrigeration. [9,10]

4. Compressed Tablet Lozenges-

If the active ingredient is heat labile, it may be made into lozenge by compression. The granulation is prepared in a manner similar to that used for any compressed tablet. The lozenge tablets differ from conventional tablets in terms of organoleptic, non- disintegrating characteristics and slower dissolution profiles. The ingredients for compressed tablet lozenges are tablet based or vehicles.

Manufacturing of Compressed Tablet Lozenges

Manufacturing of compressed tablet lozenges can either be direct compression and wet granulation. In direct compression, ingredients are thoroughly mixed and then compressed. In wet granulation, sugar content is pulverized by mechanical comminution to a fine powder (40-80 mesh size). Medicament is added and thoroughly blended. The blended mass is subjected to granulation with sugar or corn syrup and screened through 2- 8 mesh screen. This is followed by drying and milling to 10-30 mesh size. Flavour and lubricant are then added prior to compression. [11,12]

Drug Profile-

Cycloserine-

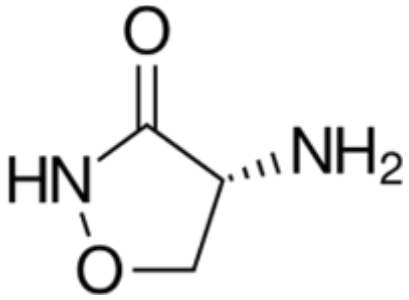

Fig. No. 1 Structure of Cycloserine

- **Systematic (IUPAC) name :** (*R*)-4-Amino-1,2-oxazolidin-3-one
- **Trade names** : Seromycin , Cycloserine.
- **Synthesis** : Antibiotic substance produced by *Streptomyce garyphalus.*
- **Category** : Anti Tuberculosis , broad spectrum antibiotics.
- **Solubility** : Freely water soluble.
- **Route of administration**: Oral

Pharmacokinetic data:

- **Bioavailability** : 70-90 %
- **Metabolism** : Hepatic
- **Half-life** :10 hours
- **Excretion** : Renal
- **Shelf life** : 18 months.

Chemical data:

- **Formula** : C3-H6-N2-O2
- **Molecular mass:** 102.092 g/mol

Physical data:

- **Melting point** : 155 °C

Biological data:

Biological Description: Partial agonist at the NMDA receptor glycine recognition site. Enhances learning and memory *in vivo*. Performance enhancer in a variety of cognitive models.

Description: NMDA glycine site agonist

Purity: > 99%

Storage instructions: Store at -20°C (desiccating conditions).

Description: Cycloserine, (*R*)-4-amino-3-isoxazoli-dinone, is a broad-spectrum antibiotic that is produced by a strain of *Streptomyces orchidaceous* and has also been synthesized. Cycloserine is a white to off-white powder that is soluble in water and stable in alkaline solution. It is rapidly destroyed at a neutral or acid p^H. Cycloserine has a p^H between 5.5 and 6.5 in a solution containing 100 mg/ml. The molecular weight of cycloserine is 102.09, and it has an empirical formula of $C_3H_6NO_2$

Pharmacology:

Cycloserine inhibits the cell wall synthesis in susceptible strains of gram-positive and gram-negative bacteria and in *Mycobacterium tuberculosis*. Cycloserine, a structural analogue of

D- alanine, antagonizes D-alanine's role in bacterial cell wall synthesis.

Pharmacokinetics:

Absorption/ Distribution - When given orally, cycloserine is rapidly absorbed, reaching peak plasma concentrations in 3 to 8 hours. It is widely distributed throughout body fluids and tissues; cerebrospinal fluid levels are similar to plasma.

Metabolism / Excretion - Approximately 65% of a single dose of cycloserine can be recovered in urine within 72 hours after oral administration. The remaining 35% is apparently metabolized to unknown substances. Renal insufficiency will lead to toxic accumulation it may be removed by dialysis. [13,14]

Dosage and Administration:

Cycloserine is effective orally and is currently administered only by this route. The usual dosage is 500 mg to 1 g daily in divided doses monitored by blood levels. The initial adult dosage most frequently given is 250 mg twice daily at 12-hour intervals for the first 2 weeks. A daily dosage of 1 g should not be exceeded.

Contraindications:

Administration is contraindicated in patients with any of the following:

- Hypersensitivity to cycloserine
- Epilepsy
- Depression, severe anxiety, or psychosis
- Severe renal insufficiency
- Excessive concurrent use of alcohol

Mechanism of antibiotic action:

Cycloserine works as an antibiotic by inhibiting cell-wall biosynthesis in bacteria. As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important in the cytosolic stages of peptidoglycan synthesis: alanine racemase (Alr) and D-alanine:D-alanine ligase (Ddl). The first enzyme is a pyridoxal 5'-phosphate-dependent enzyme which converts the L-alanine to the D-alanine form. The second enzyme is involved in joining two of these D-alanine residues together by catalyzing the formation of the ATP-dependent D-alanine-D-alanine dipeptide bond between the resulting D-alanine molecules. If both of these enzymes are inhibited, then D-alanine residues cannot form and previously formed D-alanine molecules cannot be joined together. This effectively leads to inhibition of peptidoglycan synthesis.

Adverse Reactions:

Most adverse reactions occurring during therapy with cycloserine involve the nervous system or are manifestations of drug hypersensitivity. The following side effects have been observed in patients receiving cycloserine:

Nervous system symptoms (which appear to be related to higher dosages of the drug, i.e., more than 500 mg daily)

- Drowsiness
- Headache
- Tremor
- Dysarthria
- Confusion and disorientation with loss of memory
- Psychoses, possibly with suicidal tendencies
- Hyperirritability
- Aggression
- Paresis
- Hyperreflexia [15,16]

MATERIALS AND METHOD-

Materials

Cycloserine, Polyethylene glycol, Guar gum, Polyvinyl pyrrolidone, Silica gel, Talc, Sodium Saccharine, Eosin yellow, Pineapple flavor, etc.

Formulation table-

Sr. No.	Ingredients	Quantity (mg)	Role
1	Cycloserine	250	Active molecule
2	Polyethylene Glycol	2000	Base
3	Guar Gum	300	Additive agent
4	Poly vinyl Pyrrolidone	25	Plasticizer
5	Silica gel	400	Desiccants/ Suspending agent
6	Talc	5	Antiadhesive
7	Sweetener (sod. Saccharine)	2	Sweetening Agent
8	Color (Eosin yellow)	q.s.	Coloring agent
9	Flavor (Pineapple Flavor)	q.s.	Flavoring agent

Methods-

1. Melting point-

A small amount of sample in capillary tube at one end placed in Thiele's tube melting point apparatus.

2. Solubility study-

It is determined in different solvent i.e. buffer p^H 6.8 and distilled water, analyzed by UV-Spectrophotometer.

3. UV- Spectroscopy-

Cycloserine analyzed in phosphate buffer solution at 231nm in UV- spectrophotometry.

Standard Preparation:

Cycloserine 100mg into a 100ml clean dry volumetric flask. It was dissolved in phosphate buffer p^H 6.8 and volume till 100ml to gel stock solution of 1000ug/ml. [17]

4. Fourier transforms infrared spectroscopy (FTIR)-

The dry sample of Cycloserine was prepared by triturating with dry KBr and placed in sample cell. Analyzed by FTIR for results.

5. Weight Variation:

It is also called Uniformity of weight. In this evaluation test twenty lozenges were weighed separately and then average weight was determined. The percentage deviation was calculated and check for weight variation as per IP. By randomly selecting and weighing 20 lozenges, the average weight was determined by weighing machine. Individually, each lozenge was also weighed. In each case deviation from the average weight was calculated and expressed as percentage. Not more than two of the lozenges from the sample size deviate from the average weight by a greater percentage and none of the lozenges deviate by more than double that percentage. [18]

6. Dimension:

It can be dimensionally described & controlled. The unit of the Hausner ratio is dimensionless, meaning it doesn't have any units. The thickness of a tablet is only variables. Lozenge thickness can be measured by micrometer or by another device

7. Hardness

The Hardness of the Tablet is also called as Tablet Crushing strength. Harness test is used to check

the hardness of the prepared tablet. Tablet hardness test could be defined as a tablet strength test which reflect overall tablet strength and it is measured by applying pressure to the tablet diameter. In this test we can measured the force which is required for the breaking of the tablet. Monsanto tablet hardness tester is used to check the hardness of the tablet. The hardness is express in Kg/cm the accepted hardness range for tablets, as per IP (Indian Pharmacopoeia) and USP (United States Pharmacopeia), is generally between 4 to 10 kg/cm2. [19]

8. Disintegration time-

The disintegration time of lozenges were determined by USP disintegration apparatus and disintegration apparatus time was noted in p^H 6.8 phosphate buffer at 37^0c.

9. Dissolution test-

Dissolution is the process by which a solid solute enters in the solution. It may be defined as the amount of drug substance that goes into solution per unit time. The disintegration test simply identified the time required for the tablet to break up under the condition of test and all the particles are passed through mesh no.10 screen. The rate of drug absorption of acidic drug is high in GIT. So, for that purpose, the rate of dissolution is determined. It is important to point out that quick initial release of a drug from its matrix system may be undesirable therapeutically. [20]

RESULTS AND DISCUSSION-

Sr. No.	Test	observation
1.	Melting point	155^0c
2.	Solubility	Distilled water

1. UV spectrophotometry-

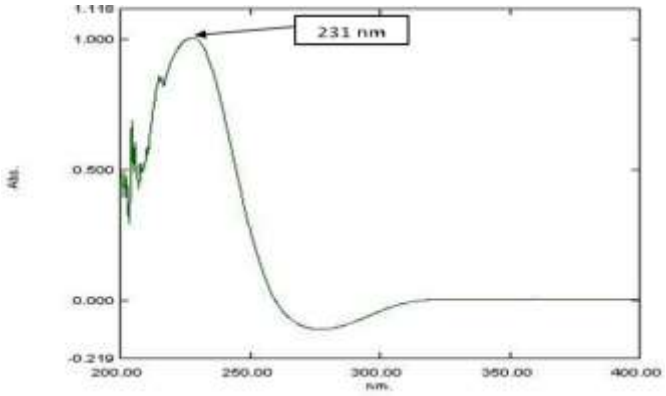

Fig. No. 02 UV spectra of Cycloserine

2. FTIR-

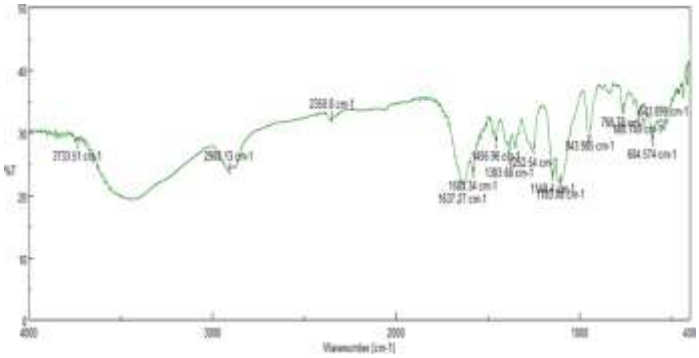

Fig. No. 03 FTIR Spectra of Cycloserine

Table no. 02 Interpretation of FTIR spectra

Interpretation of FTIR for Cycloserine Peak (cm^{-1})	Functional Group
3733.51	N-H Stretching
2908.13	C-H Stretching (Aliphatic)
1637.27	C=O Stretching (Amide)
1581.34	C-C Stretching (Aromatic)
1383.68	C-O Stretching
1252.54	C-N Stretching

Table no. 04 Test and Observation

Sr. No.	Test	Observation
1.	Weight variation (gm)	3
2.	Dimension (mm)	5
3.	Hardness (kg/cm^2)	4
4.	Disintegration study (min.)	20
5.	Dissolution study (%)	99

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