RESEARCH ARTICLE

Formulation and Evaluation of Levocetirizine Dihydrochloride and Ambroxol Hydrochloride Lozenges

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ABSTRACT

The present work aims to formulate and evaluate levocetirizine dihydrochloride and ambroxol hydrochloride hard candy lozenges to produce a slow-release of drugs for the management of cold and cough. The lozenges were prepared using sucrose, liquid glucose, hydroxyethylcellulose, and hydroxypropyl methylcellulose K4M by heating and congealing method. Sweetener with flavors was utilized to facade the bitter taste of the drug. The developed lozenges were exposed to various physical and chemical characters, and *in vitro* disintegration and dissolution. The developed formulations include hardness of 8 to 11 kg/cm², non-gritty, and agreeable mouthfeel. The optimized formula was examined for drug excipient interactions subjecting to Fourier transform infrared (FTIR) spectral analysis. Drug release for lozenges was highest in formulation FL8. The hard candy lozenges can present an attractive substitute formulation in allergic conditions.

Keywords: Ambroxol hydrochloride, Hard candy, Levocetirizine dihydrochloride, Lozenges, Polymers.

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INTRODUCTION

Lozenges are solid preparations that comprise one or more drugs, generally in a flavored, sweetened base, and are meant to be sucked and held in the mouth to lubricate, and pacify irritated tissues of the throat. They are planned to be dissolved in the posterior surface of the tongue to deliver drugs locally to the mouth, tongue, and throat, and to relieve oropharyngeal symptoms. The dosage form can be implemented for local as well as systemic treatment.[1] They can deliver medicine multi-directionally into the oral cavity or mucosal surface through the buccal linings.[2,3] Since sublingual lozenges may be unfeasible due to their size, buccal lozenges are developed and have been widely used and are placed between the cheek and the gums. Sucking and the consequent production of saliva might also lead to improved dilution of the drug and accidental swallowing.[4]

Levocetirizine dihydrochloride is an antihistamine to get rid of allergy signs such as watery eyes, runny nose, sneezing, and itching. Ambroxol hydrochloride is a mucolytic agent used in the management of respiratory diseases accompanying with viscid or excessive mucus. The work has been designed to formulate flavored slow dissolving lozenges.

MATERIALS AND METHODS

Materials

Levocetirizine dihydrochloride obtained as a gift sample from Sai Mirrainnopharm Pvt. Ltd., Chennai. Ambroxol hydrochloride was from Hetero Pharmaceuticals, Hyderabad. Hydroxypropyl methylcellulose (HPMC) K4M, and hydroxyethylcellulose (HEC), and aspartame were from SD Fine Chemicals Limited, Mumbai. Liquid glucose from Deccan Bottle Traders, Hyderabad. Color and flavor from Manju Chemicals, Chennai, and all other reagents used were of pharmaceutical grade.

Preformulation Studies

Preformulation studies are principally done to examine the physicochemical properties of drugs and to know its compatibility with excipients. Levocetirizine dihydrochloride and ambroxol hydrochloride were mixed in equal proportions, and subjected to physical observation and FTIR studies. The spectra of active pharmaceutical ingredient, excipient, and optimized formulation obtained by means of FTIR spectrophotometer (BRUKER).

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Determination of λ_{max} using UV-Visible Spectrophotometer

For the selection of analytical wavelengths, solutions of levocetirizine dihydrochloride and ambroxol hydrochloride (100 µg/mL) were prepared separately with distilled water and scanned between 200–300 nm in the spectrum mode to choose maximum absorption for further analysis.

Standard Graph of Pure Drug

Pure drug (100 mg) dissolved in 100 mL of 6.8 pH phosphate buffer (PB) to produce 1,000 µg/mL (primary stock). From the primary stock solution, 100 µg/mL secondary solution was prepared by dilution. Further required concentrations 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/mL was prepared from 100 µg/mL. The absorbance was recorded at 231 and 220 nm for levocetirizine dihydrochloride and ambroxol hydrochloride, respectively, using a UV-visible spectrophotometer.

Method of Preparation of Hard Candy Lozenges

Lozenges were developed by heating and congealing method. Sucrose was weighed accurately and dissolved in a little amount of water in a heating pan until total sugar granules were dissolved. The calculated amount of liquid glucose was then added to the boiling mixture when the cooking temperature reached to 110°C, and stirring was continued, raising the temperature to 145°C, until the mixture turned very much viscous, which was then cooled to attain a temperature of 135°C. The specified amount of drug, polymer, and flavoring agent was added to the mixture with continuous agitation. Further, cooling was carried out, and molten candy mass was poured in lubricated molds and allowed to cool to room temperature.[5,6] The formulated lozenges were subjected to various physicochemical characterization parameters. The composition for the development of lozenges was shown in Table 1.

Characterization of Prepared Lozenges

The formulated lozenges were subjected to the general look, thickness, diameter, weight difference, hardness, friability, uniformity in drug content, moisture content, *in vitro* drug release, and taste evaluation. The final appearance of a dosage form, its visual appearance, and complete elegance is crucial for consumer acceptance. It comprises the measurement of features such as size, shape, color, surface texture, and reliability. The diameter and thickness of lozenges were measured by employing Vernier caliper, and the average values were reported.[7,8]

Weight Variation, Hardness, and Friability

Lozenges were weighed individually, and percentage weight variation was determined from the average weight. Weight variation should be within the set limits.[9,10] Monsanto hardness tester was used to measure the hardness. The hardness additionally depends on the character and amount of excipients used throughout formulation.[11,12]

Roche friabilator was utilized for measuring friability. Randomly selected lozenges from every batch were weighed, positioned in friabilator, and operated at 25 revolutions per minute for 4 minutes. The lozenges were re-weighed to determine the loss percentage in weight. Generally, the lozenges were acceptable if the loss percent is less 0.5 to 1 of weight.[13,14]

Drug Content

Randomly selected lozenges were weighed, crushed to extract the drug from 6.8 pH PB by keeping on a rotary shaker overnight. The drug content was determined using a UV-visible spectrophotometer at pre-determined wavelength against blank. The amount of drug existing in the lozenge was determined with the help of a standard graph.[15,16]

Moisture Content

The moisture content study was executed by means of a gravimetric method by placing the weighed sample in a vacuum oven for 12 to 16 hours at 60 to 70°C. The difference in the weights was recorded and used for calculating the moisture content.[17,18]

In vitro Dissolution Studies

The *in vitro* study was performed in USP type-II Paddle[19] apparatus at 100 rpm using 6.8 pH PB as a dissolution medium. The 5 mL samples were drawn periodically and replaced fresh PB, and analyzed for drug content with the aid of UV-spectrophotometer at 231 and 220 nm.[20,21]

Table 1: Composition of hard candy lozenges

Ingredients (mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*
LC	5	5	5	5	5	5	5	5	5	5
AMB	30	30	30	30	30	30	30	30	30	30
Sucrose	2,009	2,209	2,409	-	-	-	-	2,003	2,197	2,391
Liquid glucose	950	750	550	950	750	550	950	950	950	950
Jaggery	-	-	-	2,003	2,197	2,391	-	-	-	-
Saccharin	-	-	-	-	-	-	2,003	-	-	-
HPMC K4M	-	-	-	-	-	-	6	6	12	18
HEC	-	-	-	6	12	18	-	-	-	-
Flavor	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Preservative	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000

In vivo Evaluation of Taste and Mouthfeel

A single-blind study was planned for the assessment of taste masking test and *in vivo* disintegration time within the buccal cavity. An institutional ethics panel was approved to carry out the study (IHEC/VGOPC/069/2017). Six volunteers selected for the test were asked to taste the dosage form of the optimized formulation by employing a scale of 0 to 3 (indicated as x, +, ++, and +++). Once the score was x, the taste was considered to be acceptable. The formulation found to be bitter if the score was higher than +. The same volunteers were also asked to contribute their view about the sense of grittiness or smoothness of the designed lozenge after it becomes completely dissolved in the oral cavity.[22]

RESULTS AND DISCUSSION

The active ingredients and other excipients' compatibility were compared by the FTIR spectrophotometer (BRUKER).

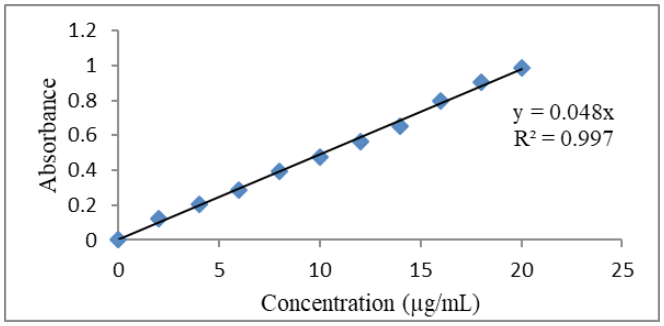

Figure 1: Standard graph of levocetirizine hydrochloride in 6.8 pH phosphate buffer

The spectrum of active pharmaceutical ingredient, a mix of two medications, and an optimized candy mixture exhibited characteristic peaks. The peaks do not seem to be affected and prominently observed in the IR spectra of medicaments and excipient that indicates that there was no interaction between active pharmaceutical ingredients and excipients. FTIR data elucidation was recorded in Table 2. The standard stock solution of the pure drug was obtained by diluting the stock solution with 6.8 pH PB, a standard curve was generated using a range of 2 to 20 µg/mL at the certain wavelength 231 and 220 nm (Figures 1 and 2). Their absorptivity data confirm the linearity. Beer Lambert's law limit was obeyed within the concentration range of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/mL. The developed hard candy lozenges were shown in Figure 3.

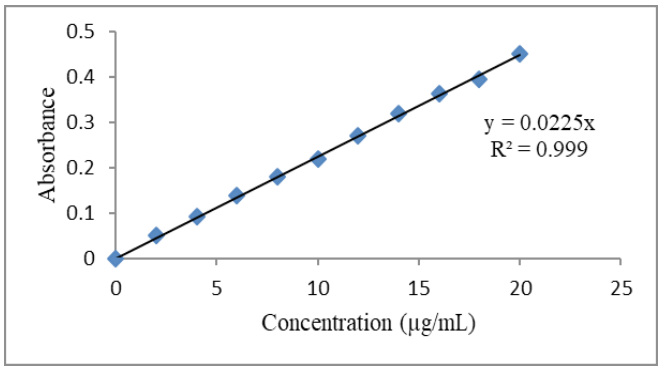

Figure 2: Standard graph of ambroxol hydrochloride in 6.8 pH phosphate buffer

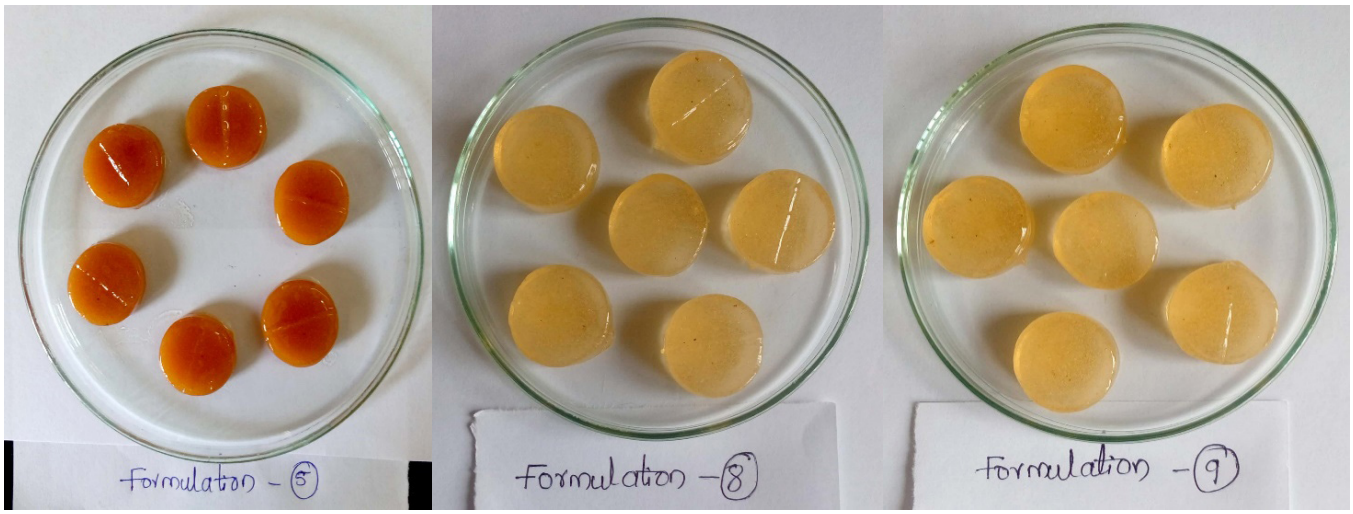

Figure 3: Hard candy lozenges

Table 2: FTIR spectra data of levocetirizine dihydrochloride and ambroxol hydrochloride

	The peak of functional groups [wavelength (cm^{-1})]			
FTIR spectra	*OH stretch (LC)*	*OH stretch (AMB)*	*N-H stretch*	*COOH stretch*
LC	1,181.31	-	1,357.17	1,741.67
AMB	-	1,059.85	3,250.12	-
LC + AMB	1,182.56	1,056.13	1,354.42	1,741.13
Optimized F	1,184.96	1,056.63	1,537.35	1,738.20

All the developed formulations were assessed for physical parameters, like weight variation, hardness, thickness, and friability, are within the pharmacopeia limits. The results of the tests were recorded in Tables 3 and 4. The developed lozenges are circular with either flat or biconvex faces having > 10 kg/cm^2 hardness with negligible variation in thickness. The diameter and thickness rely on the molds, die, and punches.

The suggested proportion of liquid glucose to sucrose was 60 to 40% for obtaining transparency and smoothness. This can be because of the prevention of sugar crystallization by liquid glucose.[18] However, in the present investigation, sufficient transparency was attained with the utilization of 13, 18, and 20% of sucrose and liquid glucose. This suggests that even a low concentration of liquid glucose will retain the capability to stop the crystallization of sugar.

Apart from liquid glucose, dextrose, gelatin, and honey are used in the preparation of lozenges. The utilization of 40% dextrose affected clearness. This could be due to the failure of dextrose to retard crystallization of sugar, use of gelatin, that was clear once heated with water (forms a clear soft gel-like uniformity) also breakdown to accomplish the transparency, as well as, a mixture with liquid glucose. The utilization of honey resulted in the transparent lozenges; however, not satisfactory because it was sticky due to absorbent nature. The resulted transparency with honey is because of its ability to slow down crystallization.

Apart from sucrose, jaggery, crystallized sugar, and sodium saccharin are utilized in the preparation of lozenges. Lozenges fabricated from jaggery are comparatively stickier than the sugar candy, and formed lozenges were not transparent as well. But the crystallized sugar gave better transparency and lack of stickiness. However, it gradually loses its transparency as time passes by. Sodium saccharine is used as an artificial sweetener, but it failed to give candy-like consistency.

The weight variation was found to be between 2,997.4 ± 1.56 to 3,000.7 ± 3.60 mg, which is among the pharmacopoeial limit. The hardness of all lozenges was maintained between 10.39 ± 0.29 and 11.60 ± 0.47 kg/cm^2. As there are no definite standard limits for the deviance in the hardness of lozenges, by comparing every formulation with each other, it could be decided that as a result of the difference between the standard deviation is not too big, the formulations had worthy consistency within the hardness. The thickness varied from 7.28 to 7.41 mm and friability between 0.41 ± 0.07 and 0.57 ± 0.12%. The weight variation, hardness, thickness, and friability of optimized formulation (FL8) were

Table 3: Characterization of LC and AMB lozenges

Formulation code	*Weight[a] (mg)*	*Hardness[b] (kg/cm^2)*	*Thickness[b] (mm)*	*Friability[a] (%)*
FL1	3,000.5 ± 1.58	11.60 ± 0.47	7.41 ± 0.05	0.53 ± 0.02
FL2	2,999.8 ± 1.97	10.81 ± 0.92	7.28 ± 0.07	0.48 ± 0.08
FL3	2,997.4 ± 1.56	11.33 ± 0.70	7.32 ± 0.05	0.45 ± 0.07
FL4	2,999.9 ± 2.21	10.41 ± 0.46	7.35 ± 0.04	0.56 ± 0.03
FL5	2,999.7 ± 2.50	10.52 ± 0.49	7.37 ± 0.05	0.41 ± 0.07
FL6	3,000.7 ± 3.60	10.40 ± 0.52	7.38 ± 0.06	0.53 ± 0.11
FL7	2,998.6 ± 2.31	10.39 ± 0.29	7.38 ± 0.05	0.57 ± 0.12
FL8	3,000.3 ± 2.30	10.57 ± 0.39	7.41 ± 0.02	0.45 ± 0.02
FL9	3,000.5 ± 2.61	11.17 ± 0.66	7.31 ± 0.04	0.42 ± 0.08
FL10	2,999.3 ± 2.65	10.78 ± 0.58	7.28 ± 0.06	0.54 ± 0.21

Results are mean of 20 observations ± SD; b. Results are mean of 10 observations ± SD

Table 4: Characterization of LC and AMB lozenges

	Content uniformity (%)		
Formulation code	*LC*	*AMB*	*Moisture content (%)*
FL1	99.13 ± 1.77	98.21 ± 1.81	0.86 ± 0.08
FL2	98.85 ± 1.79	98.53 ± 1.72	0.84 ± 0.06
FL3	98.48 ± 1.60	99.22 ± 2.40	0.87 ± 0.05
FL4	98.59 ± 1.66	98.46 ± 1.94	0.82 ± 0.06
FL5	99.13 ± 1.77	98.91 ± 2.12	0.83 ± 0.02
FL6	98.80 ± 1.65	98.10 ± 1.56	0.92 ± 0.05
FL7	98.87 ± 1.95	98.80 ± 1.82	0.87 ± 0.07
FL8	99.43 ± 2.06	99.60 ± 1.85	0.85 ± 0.05
FL9	99.26 ± 1.82	98.85 ± 1.79	0.87 ± 0.07
FL10	99.16 ± 1.71	98.47 ± 2.18	0.84 ± 0.06

*Results are mean of 3 observations ± SD

3,000.3 ± 2.30 mg, 10.57 ± 0.39 kg/cm^2, 7.41 ± 0.02 mm, and 0.45 ± 0.02%, respectively, which was within acceptable limits.

The assay was executed, and drug content uniformity of developed lozenges was found to be in between 98.48 ± 1.60 and 99.43 ± 2.06% for levocetirizine dihydrochloride and 98.10 ± 1.56 and 99.60 ± 1.85% for ambroxol hydrochloride, that were within the acceptable limits. The optimum vary of moisture content in lozenges is 0.5 to 1.5%.

The moisture content of the formulated hard candy lozenges was found to be between 0.82 ± 0.06 and 0.92 ± 0.05%, which were within the acceptable limits. The content uniformity and moisture content of the optimized formulation (FL8) were 99.43 ± 2.06% (LC), 99.60 ± 1.85% (AMB), and 0.85 ± 0.05%, respectively.

The dissolution rate and bioavailability could also be directly associated with the efficacy of the lozenge. They possess extended-release property since the drug has to be released from the congealed candy base. All the developed formulations were subjected to *in vitro* study. The cumulative amount of drug release was determined based on the mean amount of LC and AMB in the lozenge. The data are given in Figures 4 to 8. The cumulative percent drug release of formulation FL1, FL2, and FL3 of LC (hard candy lozenges without polymer) containing a varying concentration of sucrose and liquid glucose recorded the drug release of 97.06, 98.08, and 96.36%, respectively, at the end of 10 minutes whereas FL4, it was 82.08% at the end of 30 minutes. The cumulative percentage drug release of formulation FL1, FL2, and FL3 of AMB (hard candy lozenges without polymer) containing a varying concentration of liquid glucose recorded the drug release of 95.80, 96.50, and 97.65%, respectively, at the end of 15 minutes. For FL4, it was 89.45% at the end of 30 minutes.

Formulations FL5, FL6, and FL7 of LC containing a varied concentration of sucrose and liquid glucose recorded the drug release of 81.08, 84.75, and 65.88%, respectively, at the end of 30 minutes. For FL8, it was recorded 99.39% at the end of 25 minutes. The percentage drug release of optimized formulation (FL8) was 99.39%, which showed the highest percentage of drug release compared to other formulations, which can be attributed to the strategy of preparation wherever the drug is uniformly distributed within the lozenge.

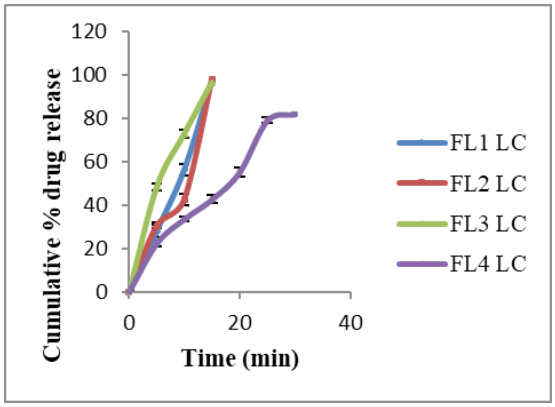

Figure 4: Cumulative percent release of LC from FL1–FL4

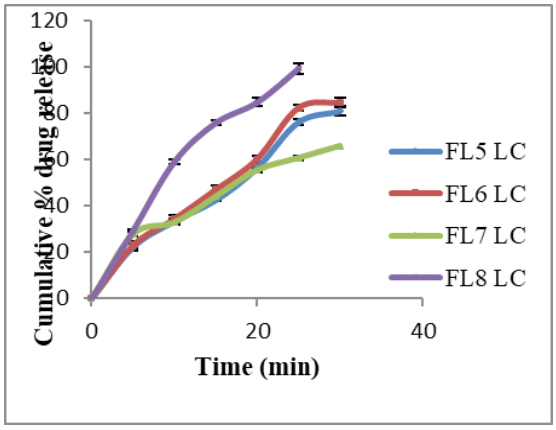

Figure 6: Cumulative percent release of LC from FL5–FL8

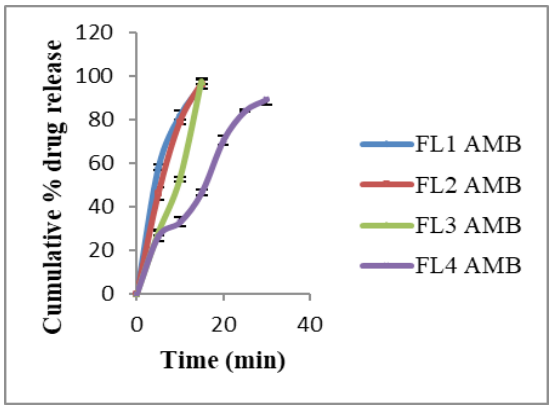

Figure 5: Cumulative percent release of AMB from FL1–FL4

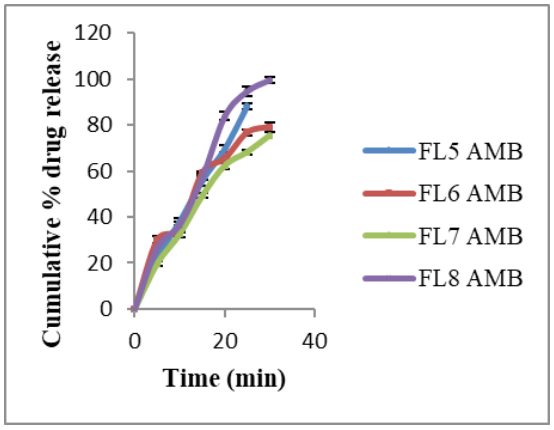

Figure 7: Cumulative percent release of AMB from FL5–FL8

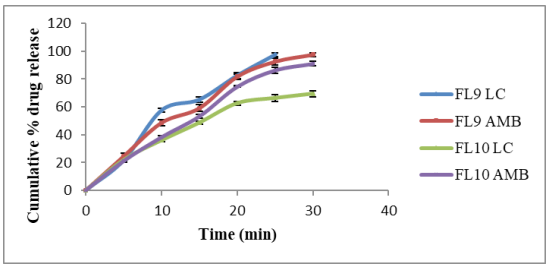

Figure 8: Cumulative percent of drug release from lozenges (FL9–FL10)

Table 5: Comparative evaluation of taste and mouthfeel for optimized formulation

Volunteers	*Taste*	*Mouthfeel*
1	x	No grittiness, good mouthfeel
2	+	
3	x	
4	x	
5	+	
6	x	

N = 3; where x = no bitterness; + = slight bitter

Formulations FL9 (AMB), FL10 (LC), and FL10 (AMB) containing variable concentrations of disaccharide and liquid glucose recorded the drug release of 97.5, 69.53, and 91.07%, respectively, at the end of 30 minutes. For FL9 (LC), it was 97.43% at the end of 25 minutes.

Informed consent was obtained from human volunteers to perform the *in vivo* taste evaluation experiment. Taste analysis was conducted on six fit human volunteers, and also the results were recorded in Table 5.

CONCLUSION

The study was targeted on the formulation and characterization of LC and AMB lozenges for patients suffering from cough and excess mucus secretion. Patient compliance is a necessary aspect in administration, particularly with pediatric, geriatrics patients, and others having difficulty in swallowing tablets. The main concern was to develop a new dosage form and to study the impact of different polymers on the *in vitro* release. At the outset, the assessment of drug content by UV spectrophotometer was studied. The FTIR analysis showed that the chosen drug and polymer are compatible with each other. Lozenges developed from sucrose and liquid glucose by fusion technique exhibited good physical properties, and the drug release was maximum in formulation FL8 (99.39 ± 1.16%) at the end of 25 minutes for LC and AMB, it was 99.42 ± 1.23% at the end of 30 minutes.

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