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FORMULATION AND EVALUATION OF LEVODROPROPIZINE LOZENGES

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ABSTRACT

In the present investigation Levodropropizine was formulated as high boiled sugar hard candies to provide slow release of medicament for the treatment of bronchial cancer induced cough and cough due to other reasons. The local acting mechanism of levodropropizine makes it more suitable to formulate as lozenges. . The hard candy lozenges were formulated using sugar as a base and the usage of corn syrup in the formulation made the lozenges transparent and smooth which helped in improving the elegancy of formulation. Formulations of hard candies were subjected to physico-chemical as well as in-vitro drug release. Among all the formulation of among all the formulation of hard candy lozenges FL13, FL14 and FT15 had shown in-vitro drug release of 99.1%, 98.2% and 95.5% at the end of 20 min.

KEYWORDS: Hard candy lozenges; corn syrup; transparent; cough.

INTRODUCTION

Lozenges are the flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. They dissolve slowly in the mouth and so release the drug dissolved in the saliva. The drugs having a large dose can be easily administered formulating as lozenges. Local Anesthetics, Antimicrobials, Antibiotics, vitamins, Decongestants, Analgesics if the active ingredient is heat labile, it may be made into lozenge preparation by compression. The granulation is prepared in a manner similar to that used for any compressed tablet with Cough suppressants, Nicotine like substances for smoking cessation.

Coughis a forceful expulsion of air from the lungs. It isnormally a protective reflex for removing foreign bodies,environmental irritants, or accumulated secretions fromthe respiratory tract. The cough reflex involves centraland peripheral mechanisms. Centrally, the cough centerin the medulla oblongata receives stimuli and initiates thereflex response (deep inspiration, closed glottis, buildupof pressure within the lungs, and forceful exhalation). Peripherally,cough receptors in the pharynx, larynx, trachea,or lungs may be stimulated by air, dryness ofmucous membranes, or excessive secretions.

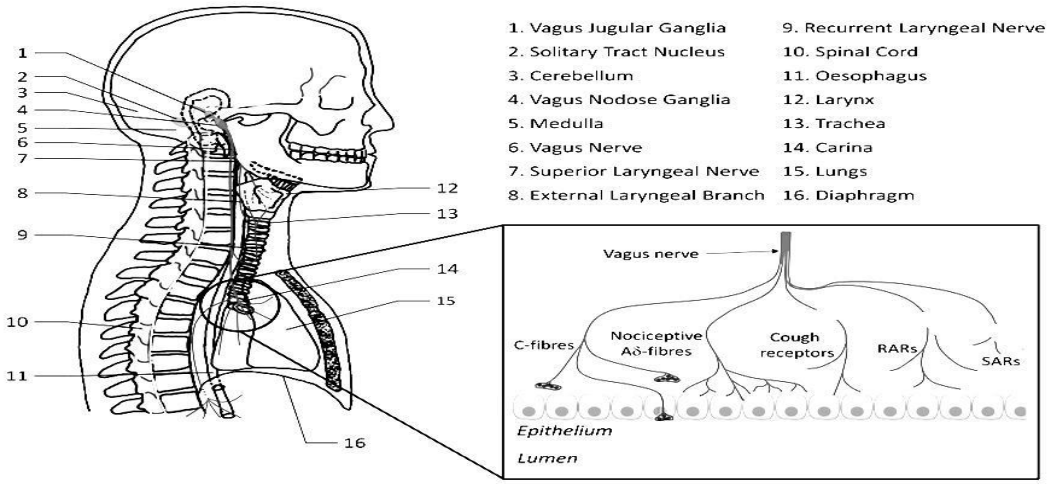


Figure. No 1 Mechanism of cough

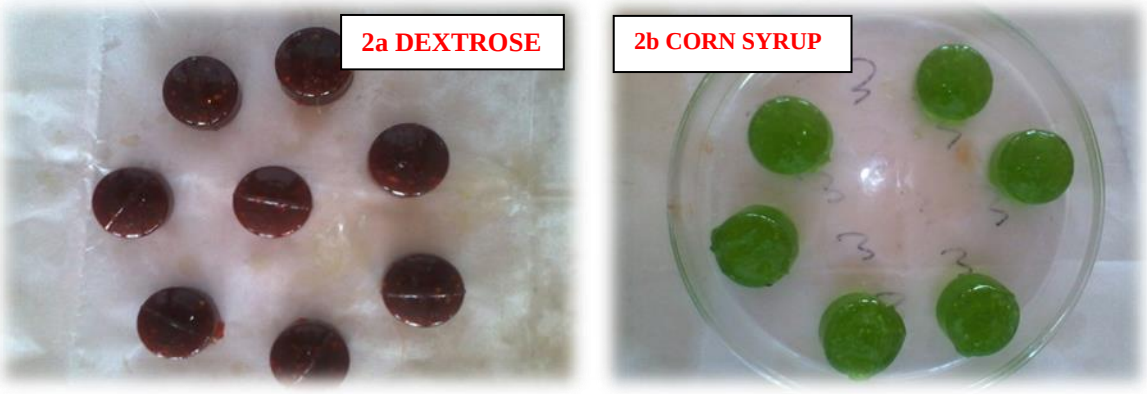
Levodropropizine is an antitussive and its Brand names are Antux, Arlicough, Bronal, **Mechanism of action:** LDP is a peripherally acting agent inhibiting the afferent pathways. That mediates the generation of the cough reflex. Its mechanism of Action is mainly peripheral at the trachea-bronchial level, although it is also associated to some anti-allergic and anti bronchospastic activity. (1 ; Mellillo G et al ., 1988) ***It is very effective in the dry cough caused in Bronchial Cancer even which can not cured by chemotherapy***.

MATERIALS AND METHODOLOGY

Levodropropizine (ANTUX,) Gift sample from Euro Drugs, Hyd., Polymers are Gift sample from Hetero Drugs, Hyd. Aspartame Gift sample from AIZANT Drugs, Hyd. Mannitol, Sugar, liquid Glucose Dextrose, Flavors and Colours are from local chemical supplers.

METHOD OF PREPARATION FOR LEVODROPIZINE TROCHES

Preparation of Levodropropizine Hard Candy Lozenges (Nagoba et al., 2011; Shojaei et al., 1998; Jelvehgari Mitra et al., 2006**)** Preparation of Candy Lozenges: Required quantity of sugar syrup was prepared mixing sugar and water and heated to 110^0C then liquid glucose was poured into the sugar syrup and heated to 160 ^{0}C. Drug and Flavors were added when the temperature was brought to 40-50 °C. Now this semisolid mass was poured into pre-lubricated moulds and subjected to cooling. Then the hard candy lozenges were taken out from the moulds and packed in aluminum foil pouches**.** Levodropropizine gives a bitter taste so in order to mask the bitter taste of LDP formulation includes aspartame and flavours.



In figure 2a dextrose was used to prevent crystallization of sugar

In figure 2b corn syrup was used to prevent crystallization of sugar

Figures. 2 prepared lozenges

EVALUATION OF THE DEVELOPED FORMULATIONS

Characterization of Lozenges. (Purushotham Rao et al., 2011; Rawlins et al,.1995)

The prepared Levodropropizine Lozenges were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content. (Lachmann et al., 1991; Bankar and Rhodes 2008).

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Lozenge hardness

Hardness of lozenge is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester and the average was calculated and presented with standard deviation.

Lozenge thickness

The Thickness and diameter of the Lozenges from production run is carefully controlled. Thickness can vary with no change in weight due to air entrapment during pouring into moulds and lack of reproducibility during pouring. Hence this parameter is essential for consumer acceptance, Lozenge uniformity and packaging. The thickness and diameter of the lozenges were determined using Digital vernier calipers. Ten lozenges from each formulation were used and average values were calculated. The average thickness for lozenges were calculated and presented with standard deviation.

Determination of drug content

Twenty lozenges were finely powdered; quantities of the powder equivalent to 60 mg of LDP (Drug) were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of 6.8 Phosphate buffer and allowed to stand for 30min with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with distilled water.The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at λ_{max} 237nm. The drug concentration was calculated from the standard curve.

In vitro drug release studies Dissolution conditions

- Apparatus : USP I apparatus
- Dissolution medium : 250ml of pH 6.8 Phosphate buffer
- Temperature : 37 ± 0.5^0 C
- Rotating speed of the paddle : 50 rpm
- Sample time intervals : 5, 10,15,20,25,30 minutes
- Detection : UV-VIS spectrophotometer at λ_{max} 237nm

The samples were withdrawn at predetermined time points, diluted appropriately and were analyzed spectrophotometrically at 237 nm. The cumulative percentage release and standard deviation were calculated and the results are presented in the table.

Release kinetics

Data of *In vitro* release was fit into different equations to explain the release kinetics of Levodropropizine Lozenges and Troches. The kinetic equations used were zero–order and first order equations.

Drug-Excipients Compatibility study

Levodropropizine (drug) was mixed with all excipients, used in the formulation in different ratios and subjected to FTIR/Physical observation.

Drug-Excipients Compatibility study by physical observation

LDP (DRUG) was mixed in different proportions with all excipients which were used in the formulation, in different ratios and kept at 40^{o}C/75%RH conditions for two months. The physical properties (Colour change) were monitored regularly. The change in colour of any mixture was considered as incompatibility and the excipients blend was discarded from study.

FT-IR

A Fourier Transform- Infra Red spectrophotometer (FTIR Spectrum BX series 2.19 version) equipped with spectrumv2.19 software was used to study the non-thermal analysis of drug-excipients (binary mixture of drug: excipients 1:1 ratio) compatibility. The spectrum for each sample was recorded over the 450 - 4000 cm^{-1} spectral region with a resolution of 4 cm^{-1}.

Standard graph of Levodropropizine

Standard graph of Levodropropizine at λ_{max} at 237nm

Standard stock solution of pure drug containing 100 mg of LDP/100mL were prepared using different buffer solutions like 6.8 pH phosphate buffer The working standards were obtained by dilution of the stock solution in corresponding buffers. The standard curves for Levodropropizine were prepared in concentration range of 4-24µg/mL at the selected wave length 237 nm. Their absorptivity values were used to determine the linearity. Solution were scanned and Beer Lamberts law limit was obeyed in concentration range of 4, 8, 12, 16, 20, 24 µg/mL.

Table.No.1Standard graph of Levodropropizine at 237 nm in 6.8 phosphate Buffer.

S.No	Concentration (µg/mL)	Absorbance
1	4	0.157
2	8	0.311
3	12	0.449
4	16	0.593
5	20	0.745
6	24	0.890

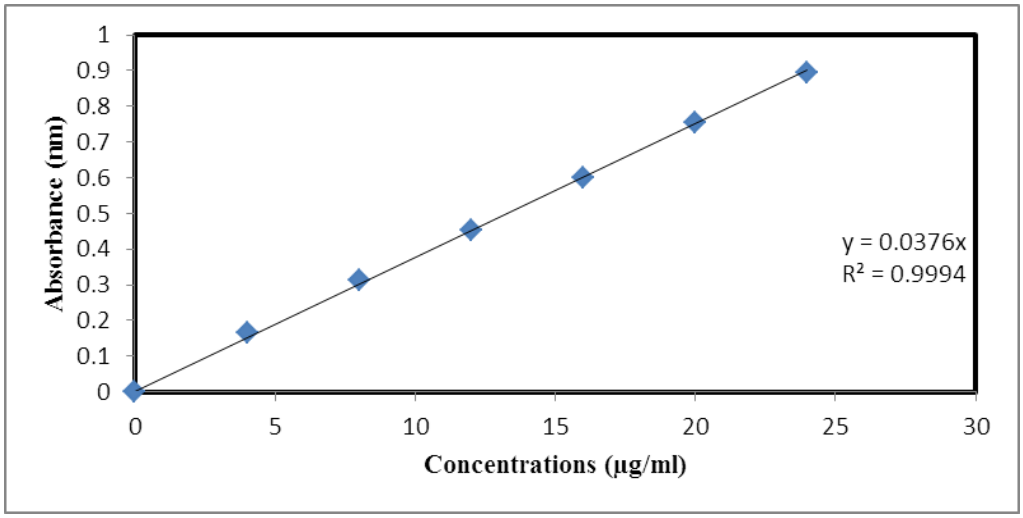


Figure. No. 3: Standard graph of Levodropropizine in phosphate buffer pH 6.8

Formulation of Lozenges of lozenges were shown in Table.No.2

Formulation Code	FL 1	FL 2	FL 3	FL 4	FL 5	FL 6	FL 7	FL 8	FL 9	FL10	FL 11	FL 12	FL13	FL 14	FL 15
Drug (mg)	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Sugar(mg)	2350	2205	2075	2197.5	2190	2175	2197.5	2190	2175	2197.5	2190	2175	2197.5	2190	2175
Liquid Glucose	370	500	620	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K 200	-	-	-	0.25 %	0.5 %	1%	-	-	-	-	-	-	-	-	-
HPMC K 4M	-	-	-	-	-	-	0.25 %	0.5 %	1%	-	-	-	-	-	-
HPMC K 15M	-	-	-	-	-	-	-	-	-	0.25 %	0.5 %	1%	-	-	-
XANTHAN GUM	-	-	-	-	-	-	-	-	-	-	-	-	0.25 %	0.5 %	1%
Citric Acid	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Sodium Citrate	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Aspartame	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Color	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs	qs	qs	qs
Flavor	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs	qs	qs	qs
Total weight	3000mg														

RESULTS

Evaluation of Levodropropizine Lozenges prepared with varying concentration of different polymers were **shown in Table. No.3** In all formulation, tablet weight and thickness were with in mean ± 7.5% and mean ± 5 % respectively. The weight variation in all the formulations were found to be, 2999.9 ± 2.2mg to 3000.6 ± 2.7 mg which was in pharamacoepial limits. The thickness varies between 7.28 to7.42 mm. Hardness of all the tablets was maintained 10.39±0.29 to 11.17±0.66 Assay was performed and percent drug content of all the lozenges were found to be between 98.48 ± 1.60 and 99.43 ± 2.06 of levodropropizine, which was with in the acceptable limits.

Table.No.3 Evaluation of Levodropropizine Lozenges prepared with varying concentration of different polymers;

Formulation	Weight[b] (mg)	Hardness[a] (kg/cm^2)	Thickness[a] (mm)	Drug[b] Content(%)
FL1	3000.6±2.7	10.25±0.51	7.38±0.05	99.16±1.71
FL2	2999.3±2.65	10.3±0.46	7.31±0.04	98.8±1.65
FL3	3000.7±3.6	10.82±0.41	7.42±0.03	99.26±1.82
FL4	2999.6±2.3	10.78±0.63	7.28±0.06	98.87±1.95
FL5	3000.2±2.3	11.07±0.47	7.35±0.05	99.43±2.06
FL6	2999.8±1.97	10.8±0.92	7.33±0.04	98.8±1.48
FL7	2999.4±1.56	10.41±0.46	7.35±0.04	99.27±1.42
FL8	2999.9±2.2	11.03±0.70	7.33±0.06	99.2±1.8
FL9	2999.7±2.5	10.51±0.49	7.31±0.05	99.15±1.58
FL10	3000.5±1.58	10.4±0.52	7.41±0.06	98.59±1.66
FL11	2999.3±2.1	10.39±0.29	7.28±0.07	98.85±1.79
FL12	2999.6±2.8	11.17±0.66	7.32±0.05	99±1.84
FL1`3	2999.6±2.7	10.47±0.39	7.35±0.04	98.48±1.60
FL14	2999.9±2.5	10.77±0.58	7.37±0.05	99.13±1.77
FL15	3000.2±1.86	10.91±0.52	7.36±0.06	98.48±1.60

a-Results are mean of 10 observations ± SD

b-Results are mean of 20 observations ± SD

Table.4: Cumulative percent of levodropropizine released from lozenges containing varying concentration of different polymer

CUMULATIVE % DRUG RELEASE OF LOZENGES						
Time(min)	**FL1**	**FL2**	**FL3**	**FL4**	**FL5**	**FL6**
0	0	0	0	0	0	0
5	61±0.53	63±0.24	65.1±0.86	40.2±0.44	39.9±0.7	40.4±0.66
10	86.2±0.6	84.2±0.61	83.8±0.45	64.1±0.49	63.7±0.2	62.8±0.32
15	98.2±0.24	98.7±0.53	99.4±0.28	83.2±0.62	81.9±0.53	79.3±0.70
20				92.7±0.57	89.2±0.18	87.8±0.66

***Results are mean of 4 observations ± SD**

Table. No 5. Cumulative percent of levodropropizine released from lozenges containing varying concentration of different polymer:

CUMULATIVE % DRUG RELEASE OF LOZENGES						
Time(min)	**FL7**	**FL8**	**FL9**	**FL10**	**FL11**	**FL12**
0	0	0	0	0	0	0
5	38±0.32	36.23±0.44	33.7±0.57	39.5±0.44	39.1±0.21	37.6±0.57
10	64.9±0.20	64±0.54	64.4±0.73	65.2±0.36	64.6±0.28	64±0.32
15	81.1±0.79	79.9±0.43	77±0.44	78.6±0.32	78.4±0.31	76±0.63
20	91.9±0.44	89.9±0.63	84.7±0.54	89.6±0.32	87.7±0.3	81.9±0.64

Table.No.6: Cumulative percent of levodropropizine released from lozenges. Containing varying concentration of different polymer:

Cumulative % Drug Release Of Lozenges			
Time(min)	**FL13**	**FL14**	**FL15**
0	0	0	0
5	415±0.48	41.1±0.82	41.3±0.74
10	65.6±0.24	66.2±0.74	63.9±0.57
15	82±0.72	83±0.85	81.1±0.78
20	99.1±0.0.58	98.2±0.65	95.5±0.48

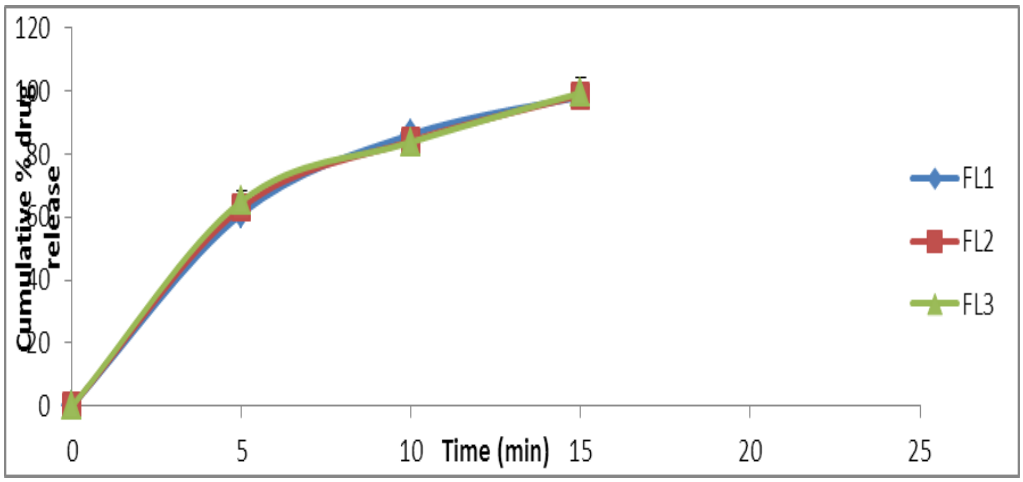


Figure. No.4: Graphical representation of cumulative percent of Levodropropizine released from Lozenges formulation FL1-FL3

Formulation FL1,FL2 and FL3 with out polymer have recorded the drug release of 98.2%, 98.7% and 99.4% at the end of 15 min. this formulation contain varying concentration of corn syrup.

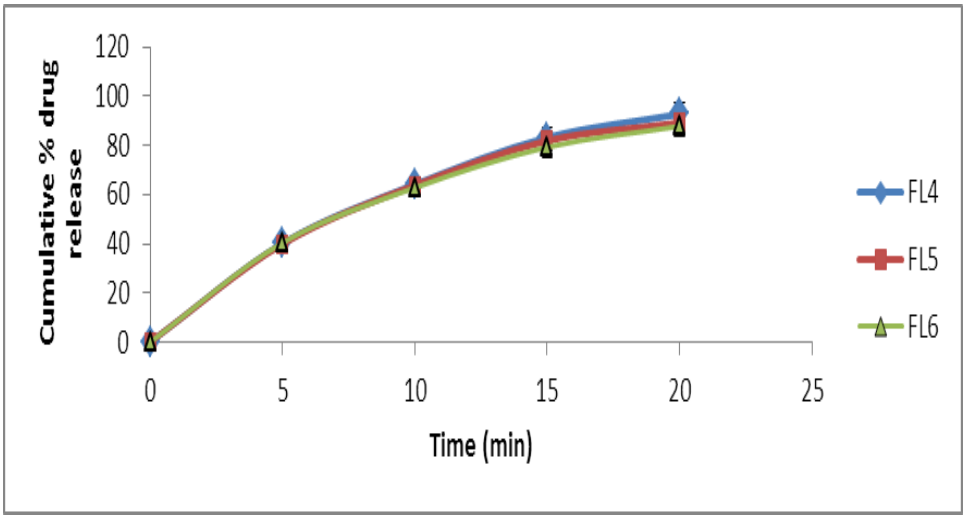


Figure.No.5: Graphical representation of cumulative percent of Levodropropizine released from Lozenges formulations FL4-FL6

Formulation FL4 ,FL5 and FL6 containing varying concentration of HPMC K 200 recorded the drug release of 92.7%, 89.2% and 87.8% at the end of 20 min.

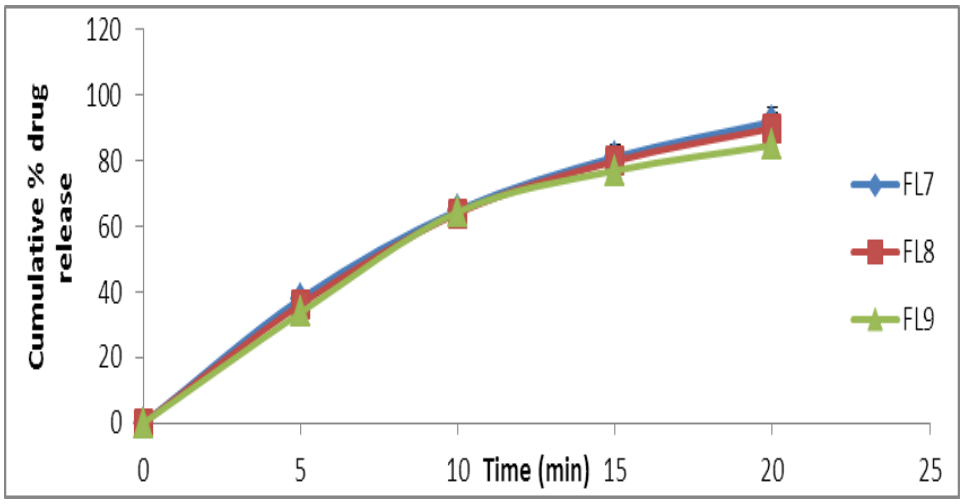


Figure.No.6 Graphical representation of cumulative percent of Levodropropizine released from Lozenges formulation FL7-FL9

Formulation FL7, FL8 and FT9 containg HPMC K 4M as a polymer of varying concentration have recorded the drug release of 91.8% ,88.9% and 84.7% at the end of 20 min.

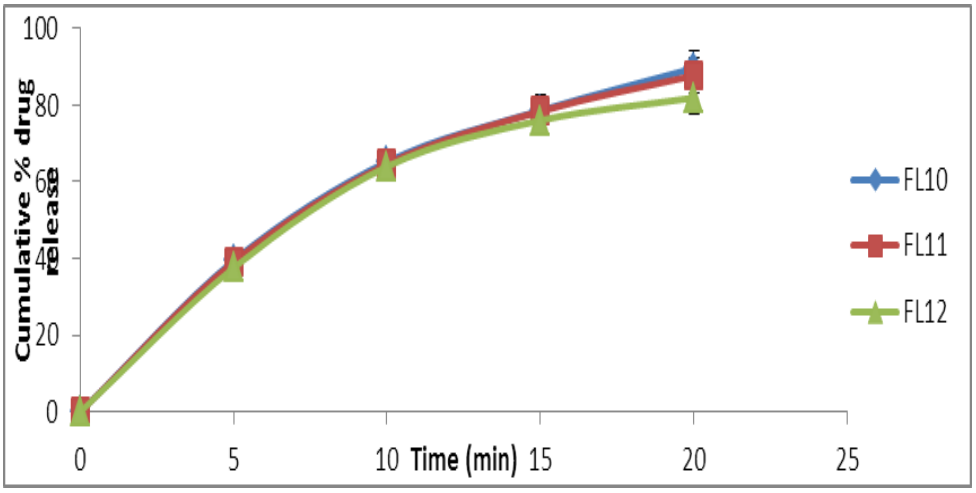


Figure. No 7: Graphical representation of cumulative percent of Levodropropizine released from Lozenges formulations FL9-FL12

Formulations FL10, FL11 and FL12 containing HPMC K 15 M as polymer of different concentration have shown the drug release of 89.6%, 87.7% and 81.9% at the end of 20 min.

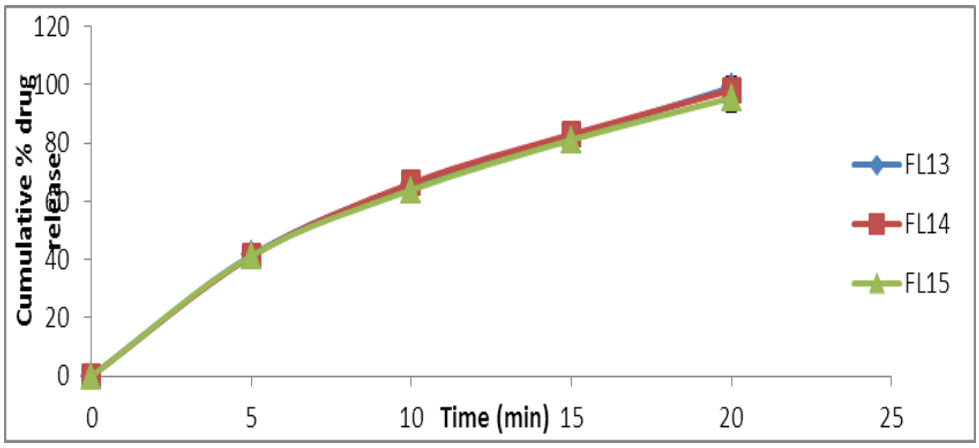


Figure.No.8: Graphical representation of cumulative percent Levodropropizine released from Lozenges formulations FL13-FL15

Formulation FL13, FL14 and FT15 containing varying concentration of Xanthan gum have shown in vitro drug release of 99.1%, 98.2% and 95.5% at the end of 20 min.

Release kinetics and correlation coefficients of lozenges shown inTable.No.7

Formulation code	Mathematical models (Release Kinetics)	
	Zero order	First order
	R^2	R^2
FL1`3	0.9552	0.8246
FL14	0.9220	0.9963
FL15	0.9334	0.9929

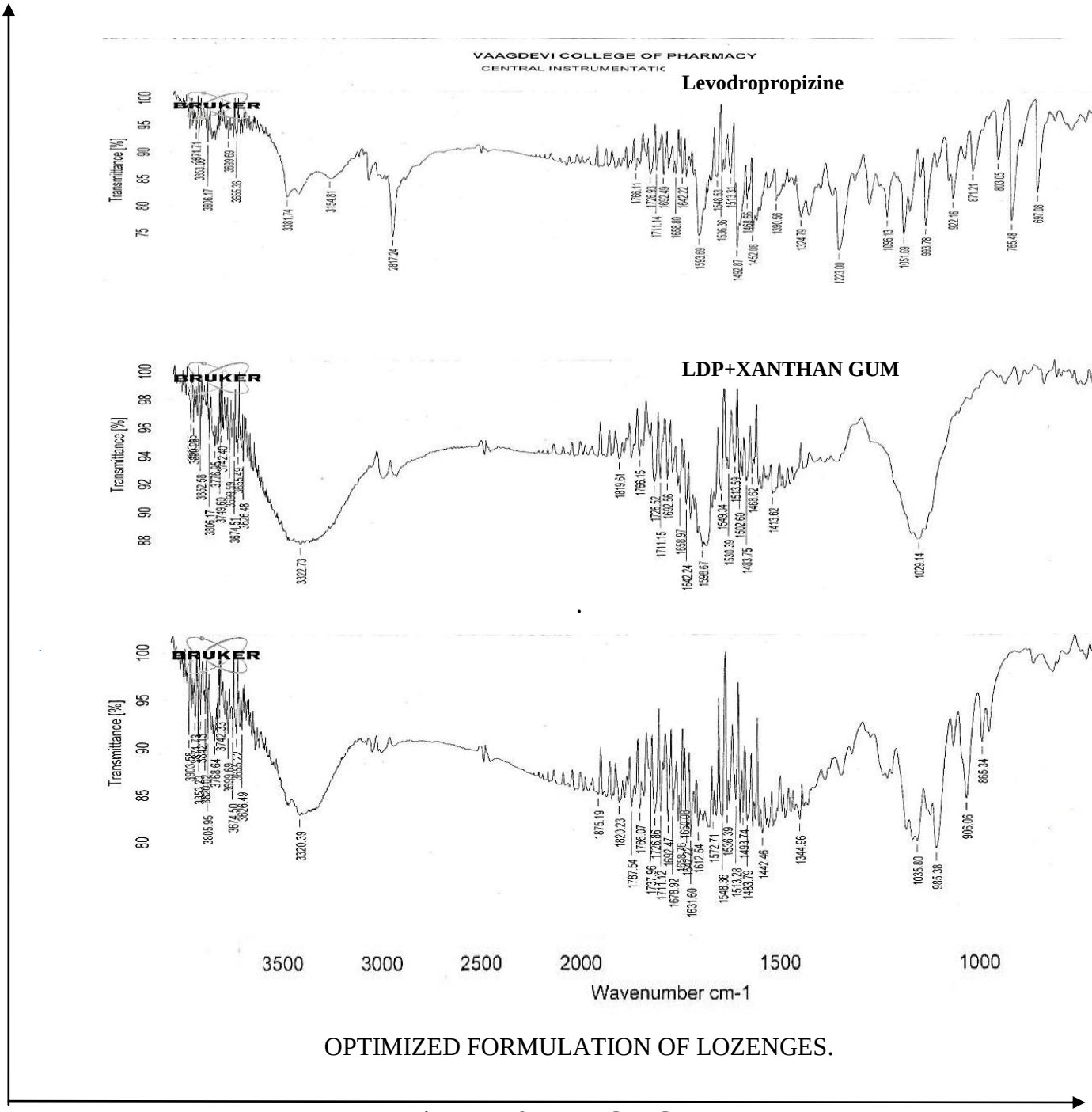


Figure.No9. FTIR SPECTRUM

Table.No.8. The Fourier transform infrared spectroscopy studies were carried out for pure drug along with drug and excipients combination. The results summarized below.

PEAK OF FUNCTIONAL GROUPS {WAVE LENGTH(cm-1)}					
IR Spectra	**C-H Stretching** (alkane)	**O-H Stretching (Free Hydroxyl)**	**C-N Stretching**	**C-H Bending**	**C=C Stretching (aromatic)**
LDP(Drug)	2817	3655	1051	765	1593
Sugar+LDP	2816	3655	1050	765	1593
Xanthan+LDP	2890	3655	1029	765	1598
Lg+LDP	2815	3655	1012	765	1548
Lozenges	2817	3655	1051	765	1548

The above peaks are considered as characteristic peaks of Levodropropizine. These peaks that not affected and prominently observed in IR spectra of drug and excipients. This indicates there is no interaction between drug and excipients.

DISCUSSION

The suggested ratio of the sugar to corn syrup is 60:40 for attaing transparency and smoothness. This is due to prevention of sugar crystallization by corn syrup. (Lachman et al., 1989).

But in the present investigation sufficient transparency was attained with the use of the 13%, 18% and 20%. This suggests that even at low concentration of corn syrup has ability to retain the capacity to prevent crystallization of sugar.

This difference in the concentration of corn syrup to attain the smoothness and transparency may be due type of apparatus used in the cooking process as follows.

20% - Open kettle

30 % - Batch vacuum cookers

35 % - Semi-continuous

40% - Continuous-cookers**.**

The difference in the requirement of corn syrup is due to increasing amountof mechanical action or turbulence to which the candy is subjected after cooking.

- More the agitation, more the requirement of corn syrup
- Other mechanism to control the crystallization are:

High Molecular weight sugar in the corn syrup

Low cooking temperatures

Minimum mixing during cooking

Dextrose is used instead of corn syrup (Purushotham Rao.K et al., 2011).Use of 40% dextrose instead of corn syrup affected the transparency. Dextrose failed to retard crystallization of the sugar. Even use of gelatin which was transparent when heated with water (forms transparent soft gel like consistency) also failed to attain the transparency alone as well as combination with corn syrup. Use of honey instead of corn syrup resulted in the transparent lozenges but was sticky and not satisfactory. The formulation developed using honey was very sticky due

to the hygroscopic nature of honey. The obtained transparency with honey is due to its ability to retard crystallization. (Raymond C Rowe et al., 2006.)

Problem with Developed Formulation

Developed formulation failed to prevent stickiness of lozenges though it was dusted with sugar powder or talc and they are stored in double wrapped aluminum foil after formulation of lozenges. Moreover dusting process affected the transparency.

CONCLUSION

Patient compliance is one of the important aspect for administration of drugs especially those which are bitter in taste. For patient compliance attractive taste masking formulations are the need of the hour. In the present study levodropropizine sweetened tablet lozenges and hard candy lozenges were designed for the effective treatment of bronchial cancer induced cough and cough due to other reasons.

Among all the Formulation of Lozenges FL13, FL14 and FT15 containing varying concentration of Xanthan gum have shown in vitro drug release of 99.1%, 98.2% and 95.5% at the end of 20 min the long lasting release of the drug from the formulation containing xanthan gum.

All the formulations of Hard Candy Lozenges were subjected various evaluations and the values obtained are within acceptable range.or any formulation, drug excipients interactions plays an important role and hence the formulations were subjected to infrared spectral analysis, it was observed that the drug peaks were undisturbed revealing the compatibility drug.

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