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Fabrication and Evaluation of Levocetizine Di Hydrochloride Lozenges

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ABSTRACT: The aim of present research was to fabricate Levocetizinedihydrochloride (LCTZ) lozenges, with good mechanical properties, dissolution and producing an acceptable taste when placed on tongue. In the present investigation Levocetizinedihydrochloride lozenges were formulated as high boiled sugar hard candies to provide slow release of medicament for the treatment of allergic rhinitis. Levocetizinedihydrochloride, an antihistaminic was incorporated to relieve the symptoms of allergic rhinitis. Fifteen batches of lozenges with drug were prepared using different combinations of sugar, liquid glucose, various grades of HPMC and Xanthan gum, citric acid, sodium citrate and aspartame. 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 elegance of formulation. Designed lozenges were subjected to physico-chemical evaluation tests. Hard candy lozenges FL13, FL14 made with Xanthan gum and had shown in-vitro drug release of 99.1%,98.2% of drug which were the best release amongst all.

KEY WORDS: Levocetizinedihydrochloride, lozenges, HPMC, Xanthan gum, in-vitro drug release.

I. INTRODUCTION

Lozenges are solid preparations to be used in the oral cavity and are intended to be dissolved inside the mouth. Lozenges contain one or more active principles in a sweetened and flavoured base which are used to treat local irritation or throat infection and may also be used for systemic effect. Lozenges are mainly used to give local action as soothing and purging the throat and are also used to relieve symptoms like cough and flu. These are also believed to give systemic effect provided that the drug is well absorbed from the linings of buccalcavity or when it is swallowed (1).

Lozenges are the flavoured medicated widely used solid dosage forms. Lozenges historically have been used for the relief of minor sore throat pain and irritation and have been used extensively to deliver topical anesthetics and antibacterial drugs. Today they are used for of drugs like analgesics, anesthetics, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, and demulcents and other classes and combinations.

Excipients of the lozenges have a demulcent effect on throat as the ingredients release slowly and uniformly over the affected area of mucosal membrane (2).

The USP currently recognizes Cetylpyridinium Chloride Lozenges and Nystatin Lozenges. However, more than five dozen over-the-counter (OTC) lozenge products are currently marketed(2).

Levocetizinedihydrochloride is a piperazine derivative and it is a potent H1 blocker with less side effects. It is very effective antihistaminic drug with the rapid action(3). Levocetizine blocks the histamine receptors and does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. Further it prevents the release of other allergy chemicals and increased blood supply to the area, such that it relieves the typical symptoms of hay fever. The manufacturers claims that it is more effective with fewer side effects than the second-generation drugs; however, there have been no published studies supporting this statement, although other studies have concluded it may be more effective (4).

International Journal of Innovative Research in Science, Engineering and Technology

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In the present investigation Levocetirizinedihydrochloride lozenges were formulated as high boiled sugar hard candies to provide slow release of medicament for the treatment of allergic rhinitis. Levocetirizinedihydrochloride, an antihistaminic was incorporated to relieve the symptoms of allergic rhinitis. Allergic rhinitis is known to be high-prevalence chronic respiratory diseases which have negative impact on the quality life of the patients, work activities, productivity or school performance as well as on healthcare costs. Because of its benign nature, the importance of this condition is often underestimated.

II. MATERIALS AND METHODS

2.1 Materials:

Levocetirizinedihydrochloride is gift sample obtained from Hetero drugs, Hyd., polymers are gift samples from Reddys laboratories, Hyderabad., Aspartame procured as gift sample from Aziant Drugs, Hyderabad., Mannitol, sugar, Liquid glucose, Flavours and colours from local suppliers. Sodium hydroxide, Potassium dihydrogen Orthophosphate purified are from sd-fine chemicals.

2.2 Method of Preparation of LevocetirizineDihydrochloride Lozenges:

Preparation of hard Candy Lozenges (5): Required quantity of sugar syrup was prepared by mixing sugar and water and it was heated to 110°C. Then weighed quantity of liquid glucose was poured into the sugar syrup while mixing and heated it to 160 °C. Flavors and other remaining ingredients were added when the temperature was brought to 40-50 °C. Immediately, the semisolid mass was poured in to the fabricated moulds which were pre-lubricated and were cooled. After the formation of hard candy lozenges, were taken out from the moulds and packed tightly in aluminium foil pouches.

Levocetirizinedihydrochloride gives a bitter taste, so as to mask the bitter taste of Levocetirizinedihydrochloride, aspartame, citric acid and flavors were added in the formulation. The formulation of lozenges was tabulated as follows.

Table 1: Formulation of Levocetirizinedihydrochloride lozenges.

FORMULATION CODE	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8	FL9	FL10	FL11	FL12	FL13	FL14	FL15
Drug (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sucrose(mg)	2405	2260	2135	2252.5	2245	2230	2252.5	2245	2230	2252.5	2245	2230	2252.5	2245	2230
Liq. Glucose	370	500	620	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K200	-	-	-	0.25%	0.50%	1%	-	-	-	-	-	-	-	-	-
HPMC K4M							0.25%	0.50%	1%						
HPMC K15M										0.25%	0.50%	1%			
Xanthan gum													0.25%	0.50%	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
Colour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

2.3 Evaluation:

The prepared formulations were studied for their physicochemical parameters like Weight variation test, hardness, thickness, friability, Determination of drug content, Drug-Excipient Compatibility study BY FT-IR, Release kinetics,

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

Drug-Excipient Compatibility study by physical observation (6,7).

2.3.1 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.

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

2.3.2 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.

2.3.3 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 verniercalipers. Ten lozenges from each formulation were used and average values were calculated. The average thickness for lozenges were calculated and presented with standard deviation.

2.3.4 Determination of drug content: Twenty lozenges were finely powdered; quantities of the powder equivalent to 60 mg of Levocetirizinedihydrochloride (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 $\lambda_{\text{max}} 232\text{nm}$. The drug concentration was calculated from the standard curve.

2.3.5 Calibration cuve of LCTZ: Standard stock solution of pure drug containing 100mg of LCTZ/100mL was prepared using 6.8pH phosphate buffer. The working standards were obtained by dilution of the stock solution in corresponding buffers. The standard curves for Levocetirizinedihydrochloride were prepared in concentration range of 1-8 $\mu\text{g}/\text{mL}$ at the selected wave length 265nm. Their absorptivity values were used to determine the linearity. Solutions were scanned and beer lamberts law limit was obeyed in the concentration range of 1, 2, 3, 4, 5, 6, 7, 8 $\mu\text{g}/\text{mL}$.

In- vitro drug release studies Dissolution conditions:

Apparatus : USP- I apparatus
Dissolution medium : 150ml of pH 6.8 Phosphate buffer
Temperature : $37 \pm 0.5^{\circ}\text{C}$
Rotating speed of the paddle : 50 rpm
Sample time intervals : 5, 10, 15, 20, 25, 30 minutes
Detection : UV-VIS spectrophotometer at $\lambda_{\text{max}} 232\text{nm}$.

III. RESULTS AND DISCUSSION

3.1 Results:

The weight variation of the formulations was found to be, $2999.3 \pm 2.2\text{mg}$ to $3000.8 \pm 2.7 \text{mg}$ which was in pharamacoepial limits. The thickness varies between 7.26 ± 0.03 to $7.40 \pm 0.06\text{mm}$. Hardness of all the tablets was maintained 10.30 ± 0.53 to 11.17 ± 0.35 . Assay was performed and percent drug content of all the lozenges were found to be between 98.44 ± 1.62 and 99.44 ± 2.08

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

Table 2: Evaluation of Levocettrizinedihydrochloride Lozenges containing different polymers.

Formulation	Weight of Logenze ^b	Hardness ^a	Thickness ^a	Drug Content ^b (%)
	(mg)	(kg/cm ²)	(mm)	
FL1	3000.8±2.7	10.30±0.53	7.33±0.03	99.17±1.72
FL2	2999.3±2.8	10.33±0.48	7.35±0.05	98.44±1.62
FL3	3000.6±3.3	10.83±0.43	7.36±0.03	99.26±1.28
FL4	2999.5±2.6	10.78±0.68	7.27±0.08	98.88±1.93
FL5	3000.3±2.3	11.08±0.43	7.35±0.05	99.44±2.08
FL6	2999.8±1.93	10.83±0.95	7.32±0.02	98.83±1.48
FL7	2999.5±1.58	10.43±0.44	7.35±0.06	99.26±1.44
FL8	2999.8±2.3	11.03±0.80	7.38±0.09	99.26±1.71
FL9	2999.3±2.5	10.58±0.53	7.32±0.04	99.13±1.58
FL10	3000.5±1.53	10.44±0.35	7.40±0.06	98.58±1.62
FL11	2999.3±2.2	10.33±0.12	7.26±0.03	98.83±1.71
FL12	2999.8±2.9	11.17±0.35	7.33±0.05	99.33±1.83
FL13	2999.6±2.8	10.53±0.38	7.35±0.03	98.49±1.62
FL14	2999.8±2.8	10.71±0.53	7.35±0.05	99.18±1.88
FL15	3000.3±1.88	10.98±0.44	7.36±0.08	98.88±1.62

^aResults are mean of 10 observations ± S.D., b. Results are meanof 20 observations ± S.D.

Table 3: Cumulative percent of Levocettrizinedihydrochloride release from lozenges without any polymer.

Time(min)	FL1 (Mean) SD	FL2 (Mean) SD	FL3 (Mean) SD
0	0	0	0
5	61±0.53	63±0.24	65.1±0.86
10	86.2±0.6	84.2±0.61	83.8±0.45
15	98.2±0.24	98.7±0.53	99.4±0.28

^aResults mean of 3 observations ± SD.

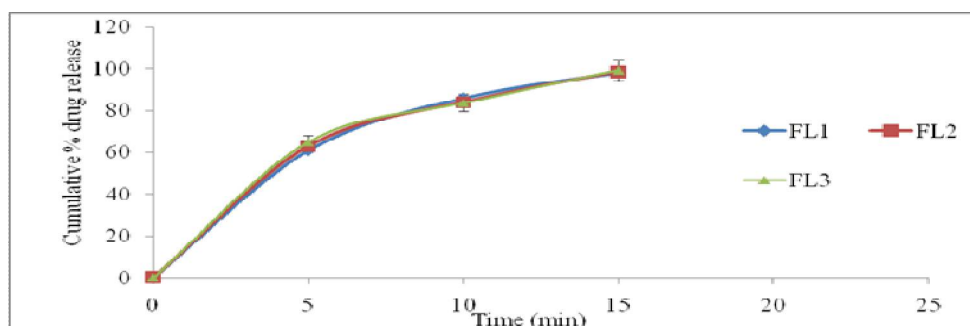


Figure 1: Graphical representation of cumulative percent of Levocettrizinedihydrochloride released from Lozenges (FL1, FL2, and FL3) (Without any polymer).

Formulation FL1,FL2 and FL3 without 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.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

Table 4: Cumulative percent of Levocetirizinedihydrochloride release from lozenges containing HPMC K 200 polymer.

Time(min)	FL4 (Mean)SD	FL5 (Mean) SD	FL6 (Mean) SD
0	0	0	0
5	40.2±0.44	39.9±0.7	40.4±0.66
10	64.1±0.49	63.7±0.2	62.8±0.32
15	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 mean of 3 observations ± SD.

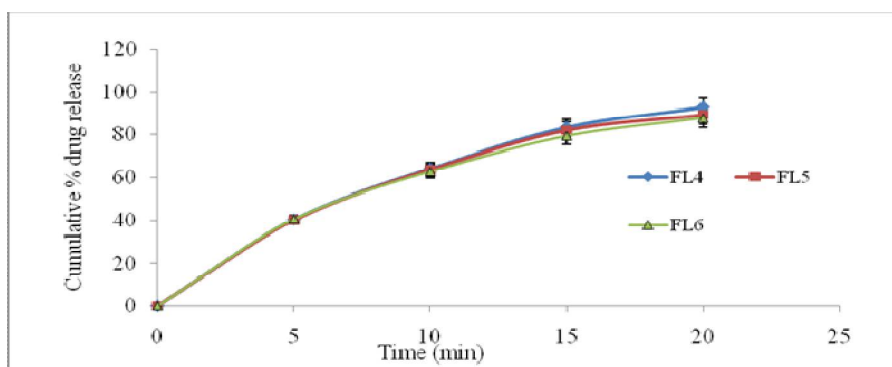


Figure 2: Graphical representation of cumulative percent of Levocetirizinedihydrochloride released from Lozenges (FL4, FL5, and FL6).

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

Table 5: Cumulative percent of Levocetirizinedihydrochloride release from lozenges containing HPMC K 4M polymer.

Time(min)	FL7 (Mean) SD	FL8 (Mean) SD	FL9 (Mean) SD
0	0	0	0
5	38±0.32	36.23±0.44	33.7±0.57
10	64.9±0.20	64±0.54	64.4±0.73
15	81.1±0.79	79.9±0.43	77±0.44
20	91.9±0.44	89.9±0.63	84.7±0.54

*Results mean of 3 observations ± SD.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

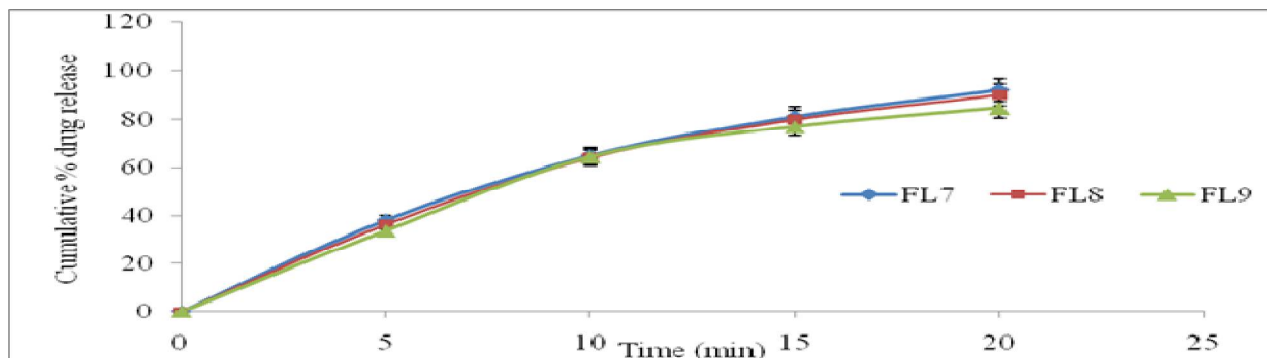


Figure 3: Graphical representation of cumulative percent of Levocetizinedihydrochloride released from Lozenges (FL7, FL8, and FL9).

Formulation FL7, FL8 and FT9 contains 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.

Table 6: Cumulative percent of Levocetizinedihydrochloride release from lozenges containing HPMC K 15 M polymer.

Time(min)	FL10(Mean) SD	FL11 (Mean) SD	FL12 (Mean) SD
0	0	0	0
5	39.5±0.44	39.1±0.21	37.6±0.57
10	65.2±0.36	64.6±0.28	64±0.32
15	78.6±0.32	78.4±0.31	76±0.63
20	89.6±0.32	87.7±0.3	81.9±0.64

Results mean of 3 observations ± SD

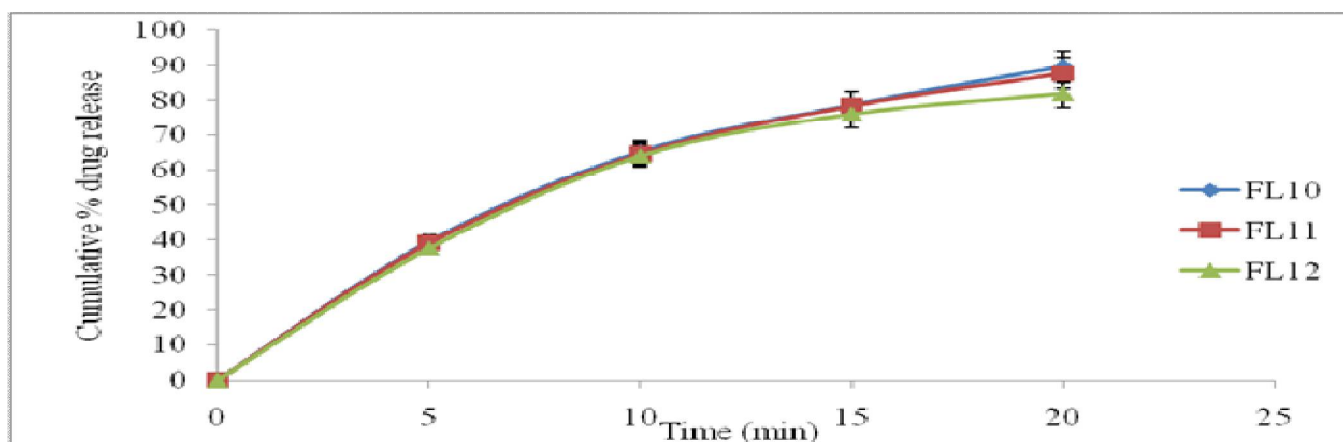


Figure 4: Graphical representation of cumulative percent of Levocetizinedihydrochloride released from Lozenges (FL10, FL11, and FL12).

Formulations FL10, FL11 and FL12 containing HPMC K 15 M as polymer of different concentration have shown the

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

drug release of 89.6%, 87.7% and 81.9% at the end of 20 min.

Table 7: Cumulative percent of Levocetirizinedihydrochloride release from lozenges containing Xanthan gum.

Time(min)	FL13 (Mean) SD	FL14 (Mean) SD	FL15 (Mean) SD
0	0	0	0
5	41.5±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±0.058	98.2±0.65	95.5±0.48

*Results mean of 3 observations ± SD.

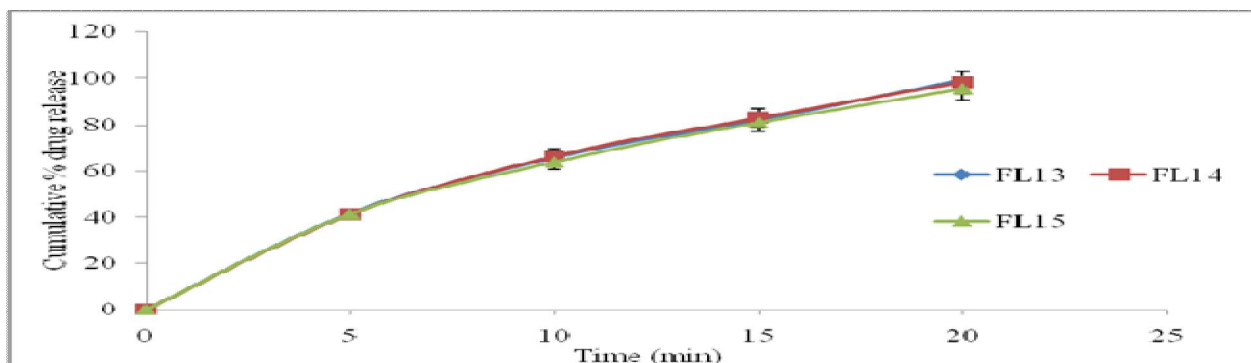


Figure 5: Graphical representation of cumulative percent of Levocetirizinedihydrochloride released from Lozenges (FL13, FL14, and FL15).

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

Table 8: Release kinetics and correlation coefficients of lozenges.

Formulation code	Mathematical models (Release Kinetics)	
	Zero order	First order
	R ²	R ²
FL13	0.9552	0.8246
FL14	0.922	0.9963
FL15	0.9334	0.9929

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, Januray 2016

Table 9: Standard graph of Levocetrizinedihydrochloride at 232 nm in 6.8 phosphate buffer.

S.No.	Concentration (mcg)	Absorbance
1	0	0
2	1	0.113
3	2	0.237
4	3	0.296
5	4	0.474
6	5	0.563
7	6	0.673
8	7	0.778
9	8	0.898

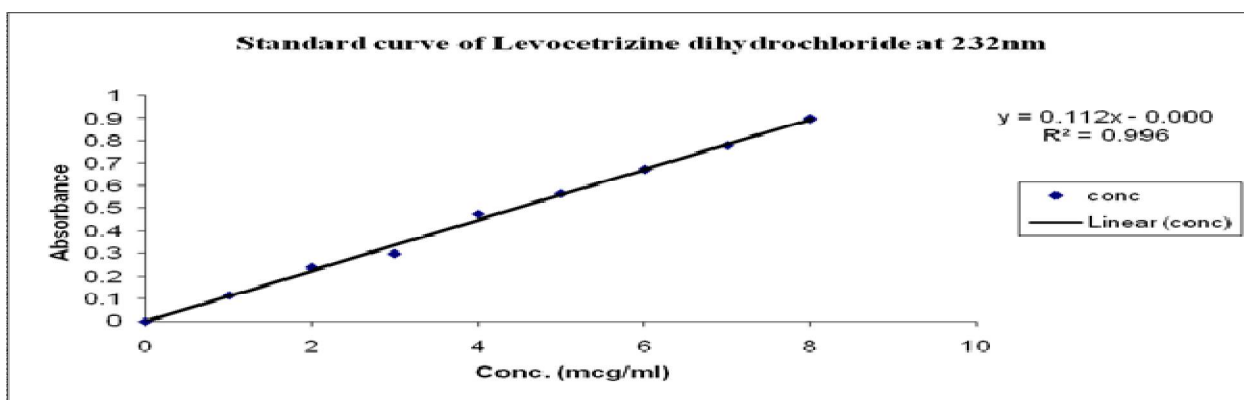


Figure 6:Standard graph of Levocetrizinedihydrochloride.

3.2 Discussion:

The suggested ratio of the sugar to corn syrup is 60:40 for attaining transparency and smoothness. This is due to prevention of sugar crystallization by corn syrup (7).

But in the present investigation sufficient transparency was attained with the use of the 13%, 18% and 20% of corn syrup. This suggests even at low concentration of corn syrup has ability to retain the capacity to prevent crystallization of sugar (8). 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 liquid glucose is due to increasing amount of mechanical action or turbulence to which the candy is subjected after cooking.

- I. More the agitation more will be the requirement of corn syrup.
- II. Other mechanism to control the crystallization are:

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 1, January 2016

High molecular weight sugar in the liquid glucose.

Low cooking temperature.

Minimum mixing during cooking.

Dextrose is used instead of corn syrup (9). Use of 40% dextrose instead of corn syrup effected the transparency. This may be due to failure of 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 not satisfactory. The formulation developed using honey was very sticky due to the hygroscopic nature of honey and the obtained transparency with honey is due to its ability to retard crystallization(10-12). The suggested ratio of the sugar to corn syrup is 60:40 for attaining transparency and smoothness. This is due to prevention of sugar crystallization by corn syrup(7,8).

IV. CONCLUSIONS

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 hour. In the present study Levocetirizinedihydrochloride sweetened lozenges were designed for the effective treatment of ulcers and used to reduce allergy.

The main interest was for the development of new dosage form and the effect of different polymers on the In-vitro release. At the outset, estimation of drug by UV spectrophotometer was carried out. The possible interaction between the drug and excipients was studied by FTIR spectroscopy, which showed that there was no interaction between the selected drug and polymer under study.

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

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

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