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Research Article

DEVELOPMENT AND IN-VITRO EVALUATION OF NICOTINE HARD CANDY LOZENGES FOR SMOKING CESSATION

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ABSTRACT

Objective: Nicotine replacement therapy is a way of getting nicotine into bloodstream without smoking. The present investigation aims to design, prepare and evaluate hard candy lozenges of nicotine 2mg for low dependent smokers and 4mg for high dependent smokers. The benefits of these prepared lozenges are increased bioavailability, reduction in gastric irritation and avoiding first pass metabolism.

Methods: The lozenges were prepared by heat and congealing method in a candy base using sucrose as base.

Results: All the formulations prepared were subjected to various physico-chemical parameters like hardness, content uniformity, friability, weight variation etc. The prepared formulations have a hardness of 8-10 Kg. /cm^2, free from gritty particles, and good taste. Stability studies of selected formulations were also carried out at 37ºC for a period of six months. Selected formulations were tested for drug excipient interactions subjecting to FTIR Spectral analysis. In-vitro drug dissolution studies showed 100% release in 30 minutes for optimized formulations NC11 and NC25.

Conclusions: The Hard candy lozenges can provide an attractive alternative formulation in the Nicotine replacement therapy.

Keywords: Nicotine, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Poly vinyl pyrrolidine, Aspartame.

INTRODUCTION

Lozenges are solid preparations that contain one or more medicaments, usually in a flavored, sweetened base, and that are intended to dissolve or disintegrate slowly in the mouth[1]. They can be prepared by molding (gelatin and/or fused sucrose and sorbitol base) or by compression of sugar-based tablets. Molded lozenges are sometimes referred to as pastilles, whereas compressed lozenges may be referred to as troches. They are intended to be allowed to dissolve 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 [2].

Smoking is a major threat to human kind which leads to several disorders of health. The major constituent in cigarettes is nicotine, Administration of nicotine without smoking may be beneficial than smoking because tobacco contains tar and other ingredients which are responsible for higher risk for health. Nicotine is readily absorbed from the gastro–intestinal tract, the buccal mucosa, the respiratory tract, and intact skin, and widely distributed throughout the tissues. Nicotine undergoes first–pass metabolism when administered orally, thus reducing the bio availability. Hence they are formulated as lozenges.

Nicotine is a drug that is inhaled from the tobacco in cigarettes. It gets into the bloodstream and stimulates the brain. Most regular smokers are addicted to nicotine.
In a regular smoker, if the blood level of nicotine falls, he usually develops withdrawal symptoms such as restlessness, increased appetite, inability to concentrate, irritability, dizziness, constipation, nicotine craving, or just feeling awful.

These symptoms begin within a few hours after having the last cigarette. If they are not relieved by the next cigarette, withdrawal symptoms get worse. If he does not smoke any more, the withdrawal symptoms peak after about 24 hours, and then gradually ease in about 2-4 weeks. So, most smokers smoke regularly to feel 'normal', and to prevent withdrawal symptoms. About 2 in 3 smokers want to stop smoking but, without help, many fail to succeed.

Main reason why so few smokers succeed, even though they want to stop smoking, is because nicotine addiction is strong and difficult to break. This is where NRT can help. Nicotine replacement therapy (NRT) is a way of getting nicotine into the bloodstream without smoking[3]

MATERIALS AND METHODS

Materials

Nicotine was obtained as gift sample from Merck schuchardt, Germany. Hydroxy propyl methyl cellulose (HPMC) K4m, K15M, HPMC 100 cps, PVP K90 were gift samples from Dr. Reddy's laboratories, Hyderabad. Mannitol, Aspartame, Sucrose, Dextrose were purchased from SD Fine chemicals.

Preparation of nicotine hard candy lozenges

Hard candy Lozenges were made by Heat and congealing method. All the ingredients like dextrose, color, and polymer except flavors were mixed together along with the medicament (nicotine) and added to molten mass of sucrose. Now the mass is mixed thoroughly to get a uniform distribution of medicament. Flavors were added when the temperature was brought to 40-45 °C. Now this semisolid mass was poured into pre-lubricated moulds and subjected to cooling[4]. Then the hard candy lozenges were taken out after cooling from the moulds and packed in aluminum foil pouches. Composition of nicotine hard candy lozenges with dose 2mg for low dependent smokers and 4mg for high dependent smokers were presented in table no 1, 2.

Evaluation of the developed formulations

Weight variation test

Twenty lozenges were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one lozenge was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percentage deviation was calculated using the following formula [9]. The results are presented in the table 3, 4.

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

Lozenge hardness

Hardness of lozenge is defined as the force applied across the diameter of the lozenge in order to break the lozenge. The resistance of the lozenge to chipping, abrasion or breakage under condition of storage transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 lozenges was

determined using pfizer hardness tester and the average was calculated and presented with standard deviation[9]. The results are presented in table 3, 4.

Lozenge thickness

Lozenge thickness is an important characteristic in reproducing appearance.

Twenty lozenges were taken and their thickness was recorded using Digital Micrometer (Digital Caliper, Aerospace, India).

The average thickness for troches is calculated and presented with standard deviation[9].

The results are presented in table 3, 4.

Table1: Composition of Nicotine Hard candy Lozenges (Nicotine dose =2mg)

Ingredients (mg)	Formulation code													
	NC1	NC2	NC3	NC4	NC5	NC6	NC7	NC8	NC9	NC10	NC11	NC12	NC13	NC14
Nicotine	2	2	2	2	2	2	2	2	2	2	2	2	2	2
sucrose	2393	2350	2348	2343	2352	2338	2313	2340	2313	2286	2261	2340	2325	2310
Dextrose	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Aspartame	-	30	30	30	25	25	25	25	25	25	25	25	25	25
PVP K90	-	7.5	10	15	-	-	-	-	-	-	-	-	-	-
HPMC E15	-	-	-	-	12.5	25	50	-	-	-	-	-	-	-
HPC	-	-	-	-	-	-	-	25	50	75	100	-	-	-
HPMC 100Cps	-	-	-	-	-	-	-	-	-	-	-	25	37.5	50
Orange colour	-	2	-	-	2	-	-	2	-	-	2	-	-	2
pink colour	-	-	2	-	-	2	-	-	2	-	-	2	-	-
Yellow colour	2	2	-	2	-	-	2	-	-	2	_	-	2	-
Orange oil	-	-	-	-	2	-	-	2	-	-	2	-	-	2
Mango flavour	2	-	-	2	-	-	2	-	-	2	-	-	2	-
Peppermint oil	-	2	2	-	-	2	-	-	2	-	-	2	-	-
Menthol	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Methyl paraben	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500

Table 2: Composition of Nicotine hard candy lozenges (nicotine dose=4mg)

Ingredients (mg)	Formulation code													
	NC15	NC16	NC17	NC18	NC19	NC20	NC21	NC22	NC23	NC24	NC25	NC26	NC27	NC28
Nicotine	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Sucrose	2392	2348	2346	2341	2350	2336	2311	2338	2311	2284	2259	2338	2323	2308
Dextrose	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Aspartame	-	30	30	30	25	25	25	25	25	25	25	25	25	25
PVP K90	-	7.5	10	15	-	-	-	-	-	-	-	-	-	-
HPMC E15	-	-	-	-	12.5	25	50	-	-	-	-	-	-	-
HPC	-	-	-	-	-	-	-	25	50	75	100	-	-	-
HPMC 100Cps	-	-	-	-	-	-	-	-	-	-	-	25	37.5	50
Orange colour	-	2	-	-	2	-	-	2	-	-	2	-	-	-
Yellow colour	2	-	2	-	-	2	-	-	2	-	-	2	-	2
Pink colour	-	-	-	2	-	-	2	-	-	2	-	-	2	-
Orange oil	-	2	-	-	2	-	-	2	-	-	2	-	-	-
Mango flavour	2	-	2	-	-	2	-	-	2	-	-	2	-	2
Peppermint oil	-	-	-	2	-	-	2	-	-	2	-	-	2	-
Menthol	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Methyl paraben	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500

Friability

It is a measure of mechanical strength of lozenges. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by following procedure. Pre-weighed lozenges (20 lozenges) were placed in the friabilator. The lozenges were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the lozenges were re-weighed [9]; loss in the weight of lozenges is the measure of friability and is expressed in percentage as:

$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$

Where W_1 = Initial weight of 20 lozenges

W_2 = Weight of the 20 lozenges after testing.

The results are presented in table 3, 4.

Determination of drug content

Twenty lozenges were finely powdered; quantities of the powder equivalent to 40mg of nicotine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of distilled water 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} 262nm[9]. The drug concentration was calculated from the standard curve. The results are presented in table 3, 4.

In vitro drug release studies

Dissolution conditions:

- Apparatus : USP I apparatus
- Dissolution medium : 500ml of pH 6.7 Phosphate buffer
- Temperature : 37±0.5^0 C
- Rotating speed of the paddle : 25 rpm
- Sample time intervals : 5, 10,15,20,25,30 minutes
- Detection : UV-VIS spectrophotometer at λ_{max} 262 nm

The samples were withdrawn at predetermined time points, diluted appropriately and were analyzed spectrophotometrically at 262 nm

[9]. The cumulative percentage release and standard deviation were calculated.

Taste evaluation of Nicotine hard candy lozenges

Taste assessment studies were conducted according to the approved protocol (with human ethical committee approval letter number UCPSc/KU/BA/2011-10/B) on ten low dependent smokers and 10 high dependent smokers. All the volunteers signed an informed consent form. Formulations NC11, NC25 with and without sweetener was provided randomly to 10 low dependent smokers and 10 high dependent smokers respectively. Subjects scored the intensity of bitterness, mouth feel and after taste by placing the given formulation on the tongue, tasting it for ten minutes, and thoroughly rinsing their mouths with water after each sample evaluation. After the taste evaluation, urge to smoke is decreased or not also reported in the volunteer evaluation sheet.

Each volunteer judged the above given parameters of the formulation using a score involving a five point scale which ranged from + to +++++.

Guide for taste evaluation was presented in the table 5.

Table 5: Guide for taste assessment studies of Nicotine lozenges

Parameter	Product Elegance		Taste		Decrease of urge to smoke	Mouth feel		After taste
1	Bad	+	Bitter	+	yes	Bad	+	yes
2	Acceptable	++	Slightly bitter	++		Unpleasant	++	
3	Good	+++	Tolerable	+++		Tolerable	+++	No
4	Very Good	++++	Acceptable	++++	No	Good	++++	
5	Excellent	+++++	Good	+++++		Pleasant	+++++	

RESULTS AND DISCUSSIONS

Preformulation studies

Drug-Excipient compatibility studies by physical observation:

Nicotine mixed with various proportions of excipients showed no color change at the end of two months, hence proving no drug-excipient interactions.

Drug-Excipient compatibility studies by FT-IR

The FT-IR spectra of pure drug nicotine are shown in the figure 1. The characteristic Peaks of nicotine are well retained in the spectrum in the lozenges. The FT-IR spectra of Nicotine hard candy lozenges containing HPC is shown in the figure 2. The characteristic peaks of nicotine are well retained in the spectrum representing that there is no significant interaction between drug and excipients.

Standard graph of nicotine in 6.7 pH phosphate buffer

Standard stock solutions of pure drug containing 100 mg of nicotine /100 ml were prepared in pH 6.7 phosphate buffer. The working standard solutions were obtained by dilution of the stock solution in pH 6.7 phosphate buffer. The calibration curves (Figure 3) for nicotine were prepared in the concentration range of 0.2-10 µg/ml at the selected wavelength 262 nm. Their absorptivity values were used to determine the linearity. Solutions were scanned and Beers Lamberts law limit was determined.

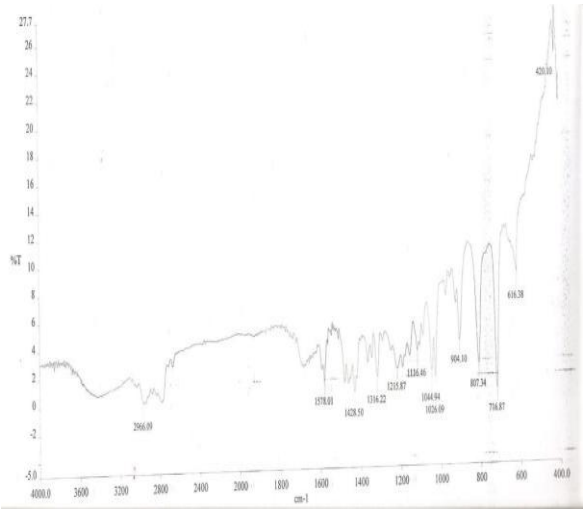

Fig. 1: FT-IR spectra of Nicotine pure drug.

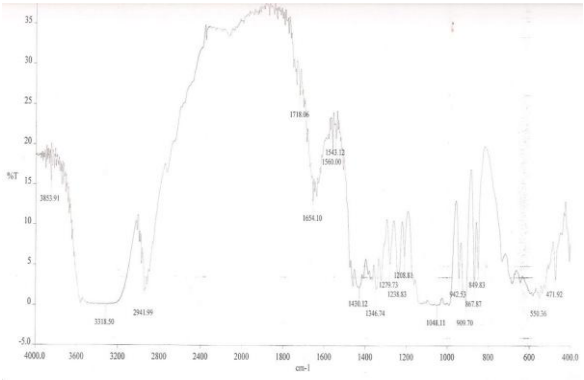

Fig. 2: FT-IR spectra of Nicotine hard candy lozenges containing HPC

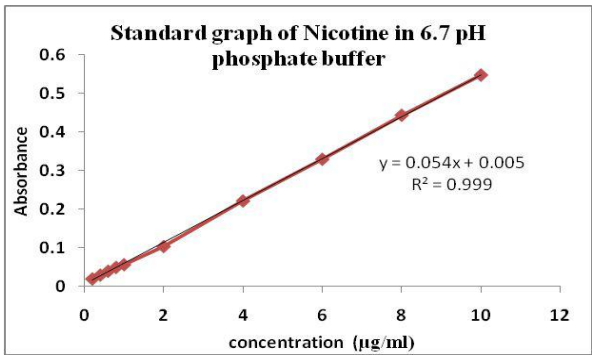

Fig. 3: Standard graph of nicotine in pH 6.7 phosphate buffer

Process variables

Thickness, Weight, content uniformity, hardness etc of lozenges were measured and presented in table 3, 4. From the table it can be seen that lozenges showed uniformity in weight, content, thickness and exhibited good hardness and friability. All these parameters were well within the limits.

***In-vitro* drug release profile**

The cumulative percentage drug release profiles from the formulations NC8, NC9, NC10, NC11 (nicotine dose is 2mg), NC22, NC23, NC24, NC25 (nicotine dose is 4mg) containing HPC in 1%, 2%, 3%, 4% concentrations respectively shown in figures 4, 5.

Table 3: Process parameters of various Nicotine hard candy lozenges formulations

Formulation	Weight variation (g)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Content uniformity
NC1	2.50±0.12	4.76±0.03	7.20±0.5	0.12	98.23
NC2	2.50±0.45	4.81±0.03	8.30±0.5	0.09.	99.65
NC3	2.50±0.63	4.80±0.05	7.50±0.5	0.11	99.12
NC4	2.50±0.43	4.87±0.04	8.30±0.5	0.08	98.44
NC5	2.50±0.23	4.79±0.08	7.40±0.5	0.14	99.23
NC6	2.50±0.45	4.85±0.05	9.50 ±0.5	0.11	98.63
NC7	2.50±0.63	4.82±0.06	8.50±0.5	0.10	99.65
NC8	2.50±0.12	4.83±0.04	7.80±0.5	0.13	98.65
NC9	2.50±0.75	4.79±0.06	7.50±0.5	0.12	98.45
NC10	2.50±0.43	4.82±0.05	8.50±0.5	0.15	99.64
NC11	2.50±0.23	4.86±0.04	9.70±0.5	0.14	98.12
NC12	2.50±0.45	4.80±0.04	8.60±0.5	0.09	99.72
NC13	2.50±0.63	4.77±0.08	7.00±0.5	0.12	97.13
NC14	2.50±0.12	4.86±0.03	8.50±0.5	0.13	99.12

Table 4: Process parameters of various formulations

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Content uniformity
NC15	2.50±0.12	4.83±0.04	7.20±0.5	0.10	98.23
NC16	2.50±0.75	4.79±0.06	8.30±0.5	0.13	99.65
NC17	2.50±0.43	4.82±0.05	7.50±0.5	0.12	99.12
NC18	2.50±0.23	4.86±0.04	8.30±0.5	0.15	98.44
NC19	2.50±0.45	4.80±0.04	7.40±0.5	0.14	99.23
NC20	2.50±0.63	4.77±0.08	9.50 ±0.5	0.09	98.63
NC21	2.50±0.12	4.86±0.03	8.50±0.5	0.10	99.65
NC22	2.50±0.12	4.83±0.04	7.80±0.5	0.13	98.65
NC23	2.50±0.75	4.79±0.06	7.50±0.5	0.12	98.45
NC124	2.50±0.43	4.82±0.05	8.50±0.5	0.15	99.64
NC25	2.50±0.23	4.86±0.04	9.70±0.5	0.14	98.12
NC26	2.50±0.45	4.80±0.04	8.60±0.5	0.09	99.72
NC27	2.50±0.63	4.77±0.08	7.00±0.5	0.12	97.13
NC28	2.50±0.12	4.86±0.03	8.50±0.5	0.13	99.12

Formulations containing HPC in pH 6.7 phosphate buffer

Formulations NC1 and NC15 without polymer showed 100% drug release within 5minutes. Formulations containing PVP K90 in low concentrations showed 100% drug release within 5minutes whereas in high concentration become too viscous and do not get dried properly so the formulations NC4, NC18 were discarded for the in-vitro drug release studies.

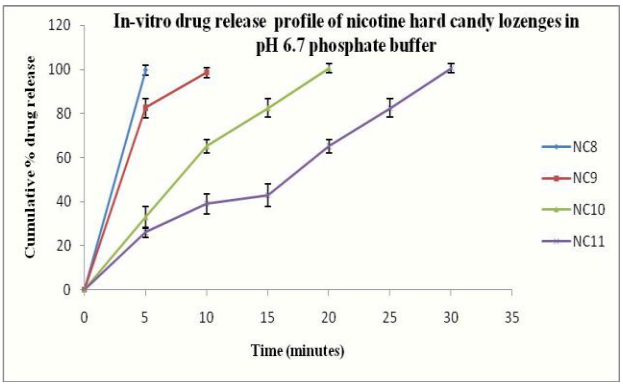

Fig. 4: *In-vitro* drug release profile of Nicotine Hard candy Lozenges (2mg)

Values are expressed as mean cumulative percentage release ± SD with n=3

Formulations containing HPMC E15 in low concentrations that is 0.5% and 1% showed 100% drug release within 5minutes whereas in high concentration that is 2% become too viscous and do not dry properly so the formulations NC7, NC21 were discarded for the in-vitro drug release studies. Formulations containing HPMC 100Cps in low concentrations that is 1%, 1.5% showed 100% drug release within 5minutes whereas in high concentration that is 2% become too viscous and do not dry properly so the formulations NC14, NC28 were discarded for the in-vitro drug release studies.

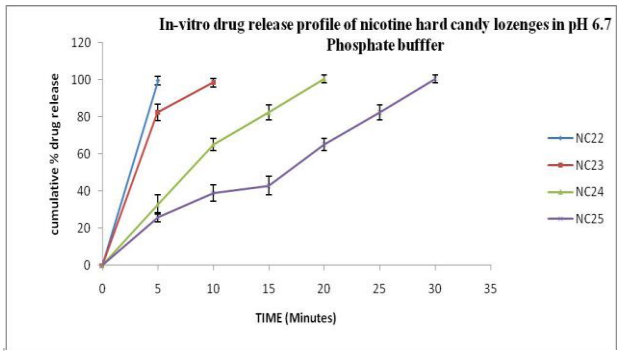

Fig. 5: In-*vitro* drug release profile of Nicotine Hard candy Lozenges (4mg)

Values are expressed as mean cumulative percentage release ± SD with n=3

From the in-vitro dissolution studies the formulation NC25 and NC11 were considered good because the release of nicotine could be extended up to 25-30 minutes. Slow release helps in better absorption from sublingual area so that first pass metabolism may be reduced. From the drug release kinetics of the final formulations NC11 and NC25, the R^2 values of zero order kinetic models is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows zero order kinetics. The results were presented in the table 7.

Table 7: Correlation coefficient (R^2) values of different kinetic models

R^2 values for nicotine lozenges				
Formulation code	**Zero order**	**First Order**	**Higuichi**	**Peppas**
NC11	0.9933	0.8048	0.9012	0.9930
NC25	0.9947	0.6117	0.9021	0.9935

Taste Assessment studies

Taste evaluation results for formulations NC11 and NC25 with and without sweetener were given in Table 6. Formulations having no sweetener were bitter to most of the volunteers. Seven out of ten volunteers rated the lozenges pleasant while the others reported an acceptable taste for formulations NC11 and NC25 (Table 6). A smooth and low grittiness was also reported which could be due to the water soluble excipients. On comparison of the results for the taste evaluation of Nicotine hard candy lozenges, it was concluded that the addition of sweetener to Lozenges further suppressed the bitter taste and provided a pleasant sweet taste. Effective taste-masking was achieved for formulations NC11 and NC25 with aspartame without any after taste effect. A pleasant mouth feel was also reported by the volunteers due to the presence of peppermint flavor.

Table 6: Taste assessment studies

Formulations NC11 and NC25	**Taste**	**Mouth feel**	**After taste**	**Urge to smoke**
Without sweetener	+	+	+	decreased
With sweetener	++++	++++	+++	decreased

CONCLUSIONS

Nicotine hard candy lozenges, with a dose of 2mg and 4mg were developed and evaluated. Drug excipient compatibility studies by FTIR showed there was no incompatibility between drug and excipients. Developed nicotine hard candy lozenges were evaluated for various physico-chemical evaluation parameters and were found to be within the standard limits. Nicotine hard candy lozenges 2mg and 4mg with HPC 4% (NC11, NC25) were optimized. The optimized formulations showed 100% release within 30minutes. By kinetic modeling it was concluded that optimized formulations NC11 and NC25 followed zero order kinetics.

From the taste assessment studies it was concluded that optimized formulations NC11 and NC25 showed good taste and pleasant mouth feel without any after taste and pungent odor of nicotine. Urge to smoke was also decreased by the optimized formulations. At last it was concluded that Nicotine hard candy lozenges were good formulations for the smoking cessation.

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