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Formulation and Evaluation of Lidocaine Lozenges

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ABSTRACT:Inspite of several dosage forms available in the market for effective localized action, the lozenges finds a special importance as they are the best dosage forms for formulating large dose medicaments. The anatomy of mouth and cheek favours easy absorption of drug, reducing the systemic absorption thus ensuring a better patient compliance especially for paediatrics and geriatrics. Lidocaine mechanism of action suites this type of formulation and easily absorbed in oral cavity. Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients. Lidocaine (DRUG) was mixed with all excipients, used in the formulation in different ratios and subjected to FTIR Physical observation. It was observed that there is no colour change and drug degradation as the peaks remained the same in the FTIR graphs. Lidocaine hard candy lozenges were prepared by heat fusion method using sugar as a base. The usage of corn syrup in the formulation made the lozenges transparent and smooth, which helped in improving the elegancy of formulation. The controlled release of medicament from Lozenges was achieved by using polymers like methyl cellulose, locust bean gum, HPMC K4M and xanthan gum. The prepared lozenges were subjected to physico-chemical as well as in vitro drug release study. Among all the formulations of hard candy lozenges FL8 showed the in vitro release of 98.7% at the end of 25 minutes.

KEYWORDS:Hard candy lozenges, Lidocaine, Lozenges, methyl cellulose, mouth ulcers, xanthan gum, FTIR studies, in-process testing, batch process testing.

I. INTRODUCTION

The medicated lozenges are generally prepared by molding and compression techniques mostly in acacia or gelatin base- Pastilles and sugar as base- Troches. The oral or buccal cavity is highly vasculated which adds an advantage of maximum local activity thus minimizing systemic activity [1]. Lozenges with antimicrobial and local anaesthetics as active ingredient are mostly advised for patients with swallowing problems, gastrointestinal blockade, paediatrics and geriatrics as they can be sucked easily into the saliva, providing localized drug delivery to the mouth, tongue and throat etc. Lozenges as the pharmaceutical dosage forms have several advantages than the oral administration as they can be manufactured with several excipients such as sweeteners for increasing solubility, colourants for elegant appearance, dyes to prevent photo degradation [2-4].

Significance of Lozenges:

1. The Lozenges are formulated based on the anatomy and physiology of oral cavity where region is covered with stratified squamous epithelium.
2. Passive absorption of the drug occurs through the areas of the buccal, gingival and sublingual mucosa.
3. The drug is delivered into the circulation unchanged by metabolic reactions of Liver as first pass metabolism is bypassed.
4. Lozenges are formulated in such a way that the drug is dissolved in saliva directly without disintegration process by using gums like acacia [5].

Commercially lozenges are made on a tablet machine using high compression pressures. Lozenges are designed to dissolve slowly in the mouth using different polymers at different concentrations.Currently available lozenges in market are of four types: Hard candy lozenges, soft lozenges, caramel based medicated lozenges and compressed tablet lozenges. In the present study the hard candy lozenges were formulated and evaluated for in-process testing such as particle size distribution, moisture content, flow, blend uniformity, hardness, tablet weight, thickness control etc and batch-release testing like dissolution. Additionally stability testing was also studied [6,7].

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II. MATERIALS AND METHODS

Materials

Lidocaine was a gift sample from Aurobindo Drugs, Hyderabad. Polymers like Methyl cellulose, locust bean gum Corn syrup and HPMC K4M were obtained from Hetero Drugs, Hyderabad. All other chemicals were of analytical grade.

Methods

a. Drug – Excipient Compatibility study:

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-excipient (binary mixture of drug: excipient 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.

b. Preparation of Lidocaine Hard Candy Lozenges:

Preparation of Candy Lozenges: Required quantity of sugar syrup was prepared by mixing sugar and water and heated to 1100C then liquid glucose was poured into the sugar syrup and heated to 160 0C. Flavours 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 aluminium foil pouches [5, 8]. Formulation codes of Lozenges with varying concentrations of polymers are shown in table 1.

Lidocaine gives a bitter taste so in order to mask the bitter taste of Lidocaine we included aspartame (artificial sweetener), Citric acid (acid diluent) in the formulation.

Table 1: Formulation codes of Lidocaine Lozenges

Formulation Code	FL1	FL 2	FL 3	FL 4	FL 5	FL 6	FL 7	FL 8	FL 9	FL10	FL11
Drug (mg)	10	10	10	10	10	10	10	10	10	10	10
Sugar(mg)	2520	2240	1960	2232.5	2225	2210	2232.5	2225	2210	2225	2210
Liquid Glucose	280	560	840	560	560	560	560	560	560	560	560
Methyl cellulose	-	-	-	0.25%	0.5%	1%	-	-	-	-	-
Locust bean gum	-	-	-	-	-	-	0.25%	0.5%	1%	-	-
HPMC K 4M	-	-	-	-	-	-	-	-	-	0.5%	1%
Citric Acid	60	60	60	60	60	60	60	60	60	60	60
Sodium Citrate	30	30	30	30	30	30	30	30	30	30	30
Aspartame	100	100	100	100	100	100	100	100	100	100	100
Colour	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Flavour	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000

*All ingredients are in milligrams.

c. Physicochemical Characteristics of Formulated Lidocaine Lozenges:

The prepared formulations were subjected to following parameters like Hardness, Weight variation,Thickness and Drug content.

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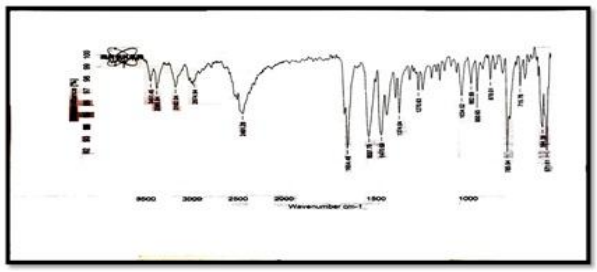
d. In vitro drug release studies:

Dissolution studies were conducted in USP type-I apparatus in 250 ml of pH 6.8 Phosphate buffer dissolution medium at 37±0.50 C temperature. Paddle was kept rotating with 50 rpm speed. The samples were withdrawn at predetermined time points 5, 10, 15, 20, 25 and 30 minutes. Samples were diluted appropriately and were analyzedspectrophotometrically at 263nm. The cumulative percentage release and standard deviation were calculated and the results are presented in the Table 3 and 4.

III. RESULTS

FTIR spectra of pure sample, Lidocaine-xanthan gum, Lidocaine-Locust bean gum and optimized formulation of lozenges can be seen in figure 1, 2, 3 and 4 respectively. The above peaks are considered as characteristic peaks of Lidocaine. These peaks were not affected and prominently observed in IR spectra of drug and drug along with excipients. This indicates that there is no interaction between drug and excipients.



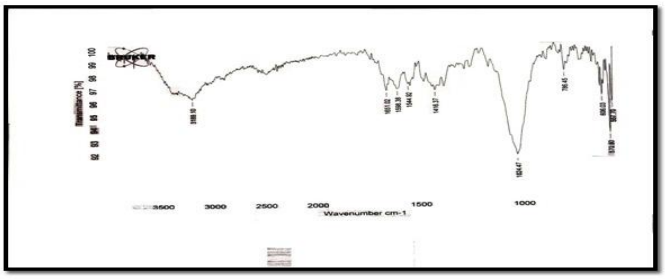
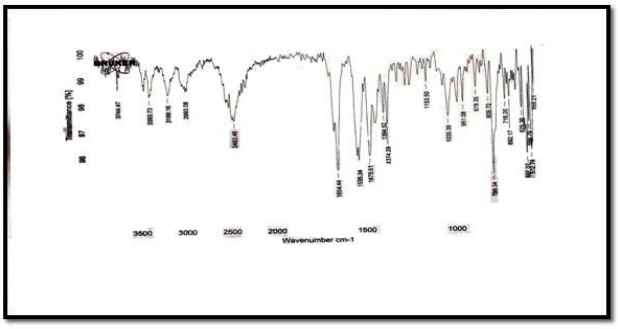


Figure 1:FTIR Spectra of pure Lidocaine.**Figure 2:**FTIR Spectra of pure Lidocaine + Xanthum gum



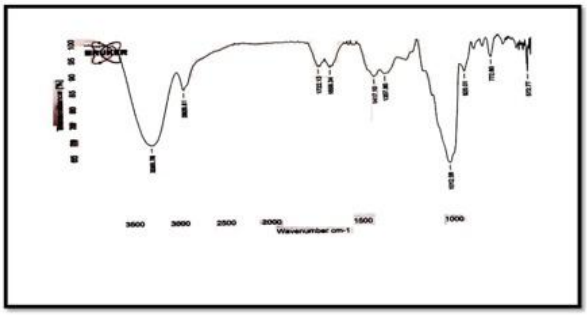


Figure 3:FTIR Spectra of pure Lidocaine + Locust bean gum**Figure 4:** FTIR Spectra of optimized Lozenges

In all formulations, Lozenges weight and thickness were within mean ± 7.5% and mean ± 5 % respectively. The weight variation in all the formulations was found to be 2998.4 ± 1.56 mg to 3050.2 ± 2.3 mg which was in pharmacopeia limits. Hardness of all the tablets was maintained 9.86 ± 0.41 to 11.07 ± 0.37 Assay was performed and percent drug content of all the lozenges were found to be between 98.5 ± 1.58 and 99.87 ± 0.95 of Lidocaine, which was within the acceptable limits (Table 2).

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Formulation	Weight (mg)	Hardness(kg/cm^2)	Thickness (mm)	Drug Content (%)
FL1	3030.6±2.7	10.15±0.51	7.21±0.04	99.35±1.51
FL2	2999.3±2.65	10.3±0.46	7.19±0.08	98.7±1.35
FL3	3000.7±3.6	9.86±0.41	7.23±0.05	99.26±1.72
FL4	3000.6±2.3	10.78±0.53	7.20±0.06	99.87±0.95
FL5	3050.2±2.3	11.07±0.37	7.21±0.03	99.73±1.86
FL6	2999.8±1.97	10.2±0.82	7.18±0.07	99.5±1.48
FL7	2998.4±1.56	10.41±0.46	7.19±0.01	99.27±1.36
FL8	2999.9±2.2	11.03±0.50	7.20±0.04	99.2±1.8
FL9	3100.7±2.5	10.51±0.49	7.21±0.05	98.5±1.58
FL10	3000.5±1.58	9.9±0.52	7.19±0.03	98.59±1.76
FL11	2999.3±2.1	10.39±0.39	7.22±0.12	98.85±1.89

Table 2: Evaluation of Lidocaine Lozenges prepared with varying concentration of different polymers.

CUMULATIVE % DRUG RELEASE OF LOZENGES						
Time(min)	**FL1**	**FL2**	**FL3**	**FL4**	**FL5**	**FL6**
0	0	0	0	0	0	0
5	54.6±0.53	41.8±0.24	61.8±0.86	16.7±0.44	18.4±0.7	40.2±0.66
10	68.5±0.6	73.3±0.61	73±0.45	47.9±0.49	41.8±0.2	62.4±0.32
15	83±0.24	86.9±0.53	86.7±0.28	64.2±0.62	61.8±0.53	73.2±0.70
20	96.4±0.54	98.7±0.42	99.4±0.2	73.1±0.57	86.9±0.18	81.4±0.66
25				85.8±0.60	88.6±0.34	90.3±0.54

Table 3: Cumulative percent of Lidocaine released from lozenges containing varying concentration of different polymer

CUMULATIVE % DRUG RELEASE OF LOZENGES					
Time(min)	**FL7**	**FL8**	**FL9**	**FL10**	**FL11**
0	0	0	0	0	0
5	37.35±0.32	42.93±0.44	39±0.57	36.2±0.44	34.6±0.21
10	66.9±0.20	62.4±0.54	55.7±0.73	58.5±0.36	54.6±0.28
15	73.1±0.79	79.8±0.43	68.5±0.44	66.9±0.32	62.2.±0.31
20	86.9±0.44	90.3±0.63	83.7±0.54	79.6±0.32	73±0.3
25	94.3±0.53	98.75±0.18	92.5±0.32	88.7±0.59	86.9±0.48

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

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Formulation FL1 which contain PVP K30 as binder without polymer have recorded the drug release of 96.4±0.54% at the end of 20 min. Formulation FL2 containing PVP K90 as a binder without any polymer have recorded the drug release of 98.7±0.42%at the end of 20 min. Formulation FL3 containing PVP K90 as a binder with Xantham gum as a polymer have showed a release of 99.4±0.2% at the end of 20 min with varying concentration of corn syrup (Table 3 and figure 5).

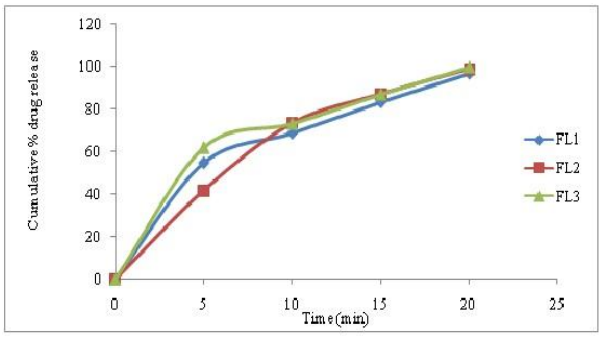

Figure 5: Graphical representation of cumulative percent of Lidocaine released from Lozenges (FL1, FL2, FL3)

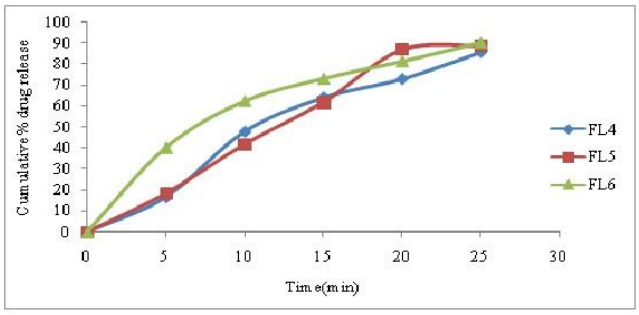

Figure 6: Graphical representation of cumulative percentofLidocaine released from Lozenges(FL4, FL5, FL6).

Formulation FL4, FL5 and FL6 containing varying concentration of Methyl cellulose recorded the drug release of 85.8±0.60%, 88.6±0.34% and 90.3±0.54% at the end of 25 min (figure 6).

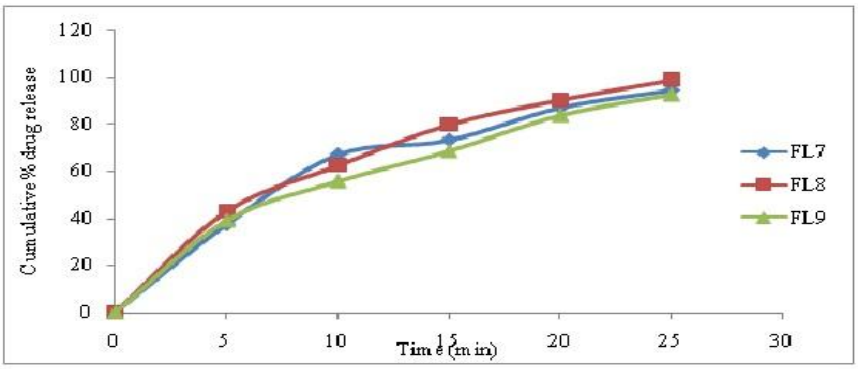

Figure 7: Graphical representation of cumulative percent of Lidocaine released from Lozenges(FL7, FL8, FL9).

Formulation FL7, FL8 and FL9 containing Locust bean gum as a polymer of varying concentration have recorded the drug release of 94.3% , 98.7% and 92.5% at the end of 25 min (figure 7).

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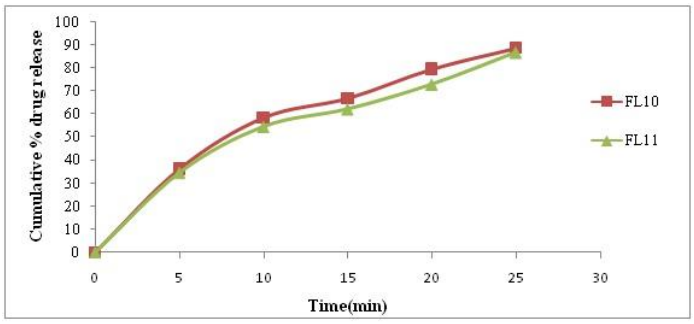

Figure 8: Graphical representation of cumulative percent of Lidocaine released from Lozenges(FL10, FL11).

Formulation FL10 and FL11 containing HPMC K4M as polymer of different concentration has shown the drug release of 88.7% and 86.9% at the end of 25 min (figure 8).

Formulation code	**Mathematical models (Release Kinetics)**	
	Zero order	**First order**
	R^2	**R^2**
FL8	0.913	0.904

Table 5: Release kinetics and correlation coefficients of lozenges.

The optimised formulation F8 was taken to test the taste of the losenzes formulation. Mango and orange flavours were used along with the sweetener aspartame. For this purpose 8 human volunteers consent was taken with the permission from human ethics committee of the college. The response from the volunteers after giving the F8 formulation with both the flavours after 2 hours interval for each is as follows shown in table 6.

S.NO	Volunteers	orange Flavour	mango flavour
1	A	+ + + + +	+ + + +
2	B	+ + + +	+ + +
3	C	+ + + + +	+ + +
4	D	+ + + + +	+ + + + +
5	E	+ + + + +	+ + +
6	F	+ + + + +	+ +
7	G	+ + + + +	+ + + +
8	H	+ + + + +	+ + +

Table 6: Test for taste masking the Lidocaine drug.

Note: + + + + + is the response for excellent taste, + + + + is the response for good, + + + is the respose for bad

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IV. DISCUSSION

The main objective of this study is to formulate and characterize Lidocaine lozenges for local anaesthetic activity suitable for patients suffering from mouth ulcers[9,10].

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.

But in the present investigation sufficient transparency was attained with the use of 13%, 18% and 20%. This suggests that even low concentration of corn syrup has the 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 to the 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 amount of mechanical action or turbulence to which the candy is subjected after cooking.

1. More the agitation, more the requirement of corn syrup
2. 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 use of 40% dextrose instead of corn syrup effected the transparency. This may be due to failure of dextrose 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. The obtained transparency with honey is due to its ability to retard crystallization [3,7].

Sorbitol is used instead of corn syrup. This may give better transparency. But it is affecting the sticking nature.

Crystallized sugar (Navodu) is used instead of sugar. This gives better transparency and loss of sticky nature, but after some day losses of transparency.

V. 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 hour. In the present study Lidocaine sweetened lozenges were designed for the effective treatment of ulcers and used to reduce pain in throat.

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 excipient was studied by FTIR spectroscopy (Figure 1-4) which showed that there was no interaction between the selected drug and polymer under study.

Lozenges could be successfully prepared by fusion method using sucrose, corn syrup, aspartame, sodium saccharine, polymers, orange flavor whose response is excellent (+ + + + +)and colour. In vitro release rate studies showed that the drug release for Lozenges was maximum in formulation FL8 98.75±0.18% which was at 25 minutes (Figure 7).

The results reveal that polymers such as Methyl cellulose, Xanthan gum and Locust bean gum can be used to prepare effective medicated Lidocaine lozenges. Among the different concentrations of Locust bean gum used, 0.5% was found to be optimized concentration.

Finally it can be concluded that, considering the ease of preparation, attractiveness and the drug release characteristics, hard candy lozenges are ideal and attractive alternatives for drug delivery from Lidocaine lozenges for its Local anaesthetic action.

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