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Formulation, development and optimization of Pediatric lozenges for medicinal purposes

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Abstract

Oral dose forms have a number of advantages over other types of dosage. They are both cost-effective and safe for the patient. They are suitable for any patient, regardless of age. Oral dosing types have their own set of drawbacks. If a patient suffers from chronic vomiting, they are not the first option of medication. They are not a good option for patients who are unwilling to cooperate, such as children and newborns. They are not appropriate in an emergency or for individuals who are unconscious[1] Physicians found morphine and heroin in the 19th century, which inhibit coughing at its source the brain. Smith Brothers Cough Drops, first advertised in 1852, and Luden's, first advertised in 1879, were two popular formulas at the time. Alternative drugs were developed in response to concerns about the potential of opiate addiction[2].

Lozenges have traditionally been used to relieve minor sore throat pain and irritation, as well as to give topical anaesthetics and antibacterials. Analgesics, anaesthetics, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, and

demulcents, as well as other classes and combinations of medications, are all delivered by them today. Chewing gum and lozenges could be used as substitutes for present dose forms. They're simple to use, the dose has been calculated, and the excipients have a soothing impact on a sore throat because the substances are delivered slowly and evenly throughout the damaged mucosal membrane[3].

Key words : Lozenges, Chlorpheniramine maleate, Antihistaminics, Soft Lozenges Method.

Lozenges are chewed and inserted in the mouth. Buccal lozenges are designed and have been extensively used and are meant to replace sublingual lozenges, which may be impractical due to their size. They are intended to be put between the cheek and the gums. Though the lozenge takes roughly 30 minutes to dissolve, the rate of disintegration and absorption is controlled by the patient by sucking on the lozenge until it melts. Molding or compression may be used to make lozenges, depending on the type[4].

Molding and compression techniques are used to make medicinal lozenges, which are typically made of acacia or gelatin as a base- Pastilles, and sugar as a base - Troches. The strongly vasculated mouth or buccal cavity provides the benefit of maximum local action while limiting systemic activity[5].

Patients with swallowing problems, gastrointestinal blockade, paediatrics, and geriatrics are often prescribed lozenges with antimicrobial and local anaesthetics as active ingredients because they can easily be sucked into the saliva, delivering localised drug delivery to the mouth, tongue, and throat. Lozenges have various advantages over oral delivery because they can be made with a variety of excipients such as sweeteners to increase solubility, colourants for a more attractive appearance, and dyes to avoid photo degradation[6,7,8,9].

Lozenges are made up of various polymers with varying concentrations that dissolve slowly in the mouth. Hard candy lozenges, soft lozenges, caramel-based medicinal lozenges, and compressed tablet lozenges are the four types of lozenges currently available on the market. The soft lozenges were created and evaluated for in-process testing such as particle hardness, weight variation, thickness and diameter, moulding time, and batch-release testing such as dissolving in the current study[10,11].

Pediatric medications :

The majority of children have difficulty taking their prescriptions. Many active pharmaceutical ingredients (APIs) have a bitter flavour and are unpalatable to both children and adults. APIs can be encapsulated to mask the bitter taste and improve adult patient compliance. Many youngsters will not readily take encapsulated drugs or pills, thus this is still an issue . Even if children suffer from the same diseases as adults and the same drug is used to treat them, paediatric formulations must

be improved and adjusted in order to improve the dosage form's safety and efficacy in children. With changes in drug regimen and poor dose, child-unfriendly formulations provide a high risk of severe outcomes[12,13].

Children may also fail to follow their prescription regimen, resulting in dangerous side effects. Children are at danger due to the lack of key safety and efficacy information for paediatric formulations[14].

Formulation challenges of the Pediatric Dosage forms :

Children are not only small people, but they are also small in terms of biological and pharmacological development. The problems in designing safe and effective drugs for children include their physiology (biology), age, size, and treatment requirements[15]. Inadequate drug formulations can generate issues in children that do not exist in adults. These complications include swallowing difficulties, excipient interactions, safety concerns, and patient adherence issues due to palatability[16]. Due to a lack of focus on age-appropriate pharmaceutical therapy, ethical issues arise when adult medications are administered off-label in children, posing additional hazards[17]. The pain, discomfort, and extra load on children during medicine administration are the main reasons for non-adherence to treatment[18].

Chemicals and Reagents :

Details of all reagents and excipient used in Lozenges Preparation.

Lactose is used as a stabilizer. Polyethylene Glycol 4000 is used as a sugar free vehicle. Acacia and MCC are used as binder and filler. Sucrose is used as a natural sweetener. Silica gel is used as the drying agent in the preferred embodiments of the present invention. Citric acid is used as a preservative. Sodium starch glycolate is a typical super-disintegrant. Clove oil is used as a flavoring agent, and amaranth is used as a coloring agent.

The following is the manufacturing process used in the formulation Chlorpheniramine Maleate lozenges using the Soft Lozenges Method, The required material for two extra lozenges, as well as the quantity of each ingredient needed to compound the recipe for 20 lozenges, were estimated and weighed. Soft lozenges were created using melting and moulding techniques. The PEG (Grade 4000) was heated in a small beaker (50 ml) without stirring. The remaining powders were mixed using a mortar and pestle and the geometric dilution method. The powder combination was strained onto a glassine sheet using a 40 mesh sieve. The heat was turned down when the PEG had melted, and a stir bar with the slowest spin rate was used.

The granules were scattered on top of the melted PEG, with each addition being thoroughly wetted before adding more. After adding the powders to the PEG, the beaker was removed from the hotplate, and colour and flavour were added before allowing it to cool until it was "slightly cool to the back of the hand." Placing the lozenge mold(s) on an electronic balance was used to determine their weight. The lozenge material was placed into each mould cavity using a digital balance to achieve the desired weight per lozenge[19,20] (Table 1).

Table-1. Composition of lozenges formulations

S. No	Ingredients	Lozenges formulations (in mg)											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	CPM	4	4	4	4	4	4	4	4	4	4	4	4
2.	Lactose	20	20	20	20	20	20	20	40	20	50	25	35
3.	PEG	700	700	900	945	1000	1000	1000	1025	1050	1075	1100	1100
4.	MCC	150	150	500	200	150	200	400	300	100	240	300	300
5.	Acacia	20	20	20	20	20	20	20	20	20	20	10	
6.	Sucrose	480	595	45	300	295	245	45	100	295	100	50	50
7.	Clove oil	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8.	Amaranth	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9.	Silica gel	5	5	5	5	5	5	5	5	5	5	5	5
10.	Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
11.	SSG	115											
12.	**Total weight**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**	**1499**

Formulation Development :

For effective formulation creation and to reach predefined product quality, lozenges include several components in addition to the medicine, such as disintegrant, lubricant, binders, candy base etc.

Evaluation of Lozenges :

The lozenges prepared by soft lozenges method was subjected for following evaluation parameters[21,22].

Weight variation :

The weight of the lozenges was frequently determined to ensure that the correct amount of medication was present in each one. Weighing 10 lozenges individually, computing the average weight, and comparing the individual weights to the average is how the USP weight variation test is done. The lozenges complied with the USP requirement that no more than 1 lozenges exceed the percentage restrictions.

$$Average\ weight = \frac{weight\ of\ 10\ lozenges}{10}$$

Hardness :

A Monsanto hardness tester was used to measure the hardness of each batch of lozenges. The hardness was measured in kg / cm^2. Three lozenges were picked at random and their hardness was examined.

Thickness and Diameter :

Vernier Calipers were used to measure the thickness and diameter. It was calculated by measuring the thickness and diameter of ten lozenges from each formulation. The extent to which each lozenge's thickness differed from the standard value ± 5% was determined.

Drug content uniformity :

A lozenges were placed in 50 ml of phosphate buffer solution of pH 6.8 for 4 hrs. on a rotary shaker. The filtered solution was measured using a UV- visible spectrophotometer.

Moisture content analysis :

In a mortar, the sample was weighed and crushed. One gram of the sample was weighed and placed in a desiccator for 24 hours as a result. The sample is weighed after 24 hours. The moisture content of lozenges is calculated by subtracting the final weight from the initial weight.

$$\%Moisture\ content = \frac{Initial\ Weight - Final\ Weight \times 100}{Initial\ Weight}$$

Friability :

The Roche Friabilator was used to determine the friability of the lozenges. The friabilator was loaded with weighed lozenges and run for 4 minutes at 25 rpm. Friability was calculated as a percentage.

In vitro Drug Dissolution study :

175ml of 0.2M sodium hydroxide (NaOH) and 250ml of 0.2M sodium dihydrogen orthophosphate (NaH_2PO_4) were combined to make the buffer, which was then diluted to 1000 ml with distilled water.[5] Dissolution tests on lozenge formulations were carried out in a calibrated 8-station dissolution test apparatus (Electrolab-AarkeyLab Edt08lx) with paddles (USP apparatus II technique) using 900 ml of 0.1 N HCl as the dissolution medium.

Throughout the experiment, the paddles were rotated at 50 rpm and the temperature was kept at 37ºC ± 1ºC. To maintain a constant volume throughout the experiment, the samples were withdrawn at 5, 10, 15, 20, and 30 minutes and replaced with an equal volume of the same dissolution medium. At various time intervals, samples were removed and diluted with the same dissolution media, and the amount of medication dissolved was determined using an ELICO double beam U.V spectrophotometer set to 227 nm. (Table-2).

Stability studies :

According to ICH requirements, stability studies for lozenges were conducted at 40°C and 75 % RH for 90 days for the optimal formulation. The lozenges were evaluated for several factors such as hardness, thickness and diameter, weight variation, drug content, and drug release using the protocols outlined above, with samples being analysed every one month.

UV- Spectroscopic Analysis :

Different solutions of the drug (10ìg/ml and 20ìg/ml) in 0.1N HCl were scanned using a UV-Visible spectrophotometer within the wavelength region of 200–380 nm against 0.1N HCl as a blank to determine the wavelengths of maximum absorption (λmax). The Chlorpheniramine Maleate has a characteristic absorption maximum at 262 nm.

Preparation of Stock solution :

The standard stock solution of Chlorpheniramine maleate was made by dissolving 10mg of the drug in 10 ml of 0.1N HCl in a volumetric flask to obtain a concentration of 1mg/ml (1000µg/ml) solutions.

Preparation of Working Standard Solutions and construction of standard graph :

Working standard solutions of 100µg/ml and 10µg/ml were made by diluting the produced stock solution with 0.1N HCl. To make the Beer's law plot for Chlorpheniramine maleate, different aliquots of the compound were obtained and diluted to 10 ml with 0.1N HCl to produce the working standard solutions given in the table-2.

Table-2. Linearity table of CPM (pure drug) in 0.1N HCl at 262 nm

Concentration (µg/ml)	Absorbance(nm)
10	0.264
20	0.538
30	0.872
40	1.105
50	1.409
60	1.710

Using 0.1N HCl as a blank, the absorbance of each solution was measured at λ max 262 nm. The standard graph for Chlorpheniramine maleate was created using the x-axis for drug concentration and the y-axis for absorbance. Figures 1 show the results. In the concentration range of 10-60µg/ml, the drug followed Beer's law.

Post moulding study :
Evaluation of optimized formulation :

All of the formulations were tested for diameter, thickness, weight uniformity, hardness, Drug Content, and moulding time, with the results presented in the table-3 below.

In-Vitro Dissolution study :

The study was conducted using the USP apparatus II (paddle type). Chlorpheniramine Maleate lozenges formulations were accurately weighed and placed in a 900 mL phosphate buffer with a pH of 6.8. The temperature was maintained at 37°C, and the mixture was stirred at 50 rpm. A 5 ml volume of the material was removed at each 5 minute time interval and replaced with an equal volume of plain buffer held at 37°C. Using a UV–visible spectrophotometer, the acquired samples were filtered (#0.45 m) and measured at 262 nm.

Physicochemical criteria such as Drug Content (% w/w), and Mouth dissolving time were used to evaluate LOZ. These studies findings were found to be within acceptable parameters.

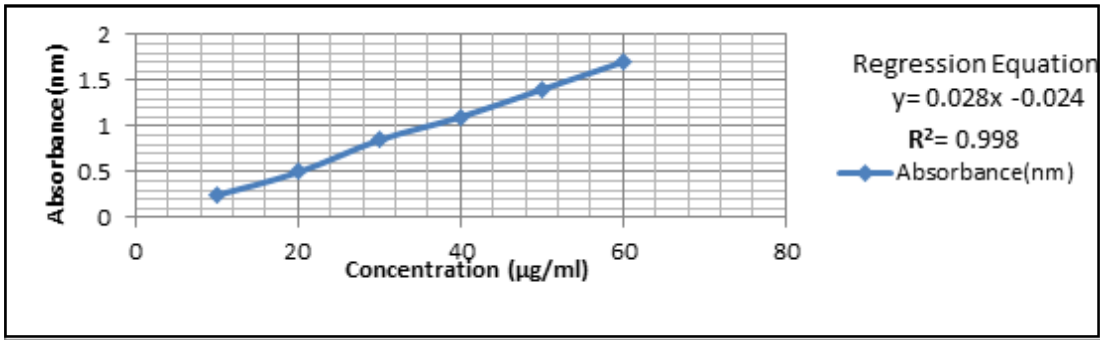

Figure 1. Linearity graph of Chlorpheniramine Maleate (pure drug) in 0.1N HCl at 262 nm

Table-3. Evaluation of formulations

Batch	Diameter (mm)	Thickness (mm)	Weight Uniformity (gm)	Hardness (kg/cm^2)	Drug Content (%w/w)	Moulding time (Min)
F1	14.87±0.77	6.94±0.25	1.476±1.64	1.2±0.8	97.25	11
F2	14.86±0.10	7.05±0.11	1.455±0.74	1.1±0.2	93.64	7
F3	14.86±0.16	7.15±0.05	1.374±1.77	1.5±0.2	95.16	5
F4	14.84±0.19	7.05±0.10	1.401±0.21	1.7±0.1	80.38	7
F5	14.86±0.12	6.99±0.19	1.525±0.11	1.4±0.4	92.27	7
F6	14.85±0.12	7.05±0.11	1.399±1.21	1.5±0.2	96.05	4
F7	14.84±0.43	7.01±0.91	1.458±0.78	1.2±0.4	91.01	14
F8	14.87±0.11	6.96±0.16	1.488±0.12	1.2±0.6	98.48	12
F9	14.86±0.20	7.00±0.01	1.507±0.22	1.3±0.2	92.80	8
F10	14.86±0.44	7.03±0.47	1.472±0.88	1.2±0.5	87.74	8
F11	14.84±0.51	6.96±0.03	1.499±1.22	1.3±0.8	96.97	10
F12	14.85±0.21	7.08±0.77	1.497±1.88	1.2±0.4	90.38	15

In Vitro drug release study :

All of the formulations were tested in vitro for release. Table 4 shows the percentage drug release from lozenges, and Figure. 2 and 3 shows the release profile.

Stability studies :

According to ICH requirements, stability studies for lozenges were conducted at 40°C and 75 % RH for 90 days for the optimal formulation [F1] Figure 4. The lozenges were evaluated for several factors such as hardness, thickness and diameter, weight variation, drug content, and drug release using the protocols outlined above, with samples being analyzed after one month. (Table 5 and table 6).

Table-4. Percentage cumulative drug release of formulations

Time (min)	Cumulative drug release %											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	15.60	6.73	4.51	7.71	5.36	6.45	9.72	12.68	10.66	11.28	8.16	9.31
10	22.18	12.07	7.25	10.99	10.86	9.05	20.8	25.69	17.65	18.43	10.89	17.63
15	40.88	21.65	18.43	25.64	23.04	24.97	39.37	42.12	34.27	41.19	27.47	31.98
20	67.35	38.37	33.06	44.49	43.14	32.64	53.22	59.38	51.83	63.77	48.23	53.57
25	87.30	65.29	65.80	61.70	59.99	71.03	79.06	72.54	71.6	79.98	63.18	69.71
30	98.25	88.64	90.16	82.38	80.27	96.05	91.01	86.48	92.80	97.74	84.63	81.86

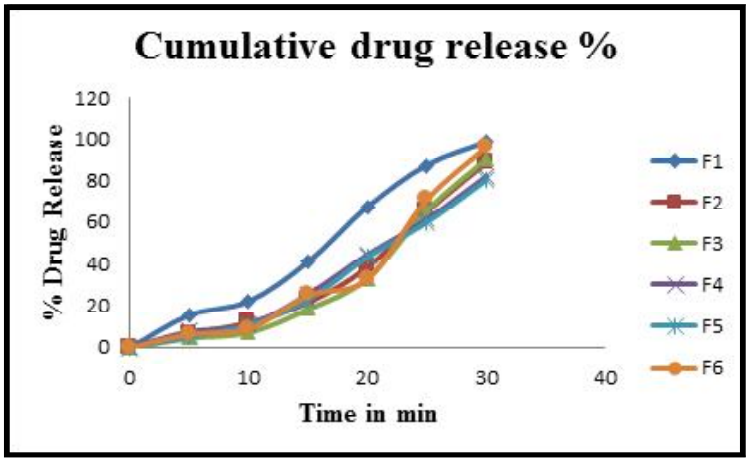

Figure 2. Cumulative drug release % of F1-F6

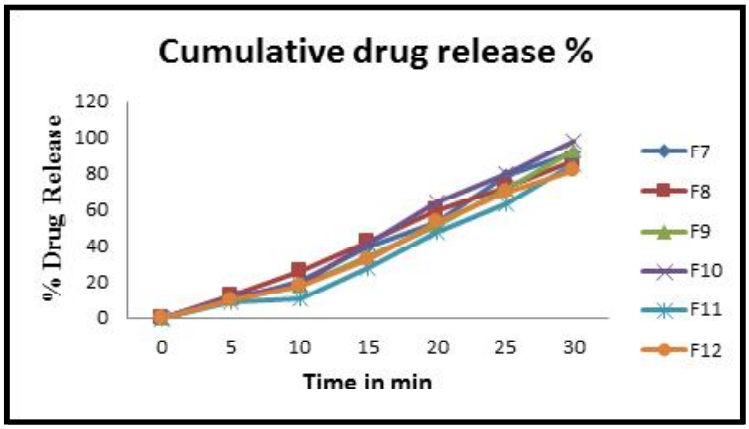

Figure 3. Cumulative drug release % of F7-F12

Table-5. Stability results of optimized F1 formulation

Evaluation parameter	Optimized formulation F1	
	0 day	After stability study of 1 month
Diameter (mm)	14.87±0.77	14.57±0.98
Thickness (mm)	6.94±0.25	6.45±0.70
Weight Uniformity (gm)	1.476±1.64	1.327±1.24
Hardness (kg/cm^2)	1.2±0.80	1.2±0.50
Drug Content (%w/w)	97.25	96.89

Table-6. Comparative in vitro dissolution data of F1 formulation after stability study

Time in minute	Cumulative % release of chlorpheniramine	
	Initial	1st month
5	15.60	14.80
10	22.18	22.17
15	40.88	41.38
20	67.35	66.20
25	87.30	85.52
30	98.25	98.70

The major purpose of this research was to develop and characterize chlorpheniramine maleate lozenges for patients with a common cold and cough. The melting point of chlorpheniramine maleate was initially used as an identifying test for the compound. The melting point of the chlorpheniramine maleate sample was found to be 130° - 135° C, which is consistent with the IP standards. When using a UV–visible spectrophotometer, the absorption maxima for chlorpheniramine maleate were determined to be at 262 nm. This can be seen in Figure. 6.1 at the peak. At concentrations of 10–60 g/ml, a calibration curve of chlorpheniramine maleate was obtained with an R^2 value of 0.998. By heating and congealing several substances, chlorpheniramine maleate lozenges were created.

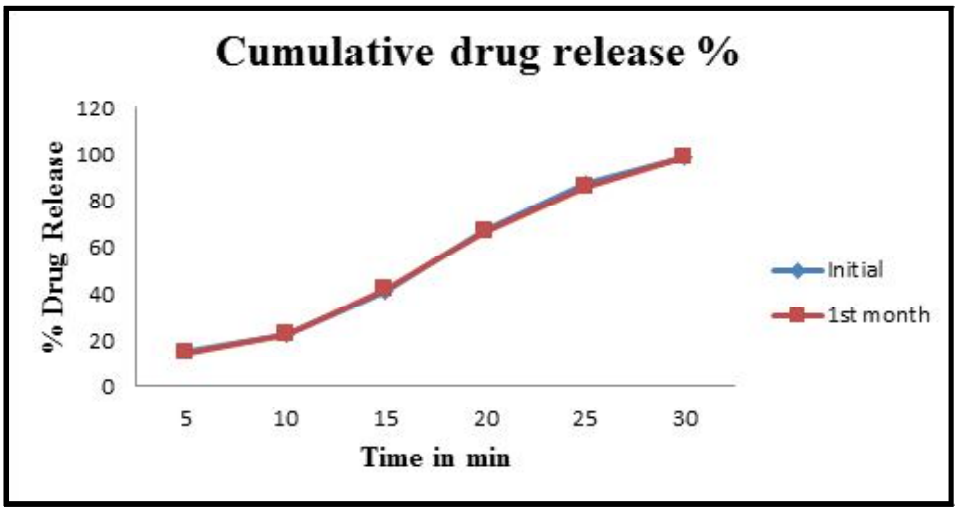

Figure 4. Cumulative drug release % of F1 after stability study

A total of 12 formulations weighing 1500 mg were created. Sucrose, lactose, acacia, Polyethylene Glycol (PEG), Silica gel, citric acid, microcrystalline cellulose, clove oil, colouring agent, and sodium starch glycolate are some of the ingredients. The binder was acacia, and the filler and super disintegrant was microcrystalline cellulose (to a lesser extent) and sodium starch glycolate. As a lubricant, glycerin was utilized. As a flavoring ingredient, clove oil was used. It also has a pleasant calming effect. Table-1 shows the composition of lozenges made with these excipients. The F2 to F5 prepared lozenges were shiny, yet had a little sticky outer surface and were hard in nature. The exterior structure of Formulas F6, and F9 was rough and dull. and the remaining formulations F1, F10 to F12

have a smooth finish, but the outer surface is little sticky.

The shape of the lozenges was determined by the mould that was chosen. Different evaluation tests were performed on the created lozenges. The findings of post-formulation parameters of lozenges including hardness, weight variation, thickness, diameter, percentage drug content, and moulding time are shown in Table-3. Due to homogeneous mould fill, the lozenges obtained were of uniform weight because all of the components were free flowing. The obtained hardness range demonstrated good mechanical strength and resistance to physical and mechanical stress. For each formulation, the percentage of drug content was calculated. According to IP 2007, the drug content for all formulations was found to be in the range of 91.01–98.48 % w/w. All of the formulations were tested in vitro for release. Table-4 shows the percentage drug release from lozenges, and Figure. 2 and 3 shows the release profile.

In vitro release experiments revealed that more than 90% of the medication was released within 30 minutes. The addition of a super disintegrating agent to F1 resulted in high and fast drug release (sodium starch glycolate). Formulation F1 was considered an optimised formulation based on the results of post-formulation parameters and in vitro drug release.

Chlorpheniramine maleate lozenges were identified as ideal dosage forms for paediatric patients with a common cold and cough in this investigation. With the addition of sodium starch glycolate and microcrystalline cellulose, the medication was released in a 6.8 pH buffer for 30 minutes. These discoveries could be useful in the future for developing formulations for common colds and coughs. Formulation F1 was deemed an optimum formulation based on the results of post-formulation parameters and in vitro drug release. The formulation was subjected to more stability testing. For a period of one month, ageing investigations were conducted at 40°C±2°C and 75% RH±5%. After a month, samples were collected and examined. Tables-5 and Tables-6 indicate the results that were achieved. The samples were tested for stability at a temperature of 40°C and a relative humidity of 75 % RH. The release characteristics and physicochemical qualities of the lozenges employed in the study did not alter significantly as a result of the aforesaid observations. Based on the findings, it can be stated that the prepared chlorpheniramine lozenges were stable during a one-month period at stability conditions (40°C±2°C and 75%±5% RH). Even though its stability was confirmed for one month, more research is needed to determine its shelf life according to ICH requirements.

Summary :

The current investigation shown that Chlorpheniramine Maleate can be formulate into lozenges. Lozenges are medicinal confections that were invented around the turn of the century and are still in use today. Lozenges are an organoleptically acceptable formulation for paediatric patients and dysphasia (difficulty in swallowing) sufferers. They are the most natural and straight forward method of drug delivery. They're simple to make and store. Lozenges are used for both local and systemic administration, and they can

include a wide range of active substances. Today's requests are for sweetened and flavoured lozenges.

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