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Formulation and Evaluation of Doxofylline Lozenges

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Abstract

Doxofylline was formulated as lozenges to provide slow release medicament for the management of asthma for cough and itchy throat. The present investigation has been taken up to design, prepare and evaluate hard candy lozenges to meet the need of improved bioavailability. The benefits of these prepared lozenges showed increase in bioavailability, reduction in gastric irritation by passing of first pass metabolism and increase in onset of action. The lozenges were prepared using sucrose as base; liquid glucose in the formulation made the lozenges transparent and smooth; hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) are used as polymers. Aspartame and saccharin are used as artificial sweeteners. Sweeteners along with flavours are used to mask the bitter taste of drug. All the formulations prepared were subjected to various physicochemical parameters like hardness, content uniformity, friability, weight variation, moisture content etc. The prepared formulations have a hardness of 8-11 Kg/cm², non-gritty and pleasant mouth feel. Some selected formulations were tested for drug excipients interactions subjecting to infrared (IR) Spectral analysis. *In vitro* drug dissolution studies showed least of 82.7% for FL7 and maximum of 98.8% for FL6 release following zero order release in 30 minutes.

Keywords: Hard candy lozenges, Doxofylline, anti-asthma, polymers.

Introduction

The word “Lozenge” is derived from French word “Losenge”, which means a diamond shaped geometry having four equal sides. Development of lozenges dates back to 20th century and is still in commercial production (1). Lozenges are solid preparations that contain one or more medicaments, usually in a flavoured, sweetened base, and are intended to dissolve slowly in the mouth. In short, lozenge is a small medicated candy intended to be dissolved slowly in the mouth to lubricate and soothe irritated tissues of throat. Most of the lozenge preparations are available as over-the-counter medications. They are intended to be dissolved on the back surface of the tongue to provide drug delivery locally to the mouth, tongue, throat, etc. to minimize systemic and maximize local drug activity. The dosage form can be adopted for local as well as systemic therapy and a wide range of activities can be incorporated in them. They can deliver drug multi- directionally into the oral cavity or to the mucosal surface (2). Lozenges currently available in market are of four types: caramel based medicated lozenges, soft lozenges, hard candy lozenges and compressed tablet lozenges. Hard candy lozenges are prepared by moulding. Moulded lozenges are sometimes referred to as pastilles, whereas compressed lozenges prepared on tablet compression machine, may be referred to as troches (3).

Lozenges are placed in oral cavity. Since the sublingual lozenges may be impractical due to their size, buccal lozenges are formulated and have been extensively used and are intended to be placed between the cheek and the gums. Though the lozenge dissolution time is about 30 minutes, it also depends on the patient, as patient

controls the rate of dissolution and absorption by sucking on lozenge until it dissolves. Sucking and the subsequent production of saliva may also lead to increased dilution of the drug and accidental swallowing (4).

Drug candidates which can be incorporated in lozenges belong to one of the following categories: antimicrobials and local anaesthetics for throat pain; aromatics, herbals, zinc salts, decongestants, anti-histamines and cough suppressants for cold, allergy, cough, congestion and nicotine like substances for smoking cessation.

Materials and Methods

Doxofylline was a gift sample from Hetero Labs, Hyderabad. Hydroxypropyl methylcellulose (HPMC) K4M and hydroxyethyl cellulose (HEC) were purchased from the S D Fine-Chem Limited, Mumbai. Aspartame was a gift sample from Merck Ltd., Mumbai, India. Sucrose, liquid glucose, colour and flavour from local chemical suppliers.

Method of Preparation : Hard candy lozenges are prepared by heating and congealing technique. Sucrose is accurately weighed and is dissolved in one third amount of water by heating on fire cookers until all sugar granules are dissolved. Liquid glucose is added when cooking temperature reaches 110° C and heating is continued until final temperature is 145° C to 156° C. The mixture is cooled to 135°C and colour is added. Further, cooling is carried out and mixed until temperature reaches 40° C. The flavour, drug and polymer are added and mixed for 4 to 6 minutes and poured in lubricated moulds (5). These prepared lozenges are further subjected to various evaluation parameters. The formulations of prepared lozenges are shown in table 1.

Evaluation of Lozenges

Physical parameters : The general appearance of a lozenge, its visual identity and overall elegance is essential for consumer acceptance, control of lot-to-lot uniformity, tablet-to-tablet uniformity and monitoring trouble-free manufacturing. It involves the measurement of attributes such as size, shape, colour, surface texture and consistency.

Thickness Test : The thickness in millimeters (mm) was measured individually for 10 pre-weighed lozenges by using a Vernier Calipers. The average thickness and standard deviation were reported. The thickness of a lozenge can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness variation limits allowed are 5% of the size of the tablet.

Diameter : The diameter size and shape of candies depend on the moulds. The lozenges of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces (6).

Weight Variation Test : Twenty (20) lozenge from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviations were calculated. Individual weight of each lozenge was also calculated using the same and compared with average weight. If any weight variation is there, that should fall within the prescribed limits (generally 10% for lozenge weighing 120 mg or less, 7.5% for lozenge weighing 120 mg to 300 mg and 5% for lozenge weighing more than 300 mg):

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

Hardness Test : The hardness of lozenges was measured using a Monsanto Hardness Tester. The crushing strength of the 10 lozenge with known weight and thickness of each batch was recorded in kg/cm^2 and the average hardness and the standard deviation was reported. The hardness of lozenge depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipients used during formulation (7).

Friability Test : Twenty (20) lozenges were selected from each batch and weighed. Each group was rotated at 25 rpm (rotations per minute) for 4 minutes (i.e.100 rotations) in the Roche friabilator. During each revolution, the lozenge fall from a distance of six inches to undergo a shock. The

Table 1: Formulae to prepare hard candy lozenges

INGREDIENTS (mg)	FORMULATION CODE									
	FL1	**FL2**	**FL3**	**FL4**	**FL5**	**FL6**	**FL7**	**FL8**	**FL9**	**FL10**
Drug (mg)	200	200	200	200	200	200	200	200	200	200
HPMC K4M	12	24	30	60	-	-	-	-	-	-
HEC	-	-	-	-	12	24	30	60	-	-
Saccharin sodium	90	100	100	95	74	90	95	90	114	95
Aspartame	90	116	140	109	100	120	130	110	120	120
Sucrose	1893	1851	1824	1845	1899	1857	1859	1849	1845	1857
Liquid glucose	854	848	845	830	854	848	845	830	860	840
Preservative	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Colour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Flavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

lozenge were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets. Compressed lozenge that lose less than 0.5 to 1 % of weight are generally considered acceptable (8):

% Friability = Initial weight – Final weight / Initial weight x 100

Drug Content Uniformity : The content uniformity was tested by powdering one lozenge and dissolving the powder content in 100 ml volumetric flask containing 50 ml of 6.8 phosphate buffer and allowed to stand for 30 min. The mixture was made up to volume with buffer pH 6.8. The diluted samples absorption was recorded at 274 nm. For most of the larger dose drugs in lozenge form, the official potency range permitted is not less than 95% and not more than 105% of the labelled amount (9).

Moisture Content : By Gravimetric method, one gram sample is weighed and placed in vacuum oven at 60-70°C for 12-16 hrs. Final weight is subtracted from initial and the difference in moisture content is calculated:

% Moisture content = Initial – Final weight × 100

***In vitro* Drug Release Studies :** The rate of the drug absorption was determined by the rate of drug dissolution from the lozenges. Thus, the rate of dissolution and bioavailability may be directly related to the efficacy of the tablet lozenge. The *in vitro* drug release study was performed for the prepared lozenges using USP Apparatus II (Paddle type). A 250 ml of the dissolution medium phosphate buffer pH 6.8 was placed in the beaker containing the lozenge and stirred at 100 rpm. A 5 ml aliquot sample was withdrawn at 5 min and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 274 nm (10).

Fourier Transform Infrared (FTIR) Spectroscopy : The Fourier Transform Infrared (FTIR) spectra of samples were obtained using FTIR Spectrophotometer (Perkin Elmer) for drug excipients compatibility. Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide (KBr) of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1} (12).

Standard graph of Doxofylline at 274 nm : Standard stock solution of pure drug containing 100 mg of Doxofylline/100 ml was prepared using different buffer solutions like 6.8 pH phosphate buffer. The working standards were obtained by dilution of the stock solution. The standard curves for Doxofylline were prepared in concentration range of 2-12 µg/ml at the selected wave length

274 nm. Their absorptivity values were used to determine the linearity. Solution was scanned and Beer-Lambert law limit was obeyed in the concentration range of 2, 4, 6, 8, 10 and 12 µg/ml (figure 1).

Results

Construction of Calibration curve : The study started with the construction of standard calibration curve. The λ_{max} of Doxofylline in 6.8 pH phosphate buffer was scanned and found to have the maximum absorbance at 274 nm. The standard graph of Doxofylline in 6.8 pH phosphate buffer was plotted by taking concentration ranging from 2-12 µg/ml and a good correlation was obtained with R^2 values of 0.996 respectively.

Drug Excipient Compatibility Studies : The compatibility between the drug, polymer and excipients was compared by FTIR spectroscopy (Perkin Elmer). FTIR spectrum of pure drug exhibits characteristic peaks at 3108.20, 1692.45, 1427.09 and 1010.35 cm^{-1} due to O-H, C-O, C-H and N-H stretching respectively. FTIR spectrum of optimized candy mixture showed characteristic peaks at 3310.35, 1657.62, 1426.96 and 984.80 cm^{-1}. The presence of above peaks confirm undisturbed drug in the formulations. It was observed that, there was no disappearance or shift in peak position of drug in any spectra of drug and polymers which proved that drug and polymers were compatible. Hence, it can be concluded that drug can be used with the selected polymers and excipients without causing instability in the formulation. FTIR data interpretation of drug and formulation was shown in table 4.

Evaluation parameters of Hard Candy Lozenges : All the prepared formulations were tested for physical parameters like weight variation, hardness, thickness and diameter are found to be within the Pharmacopoeia limits. The results of the tests were tabulated and was shown in table 2.

The total weight of each formulation was maintained constant; the weight variation of the lozenges was within the permissible limits of 5%. Weight of the tablet was fixed at 3.00 grams and the weight variation for every batch was tested. The formulations FL1, FL2, FL3 and FL4 containing HPMC were weighed and the increase in weight variation order is FL3< FL4 <FL2<FL1. For the formulation containing HEC the increasing order of weight variation is FL8<FL7<FL6<FL5. The formulation containing no polymer was also weighed and all the formulations were found within the acceptance limits.

Hardness of the tablet was maintained at 10.2-11.5 kg/cm^2 for all the batches. The highest hardness was found in formulation FL4 i.e.11.51±0.29 kg/cm^2 and least hardness was determined in FL2 i.e.10.2±0.64 kg/cm^2. Since there is no specified standard limits for the deviation in the hardness of lozenges, comparing each formulation with one

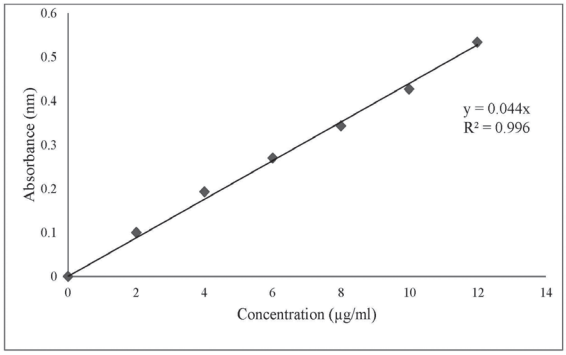


Fig. 1: Standard graph of Doxofylline in phosphate buffer pH 6.8

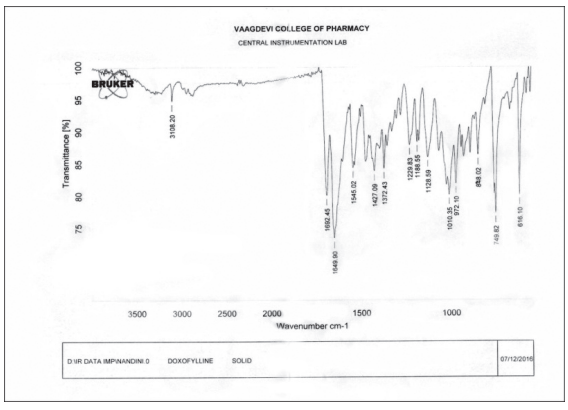


Fig. 2: FTIR Spectrum of Doxofylline

another it could be concluded that, because the difference between the standard deviations are not too large, the formulations had good uniformity in the hardness.

The thickness and diameter values were almost uniform in all the ten formulations. It was found to vary between 7.25 to 7.43 mm and 19.12 to 19.19 mm. Friability was not conducted for candies as they are sufficiently hard to resist the mechanical abrasion.

Moisture Content : The moisture content of all the lozenges was within 2%. The results are shown in table 3.

Drug Content : The drug content was calculated for all the prepared formulations. Table 3 shows the result of drug content of each formulation. Three replications of each test were analyzed for mean and standard deviation. The drug content found in the formulations containing HPMC was found to be highest for FL1 and lowest for FL2 and for HEC containing formulations the drug content is highest

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

FORMULATION CODE	WEIGHT VARIATION (mg)	HARDNESS (kg/cm^2)	THICKNESS (mm)	DIAMETER (mm)
FL1	3000.9±3.1	10.41±0.41	7.25±0.01	19.17
FL2	3000.7±1.3	10.54±0.45	7.38±0.04	19.16
FL3	2999.2±2.3	10.79±0.52	7.29±0.03	19.17
FL4	2999.7±2.8	11.51±0.29	7.36±0.01	19.17
FL5	3000.5±2.0	10.9±0.42	7.43±0.04	19.19
FL6	2999.8±3.5	10.2±0.64	7.33±0.05	19.12
FL7	2999.5±1.4	10.8±0.9	7.29±0.04	19.17
FL8	2999.3±2.4	10.4±0.41	7.39±0.03	19.19
FL9	3000.6±1.4	11.3±0.72	7.38±0.01	19.17
FL10	2999.8±2.3	10.7±0.51	7.42±0.04	19.14

Table 3: Moisture content and drug content of Doxofylline Lozenges

FORMULATION CODE	MOISTURE CONTENT	DRUG CONTENT (%)
FL1	0.92±0.05	99.5±1.64
FL2	0.84±0.07	98.34±1.47
FL3	0.83±0.05	98.7±2.0
FL4	0.87±0.07	98.8±1.57
FL5	0.86±0.08	99.6±1.41
FL6	0.87±0.07	99.8±1.45
FL7	0.87±0.05	98.5±1.71
FL8	0.85±0.07	99.3±1.64
FL9	0.85±0.05	99.6±1.94
FL10	0.85±0.05	98.33±1.46

for FL6 and lowest for FL7.The formulation without polymer i.e.FL9 and FL10 contain 99.6±1.94% and 98.33±1.46% of drug and hence all the formulations were found to be within the standard limits.

***In vitro* release data for candy based Lozenges :** All the ten formulations prepared were subjected to *in vitro* release study. The *in vitro* method for studying the release rate is maintained so that it must simulate the mouth condition. In the present work *in vitro* release study was carried out using dissolution apparatus. For different time interval, sample was withdrawn and cumulative drug release was calculated. The dissolution apparatus USP II (Paddle type) was used. The temperature was maintained at 37±0.5°C and stirred at 50 rpm. The dissolution medium is 6.8 pH phosphate buffer. The samples were withdrawn at 5 min interval for 30 min.

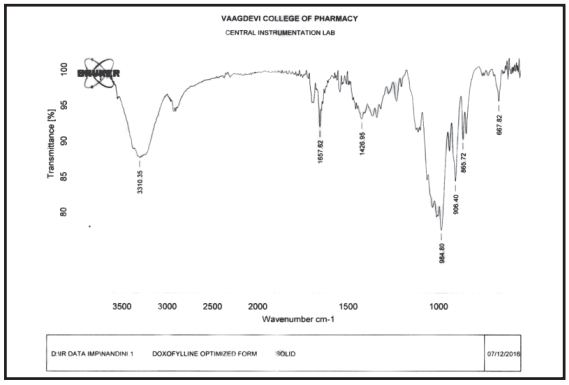


Fig. 3: FTIR Spectrum of Optimized formulation

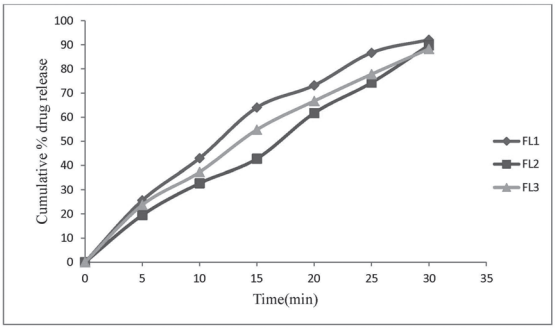


Fig.4: Graphical representation of cumulative percent of Doxofylline release from Lozenges

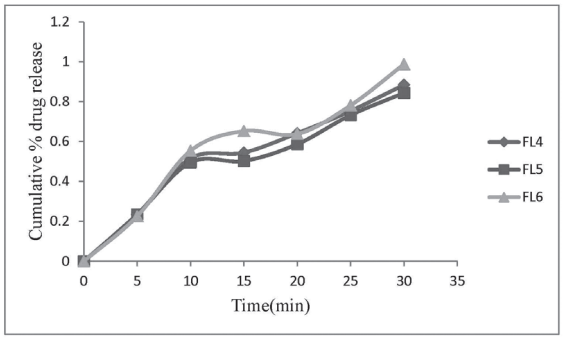


Fig. 5: Graphical representation of cumulative percent of Doxofylline release from Lozenge

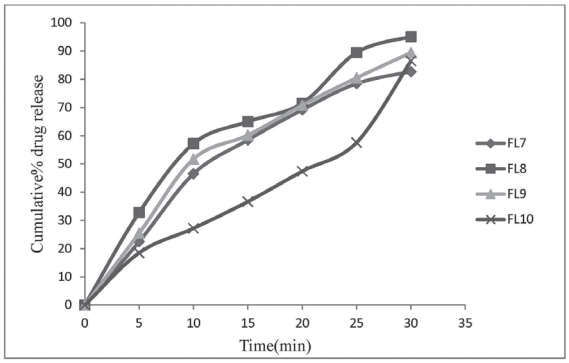


Fig. 6: Graphical representation of cumulative percent of Doxofylline release from Lozenges

Cumulative percentage drug release was calculated on the basis of mean amount of Doxofylline present in the respective lozenges. The results are given in table 5, 6, 7 and figure 4, 5, and 6. The cumulative percentage drug release of FL1 and FL8 was 86.7% and 89.5% respectively within 25 min and for FL7, it was 82.7% at the end of 30 min. For FL6, the drug release was 98.8% at 30 min. The cumulative percentage drug release of FL2, FL3, FL4, FL5, FL9 and FL10 was 89.8%, 88.3%, 88.5%, 84.4%, 89.44% and 86.5% respectively by the end of 30 min. Hence by the determination of the *in vitro* release data, it can be concluded that, the drug release was faster in case of FL1, FL6 and FL8.

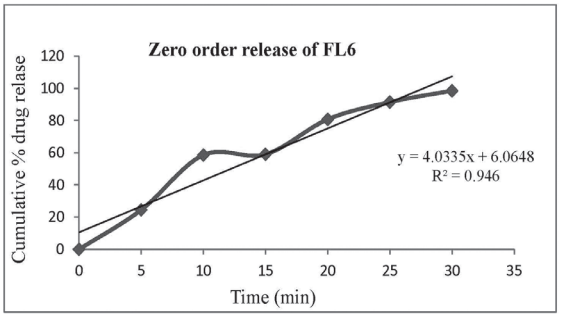
Drug Release Kinetics of Doxofylline : The release kinetics and correlation coefficients were calculated for all the optimized formulations. All

Table 4: FTIR studies were carried out for pure drug along with drug and excipient combination

FTIR SPECTRA	O-H STRETCHING	C-O STRETCHING	C-H STRETCHING	N-H STRETCHING
Drug	3310	1693	1427	1010
Optimized formulation	3310	1692	1426	984

Table 5: Cumulative percent of Doxofylline release from lozenges containing polymers

Time (min)	FL1 (Mean) SD	FL2 (Mean) SD	FL3 (Mean) SD
0	0	0	0
5	25.6%	19.5%	23.7%
10	43%	32.7%	37.3%
15	64%	42.8%	54.8%
20	73.2%	61.7%	66.7%
25	86.7%	74.3%	77.8%
30	92.1%	89.8%	88.3%



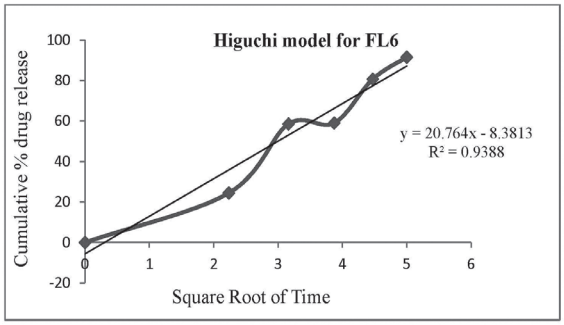


Fig. 7: Release plots for FL6.

Table 6: Cumulative percent of Doxofylline release from lozenges containing polymers

Time (min)	FL6 (Mean) SD
0	0
5	22.6%
10	55.4%
15	65.3%
20	63.8%
25	78.2%
30	98.8%

the formulations followed Higuchi profiles with R^2 values more than 0.9, followed by zero order which account for the diffusion controlled release.

Discussion

The objective of this study was to formulate and evaluate Doxofylline lozenges for anti-asthmatic activity suitable for patients suffering from cough and itchy throat.

The drug content of all formulations was between 98.3 to 99.8% indicating the presence

Table 7: Cumulative percent of Doxofylline release from lozenges containing polymers

Time (min)	FL7 (Mean) SD	FL8 (Mean) SD	FL9 (Mean) SD	FL10 (Mean) SD
0	0	0	0	0
5	22.45%	32.8%	25.45%	18.5%
10	46.5%	57.2%	51.72%	27.2%
15	58.5%	65.01%	60.2%	36.65%
20	69.2%	71.5%	70.85%	47.39%
25	78.5%	89.5%	80.49%	57.57%
30	82.7%	95.1%	89.44%	86.5%

of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed acceptable weight variation, hardness, thickness and moisture content. The aim of the study was to show good oral retention time and moderate release of the drug for a period of 20 to 30 min. All the formulations containing the polymers showed good oral retention time of 20-30 min. Change in the physical form of the lozenge was observed within 10-15 min for candies. The drug release rate study revealed that release from HEC containing formulations was found to be rapid and maximum for candies compared to HPMC K4M. Increase in the concentration of polymers increased the drug release but further increase has led to decrease in the drug release. Initial low release rate might be due to fast rate of hydration followed by quick gelation and further release rates might be due to diffusion through the hydrated polymer layers.

For any formulation, drug excipient interactions play an important role and hence the formulations were subjected to infrared spectral analysis, it was observed that undisturbed drug peaks revealing the compatibility drug.

The suggested ratio of the sugar to liquid glucose is 60-40% for attaining transparency and smoothness. This is due to prevention of sugar crystallization by liquid glucose.

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

This difference in the concentration of liquid glucose to attain the smoothness and transparency may be due to the type of apparatus used in the cooking process: 20% open kettle, 30% batch vacuum cookers, 35% semi-continuous, and 40% continuous cookers.

The difference in the requirements of liquid glucose is due to increasing amount of mechanical action or turbulence to which the candy is subjected after cooking like more agitation and more requirement of liquid glucose.

Other mechanisms to control the crystallization are:

a. High molecular weight sugar in the liquid glucose

b. Low cooking temperatures

c. Minimum mixing during cooking.

Dextrose is used instead of liquid glucose (12). Use of 40% dextrose instead of liquid glucose 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 liquid glucose. Use of honey instead of liquid glucose resulted in the transparent lozenges but was not satisfactory. The formulation developed

using honey was sticky due to hygroscopic nature of honey. The obtained transparency with honey is due to its ability to retard crystallization.

Conclusion

Patient compliance is one of the important aspects for administration of drug especially those which are bitter in taste. In the present study, Doxofylline sweetened hard candy lozenges were designed for the effective treatment of asthma.

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

Lozenges could be successfully prepared by heating and congealing method using sucrose, liquid glucose, aspartame, polymers, dextrose, flavour and colour.

In vitro release rate studies showed that the drug release for lozenges was maximum in formulation FL6 (98.8±1.57%) which was at 30 min.

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