

Formulation and Evaluation of Nicotine Buccal Films for Smoking Cessation

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Abstract: Smoking is injurious to health. Smoking cessation is the process of discontinuing smoking. Nicotine present in tobacco is addictive & makes the process of quitting very prolonged & complex. Nicotine causes pulmonary diseases, lung cancer & heart diseases. Quitting smoking drastically reduces risk of dying from tobacco-related diseases. The current established procedures for smoking cessation have wide variety of side effects & in comparison buccal thin films are better alternative due to negligible side effects & fast discharge of nicotine, which also avoids first pass metabolism. So the aim of the study was to develop the films for potential delivery of Nicotine by the buccal mucosa of Adult patients. Films were prepared using hydroxypropyl methyl cellulose (HPMC K-15), hydroxypropyl methyl cellulose (HPMC E-5), glycerin as plasticizer, sucrose as sweetener, citric acid as saliva stimulating agent and water as solvent. Nicotine is freely soluble in alcohol & miscible in Water. Hence alcohol is used as a co-solvent to enhance the solubility of nicotine in water. The films were prepared by using solvent casting method & then evaluated. Buccal film is useful for improving the patient compliance due to ease of use.

Keywords: Nicotine, Smoking cessation, FTIR, Drug release

1. Introduction

Oral fast dissolving film (ODF) is one of the novel approach to increase consumer acceptance by rapid dissolution, self-administration without water or chewing. The need for non-invasive delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management. Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. A new oral fast dissolving dosage form such as fast dissolving film has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid. Most of the existing fast-dissolving drug delivery systems are in the form of solid tablets and designed to dissolve in the patient's mouth and to disintegrate within a few seconds or minutes, without the need to drink or chew. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place. A wide range of drugs (eg; antihistaminics, anti-asthmatic, analgesics, cardiovascular drugs) can be considered for this dosage form.

Oral cavity as a site for drug delivery –^[1]

Anatomy and nature of oral cavity–

The oral cavity maybe divided into two regions, the outer oral vestibule bounded by the lips and cheeks and the oral cavity itself the border of which is formed by the hard and soft palates the floor of the mouth and tonsil. (Figure.1)

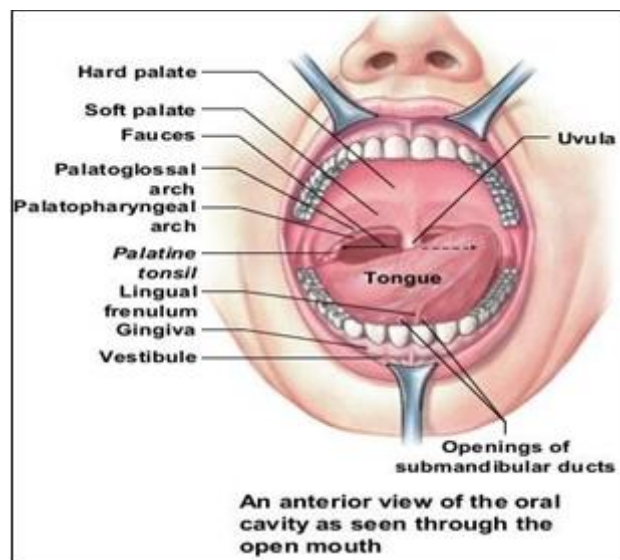


Figure 1: Schematic representation of the “open” oral cavity

a) Physical description of oral cavity

As given in fig-1, the mucosa that lines the oral cavity may be divided into three types, classified according to their function as:-

- Masticator mucosa- which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.
- Lining mucosa- which covers the lips, cheeks, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non- keratinized epithelium.
- Specialized mucosa- which covers the dorsum of the tongue with high Keratinization.

b) Regional variation in the composition of oral mucosa

The difference in structure thickness and blood flow depending on their location. Membrane that lines the oral cavity has a total area of 200 cm² and shows Keratinized and

non – keratinized tissue occupies about 50% and 30% respectively.

c) Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick) a lamina propriety followed by the sub mucosa as the innermost layer (Fig1). The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratin neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual and the buccal regions however are not keratinized contain only small amounts of ceramides.

d) Composition of mucus layer

Mucus is a translucent and viscid secretion which forms a thin gel, mean thickness of this layer varies from about 50-450 am in humans secreted by the goblet cells lining the epithelia or by special glands with mucus cell acini. It has the following general composition.

Water -95%

Mineral salts – 1%

Glycoprotein and lipids – 0.5-3%, and

Free proteins – 0.5-1.0%

e) Functions of mucus layer

- Protective/Defense: resulting particularly from its hydrophobicity.
- Barrier: The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.
- Adhesion: Mucus has strong cohesion properties.
- Lubrication: It is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

f) Salivary Secretion

There are mainly three glands which secrete saliva in the oral cavity such as parotid, sublingual, and sub-mandibular. Saliva is composed of 99% water and is a complex fluid containing organic and inorganic material. Secretion of saliva is highest during the working hours. The amount of saliva produced throughout the day is 1-1.5 L but this flow is variable. According to researchers, the pH of saliva ranges from 5.5 to 6.8, the saliva of oral cavity has a low buffering capacity. The functions of saliva include moisten the oral cavity, aid the digestion of foods, lubricate the food for mastication and swallowing, provides protection to the tissue from abrasion by rough materials that may enter into mouth.

1.1 Advantages of mucoadhesive buccal drug delivery:^[2]

- 1) Drug administration by the oral mucosa offers several advantages.
- 2) Ease of administration and termination of therapy in emergency.
- 3) Permits localization of the drug for a prolonged period of time.
- 4) Administered to unconscious and trauma patients.
- 5) Offers an excellent route for the systemic delivery of drugs which by passes first pass metabolism, thereby offering a greater bioavailability.
- 6) Significant reduction in dose can be achieved thereby

reducing dose dependent side effects and eliminates peak-valley profile.

- 7) Drugs, which are unstable in acidic environment of stomach and are destroyed by the enzymatic or alkaline environment of the intestine, can be administered.
- 8) It offers passive diffusion for drug absorption.
- 9) It can be made unidirectional to ensure only buccal absorption.
- 10) It allows for the local modification of tissue permeability inhibition or reduction in immunogenic can be achieved.
- 11) Flexibility in physical state, shape, size and surface.
- 12) Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion response. Thus selective uses of therapeutic agents like peptides, proteins and ionized species barriers.
- 13) It satisfies several features of the controlled release system.
- 14) The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.
- 15) The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- 16) Rapid onset of action.

1.2 Disadvantages of mucoadhesive buccal drug delivery:

- 1) Once placed at the absorption site & the dosage form should not be disturbed.
- 2) The drug swallowed in saliva is lost.
- 3) Properties like unpleasant taste or odour, irritability to the mucosa & stability at salivary pH possess limitations to the choice of drug.
- 4) Only drugs with small dose can be administered.
- 5) Eating and drinking may become restricted.

1.3 Limitations of mucoadhesive buccal drug delivery:

- 1) Drugs, which are unstable at buccal pH can not be administered.
- 2) This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
- 3) The maximum dose should not exceed 50mg.
- 4) This route can administer the drugs which are absorbed only by passive diffusion.
- 5) Eating and drinking may become restricted.
- 6) There is an ever present possibility of the patient swallowing the dosage form.
- 7) Over hydration may leads to slippery surface and structural integrity of the formulation which may get disrupted by this swelling and hydration of the bioadhesive polymers.
- 8) Drugs contained in the swallowed saliva follow the pre-oral and advantages of buccal route are lost.

1.4 Nicotine for Smoking Cessation^[3] :

Tobacco smoking is globally far more widespread than the use of any other form of Substance abuse. Its use remains the leading preventable cause of morbidity & mortality, each year causing more than 6 million deaths globally. The World Health Organization estimates that there are 1.3 billion smokers worldwide, & each year 5 million smokers die because of tobacco-related diseases. Data suggests that up to 70% of current smokers want to quit & 40% attempt to do so each year. Of the 4000 chemicals identified in tobacco smoke, nicotine is the main active ingredient in tobacco products, which is highly toxic & potentially lethal that reinforces the individual to tobacco addiction behavior.

Nicotine replacement therapy (NRT) replaces nicotine obtained from cigarettes to reduce withdrawal symptoms associated with smoking cessation, thus helping resist the urge to smoke cigarettes. NRT provides lower & slower increasing plasma concentrations, without exposure to toxic combustion products & is considered safe. Smoking is injurious to health. Smoking cessation is the process of discontinuing smoking.

2. Review of Literature

Prshant Deore and Rajveer Bhaskar et al^[7], reported formulation of effective Nicotine Buccal Film with HPMC and propylene Glycol and formulation was evaluated at varied physical and chemical parameters. Varied polymer concentrations were used & effect on dissolving Properties of films. Among the varied concentration of polymers examined, the result have shown that the F5 films were versatile with good dissolving time, high folding endurance & drug uniformity content as compared to alternative concentrations of polymers. Thus films with 3% HPMC with 1% propylene glycol could be a good base for the preparation of nicotine buccal films.

Sandeep D Jadhav et al^[8], The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. Film forming agent HPMC, sodium CMC was considered as independent variables. Drug release rate from 45sec to 990sec, T50% and release exponent (n) were taken as responses. Decrease the viscosity of film former a specific limit, changes the release from zero order to Hixson-Crowell based release. The optimized formulation F1 was found superior than remaining 8 batches. Amongst all the formulation, formulation F1 releases the complete drug in 360 sec. but other formulation takes more time for complete release. The IR and DSC studies revealed that no physicochemical interaction between excipient and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through disintegration. Stability studies revealed that optimized formulation was stable. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of fast dissolving oral film containing levocetirizine Dihydrochloride by using HPMC, sodium CMC and PEG-400 as key excipient.

Krishna Mohan Chinnala and Mayuri Konda et al^[9], studied on making choice of Nicotine buccal thin films for Nicotine replacement therapy. Smoking is the foremost unnecessary basis of demise worldwide and quitting smoking drastically reduces the risk of dying from tobacco related diseases. The current established procedures for smoking cessation embrace wide variety of side effects, but as a comparison buccal thin films are a better alternative due to negligible side effects & fast discharge of nicotine which also avoids first pass metabolism. So these films are used for smoking cessation.

Sumedha Bansal et al^[6], carried out formulation & evaluation of fast dissolving film of an Antihypertensive drug Losartan potassium by using polymers such as Poly vinyl alcohol & Maltodextrin in different concentrations by solvent casting method. Films showed satisfactory in-vivo permeation & effective in vitro drug release.

Mayuri Konda, Krishna Mohan Chinnala et al^[4], carried out study on Formulation & Characterisation of Nicotine thin films for Smoking Cessation through Buccal Delivery. Prepared films were subjected to accelerated stability testing & have not revealed remarkable change in weight, disintegration time, surface pH, etc.

Apoorva Mahajan, Neha Chhabra, Geeta Aggarwal et al^[10], Carried out study on formulation and characterization of fast dissolving buccal films. This fast dissolving drug delivery system is suited for the drugs which undergo high first pass metabolism is used for improving bioavailability & reducing dosing frequency which minimizes side effects & also makes it cost effective.

S. Garg, G.Kumar et al^[11], developed & evaluated buccal bioadhesive system for smoking cessation therapy. They developed a bilayered buccal bioadhesive film formulation of nicotine hydrogen tartrate for smoking cessation therapy, comprising a bioadhesive drug layer & a backing layer, which released a drug at a pre-determined rate for a period of 4 hours.

Kathpalia et al^[12], To formulate taste masked orally disintegrating films of levocetirizine dihydrochloride to enhance acceptance by adults and pediatric patients using various film formers like starch, HPMC, pullulan, polyvinyl alcohol, polyethylene glycol 400. The films are formed by solvent casting method, plasticizer have been used as glycerin, propylene glycol, sorbitol. The films formed having better flexibility, non-tackiness. The films prepared were used in emergency treatment like allergic reactions.

Bailwal et al^[13], To formulate and evaluate fast dissolving films of Chlorpheniramine maleate. The films was prepared by solvent casting method, the superdisintegrants Crosspovidone (2, 4, 6, 8, 10% w/w) and Microcrystalline Cellulose (5, 10, 15, 20, 25% w/w) were used in different concentrations with HPMC & PVA as a film forming base. Along with polymers and superdisintegrants the plasticizer PEG, mint flavor and sucrose were used in preparation of films. The formulated films were evaluated for thickness measurement, weight variation, folding endurance, disintegration time, *in vitro* drug release. It was concluded

that the films containing Crosspovidone shows better drug release and less disintegration time as compared to the films containing Microcrystalline Cellulose.

Ali MS et al^[14], Films were prepared by diazepam as an anti-epileptic drug using HPMC E-5, E-15, K-15 as film formers and PEG 400, propylene glycol as plasticizers which avoid first pass metabolism prepared using solvent casting method. The prepared films were superior in drug release compared with marketed valium tablets. The film showed good mechanical property and drug release and disintegrating time and good stability.

Dipal M Patel et al^[15], Cetirizine is widely used in allergic induced asthma and dextromethorphan in sore throat conditions. Combination have more potent effect compared to single drug. Fast dissolving and disintegrating dosage forms are gaining popularity in recent time which requires no matter for administration. The films were prepared using solvent casting method by using HPMC E-5, K-15, E-15. PEG-400, aspartame, tartaric acid, citric acid for taste masking of cetirizine, tartaric acid and citric acid were used as salivary stimulating agents.

Preeti Tomar et al^[16], Diphenhydramine hydrochloride an antihistamine drug belongs to BCS class I was used for oral thin film preparation. The aim was to develop a fast releasing oral polymeric thin film prepared by solvent casting method with good mechanical properties. The films were prepared by using Tween 80 which was used as solubility agent has more percentage of drug release. The optimized film disintegrate in less than 30s releasing more than 90% of drug with in 90sec.

3. Aim & Objectives

3.1 Aim

Formulation development and evaluation of Nicotine buccal films for smoking cessation.

3.2 Objectives of the study

- Preparation of blank polymeric patches using different polymer composite.
- Evaluation of blank polymeric patches for different characteristics like
- Surface pH.
- Swelling studies.
- Weight uniformity.
- Patches thickness.
- Folding endurance of the patches.
- Drug content uniformity.
- In-vitro residence time.
- In-vitro release studies.
- Selection of best composite for incorporation of drug and optimization of the Formulations.
- To study in-vitro release of Nicotine from prepared film.

4. Materials and Methods

4.1 Materials used with their source

Table 2: Material used with their source

S. No	Material	Property	Source
1.	Nicotine	Pure Drug	Shree Chemicals, Pune
2.	HPMC K-15, HPMC E-5.	Film Former & Disintegration Agent	Ozone International
3.	GLYCERINE, PEG-400.	Plasticizer	Ozone International
4.	Citric Acid	Saliva Stimulating Agent	Ozone International
5.	Sucrose	Sweetning Agent	Ozone International

4.2 Equipments used with their source

Table 3: Equipments used with their source

S.No	Equipment	Make
1.	Oven Rotek	LABINDIA
2.	Disintegration Apparatus	ELECTROLAB
3.	UV-Spectrophotometer	SHIMADZU JAPAN
4.	Digital Balance	SHIMADZU JAPAN
5.	PH Meter	LABINDIA
6.	Magnetic Stirrer	DOLPHIN INSTRUMENTS
7.	Screw Gauge	ELECTROLAB
8.	Sonicator	PCI ANALYTICS

5. Experimental Methods

Preparation of phosphate buffer solution (pH 6.8): Take a 6.8 gm of Di-Sodium Hydrogen Orthophosphate and 0.900 gm of sodium hydroxide in a 1000 ml volumetric flask.

Standard solution:

The nicotine standard solution was prepared by dissolving 10 mg (0.01 ml) nicotine in 10ml of 6.8 phosphate buffer to give a concentration of 1 mg/ml (1000 µg/ml).

Preparation of Nicotine stock solution in pH 6.8 Phosphate buffer:

From the above standard solution 1 ml solution (1000 µg/ml) is pipette out and diluted up to 10 ml which gives 100 µg/ml. From this solution 1 ml, 2 ml, 3 ml, 4 ml, 5 ml pipette out in a 10 ml volumetric flask and finally diluted up to the mark which gives required concentration that is 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, and 50 µg/ml.

Determination of Analytical Wavelength

Calibration curve of Nicotine in phosphate buffer (pH 6.8):

From the Nicotine standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and made up to 10 ml with phosphate buffer (pH 6.8), so as to get drug concentrations of 10.0 to 50.0 µg/ml. The absorbance of these drug solutions were estimated at λ_{max} 263nm by using Shimadzu UV/visible 1800 Spectrophotometer by using phosphate buffer of pH 6.8 as blank. This procedure was performed in triplicate to validate the calibration curve. The standard calibration curve yields a straight line, which indicates that the drug obeys Beer's Lambert's range in the concentration range of 10 - 50 µg/ml.

Formulation of blank polymeric fast dissolving film:

The blank Fast dissolving films were prepared using Hydroxypropyl methyl cellulose K-15, E-5 by solvent casting technique. Detailed composition is given in table No-6

Method:

Accurately weighed quantity of hydroxypropyl methyl cellulose was dissolved in distilled water and glycerine (plasticizer) was added gradually with continuous stirring then 10ml resultant mixture was poured into each fabricated glass ring placed on a mercury substrate in a petri dish. Drying was carried out at 40°C for 24 hours in hot air oven or in hot area.

Table 6: Formulation Details of Blank Fast Dissolving Film

Ingredient(mg)/ Formulation	F1	F2	F3	F4	F5	F6	F7	F8
HPMC K 15	100	200	300	400	-	-	-	-
HPMC E 5	-	-	-	-	100	200	300	400
GLYCERINE	0.2	-	0.2	0.2	0.2	-	0.2	-
CITRIC ACID	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
SUCROSE	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
WATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
RESULT	+	+	++	+++	+	+	++	+++

+ -Poor + + -Average + + + -Excellent

Formulation of Nicotine Buccal Film by Solvent Casting Method^[4]:

From the preliminary physical observation of the films prepared the best compositions were used for the incorporation of Nicotine.

Petri plate calculation:

Calculation of API loaded inside the film:

Diameter of the Petri dish = 9.8 cm

Radius of the Petri dish = Diameter/2 = 4.9 cm

Radius of large Petri plate = πr^2
 $= 3.14 \times 4.9 \times 4.9 = 75.39 \text{ cm}^2$

Now, drug coated film is cut into pieces as 2 cm x 2 cm = 4 cm²

4 cm² contain 2 mg drug so, 75.39 cm² contain (?) Drug = 37.69 mg = 40 mg.

Calculated amount of Nicotine was dissolved in the ethanol & distilled water & added to polymeric solution, after complete dissolution of the drug; glycerine (plasticizer) was added and stirred to form a homogeneous solution. The solution was casted on petridish then kept in hot air oven at 40°C for 24 hours. The film thus formed was cut into size of 2X2 cm diameter. Each containing 2mg Nicotine. The detailed composition of the Nicotine fast dissolving film is given in table No: 7

Table 7: Formulation Details Of Nicotine Buccal Film

Ingredient (mg/10ml) Formulation	F1	F2	F3	F4	F5
NICOTINE	40	40	40	40	40
HPMC K 15	400	300	-	100	200
HPMC E 5	-	100	400	300	200
GLYCERINE	3.0	3.0	3.0	3.0	3.0
CITRIC ACID	0.5	0.5	0.5	0.5	0.5
SUCROSE	q.s	q.s	q.s	q.s	q.s
WATER	q.s	q.s	q.s	q.s	q.s

Evaluation of Nicotine Buccal Film^[4]:

The Nicotine Buccal film was evaluated for the following properties:

1) Physical properties

- Physical appearance and surface texture
- Weight Uniformity
- Thickness uniformity
- Folding Endurance
- Surface pH
- Disintegration Time
- Transparency

2) Evaluation of Nicotine Buccal film for

- Drug-excipient interaction studies
- Drug content uniformity
- In vitro drug release
- Stability study

Physical properties:

a) Physical appearance and surface texture of films: This parameter was checked simply with visual inspection of patches and evaluation of texture by feel or touch.

b) Weight Uniformity of films: Buccal films weighed on analytical balance individually by random selection. The average of five observations of each batch was calculated. Such determinations were carried out for each batch.

c) Thickness of films: Film thickness was measured by using a micrometer screw gauge apparatus. A strip of 2 X 2cm was placed between the thickness rods and thickness was measured in five different positions & then sequentially mean average was calculated.

d) Folding Endurance of films^[5]: The flexibility or elasticity of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance was measured manually / practically for the prepared films. Buccal film of 2X2cm was folded repeatedly at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

e) Surface pH of fast dissolving film: The 2 cm x 2 cm film was dissolved completely in 2 ml of distilled water. The pH was measured by making the electrode get in touch with the surface of the film & allowing it to equilibrate for 1 minute.

f) Disintegration Time: 10ml distilled water was held in a petri plate & single film was added on the outside of the water & the point measured until the oral film was softened completely. This test was conducted on randomly selected three films from each lot & average values were calculated.

Evaluation of Nicotine Buccal film for:

a) Drug-Polymer Interaction Study of fast dissolving film: There is always a possibility of drug-excipient interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipient interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offers

the possibility of chemical identification. Infra-red spectra of pure drug Nicotine and formulations were scanned by using spectrophotometer by a thin film method.

b) Drug content uniformity of patches^[6]: Standard solution: Accurately about (2 mg) 0.002 ml of Nicotine was taken by pipette and transferred in to a 10 ml of volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml and then this solution was filtered through the whatman filter paper. Then 0.5 ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask so as to get 10 µg/ml final concentration.

Test solution:

One film of Nicotine was dropped into a 10 ml of volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml. Then this solution was filtered through the whatman filter paper. Then 0.5 ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask so as to get 10 µg/ml final concentration. Content uniformity was calculated using following formula: %Label claim = $\frac{Abt}{Abs} \times \frac{Ds}{Dt} \times \frac{100}{Lc} \times 100$. Where, Abs = Abs. of standard solution, Lc = Label claim, Ds = Dilution of standard, Dt = Dilution of test, Abt = Abs. of test solution.

c) In vitro DrugRelease^[6]: The release rate of the Nicotine buccal film was determined by the help of USP Dissolution Test Apparatus-II. The dissolution test was performed using 900 ml Phosphate Buffer Solution pH 6.8, at $37 \pm 0.5^\circ\text{C}$ with 50 rpm of the paddle speed. Aliquot 5 ml of the solution was collected from the dissolution apparatus at time interval of 1 min and at the same time add 5 ml of same amount of fresh

dissolution medium. The Aliquot filtered through the whatman filter paper. The absorbance of the filtered solution was measured at 263 nm. The aliquot should be withdrawn at the zone between the surface of the dissolution medium and the top of rotating paddle not less than 1cm apart from the vessel wall. Cumulative percent drug release can be calculated by using the equation obtained from the standard curve or % drug release formula. $(A = \text{Con. Of Std.} / \text{Abs. of Std.} \times \text{Abs. of sample} \times \text{volume of dissolution apparatus} \times \text{Dilution factor} / 1000, B = A\text{-Value} / \text{Label claim} \times 100)$

6. Observations

UV Spectroscopy: The UV spectrum of Nicotine in Phosphate buffer solution pH 6.8 in the range of 400 – 200 nm. The spectrum indicated that the observed λ_{max} of Nicotine was 263 nm which is matched with pharmacopoeial value.

Preparation of standard Calibration curve of Nicotine: Nicotine showed maximum absorption at wavelength 263 nm in PBS pH 6.8. Standard curve was plotted by taking absorption of diluted stock solutions (10, 20, 30, 40, 50 µg/ml) at wavelength 263nm.

Table 8: Calibration curve readings (Conc. vs. Abs)

Conc.(µg/ml)	Abs.
10	0.130
20	0.257
30	0.384
40	0.501
50	0.628

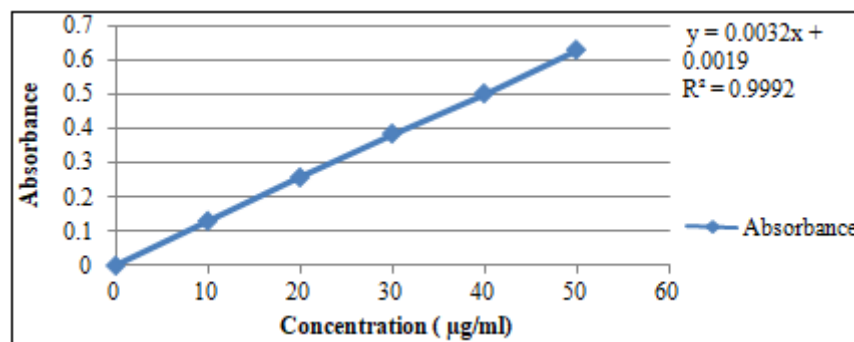


Figure 12: Calibration curve of Nicotine in PBS (pH 6.8)

Calibration curve for: Nicotine
Solvent / Mobile Phase: PBS PH 6.8
Wavelength (nm):263
Unit for Concentration: mcg/ml
Equation of Regressed line: $Y = 0.0032x + 0.0019$
Where, X =Value of concentration
Y =Regressed value of absorbance
Correlation coefficient (R) =0.9992

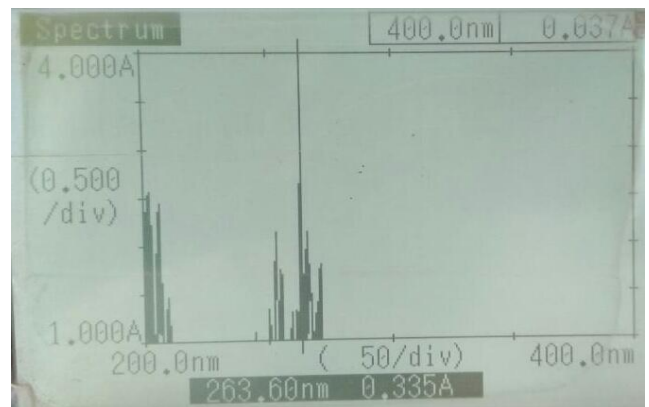


Figure 13: UV Spectra of Nicotine in PBS (pH 6.8)

FTIR:

FTIR studies were carried out for detection of drug polymer interaction. In the present study the IR study of pure drug Nicotine, polymer HPMC E- 5, and HPMC K-15 with drug. The infrared spectrum of Nicotine recorded in a KBrpellet on Perkin Elmer Infrared Spectrophotometer. From the Infrared frequencies , the respective assignments are given below.

Table 9: FTIR Study observed values

Standard frequencies	Observed Peak	Assignment
3300-3500	3397.07	N-H Stretching
1200-1350	1343.21	N - Aromatic
1677	1679.16	C=N Double bond Stretching
1400-1600	1576.73	C=C Double bond Stretching

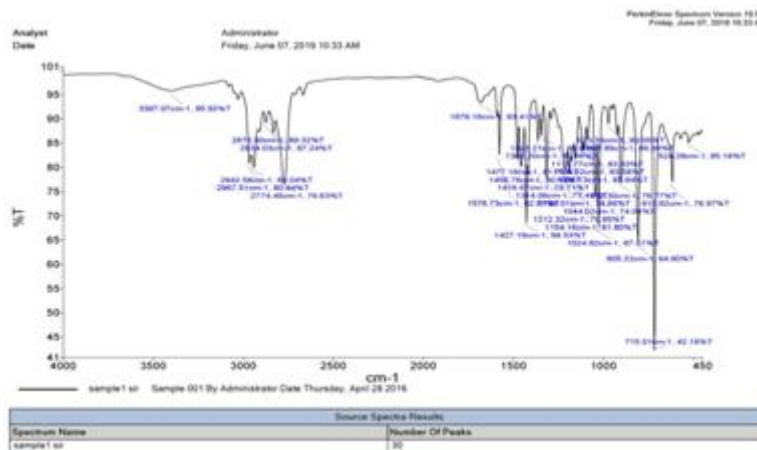


Figure 14: FTIR spectra of Nicotine

The infrared spectrum of Nicotine + hydroxy propyl methyl cellulose K-15 recorded in a KBr pellet on Perkin Elmer Infrared Spectrophotometer. From the Infrared frequencies & the respective assignments are given below.

Table 10: FTIR Observed Values

Standard frequencies	Observed Peak	Assignment
3300-3500	3369.15	N-H Stretching
1638-1648	1644	C=C Stretching
1350-1480	1374	C-HBending
2850-3000	2928.3	C-H Stretching

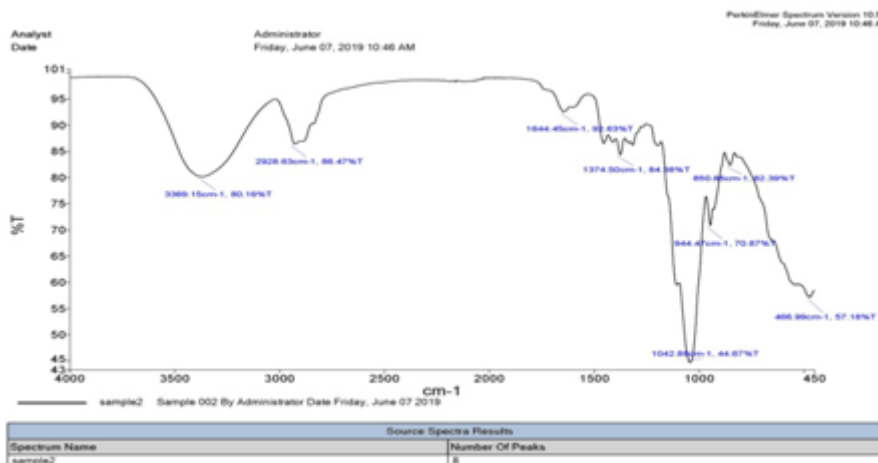


Figure 15: FTIR Spectra of Nicotine + HPMC K-15

In-Vitro Dissolution Studies

In present work an attempt has been made to increase the % drug release of Nicotine with changes in concentration of polymers & plasticizers by solvent casting method.

Table 11: In-vitro dissolution study of Nicotine [F1-F5]

	Time (min)	% Drug release				
		F1	F2	F3	F4	F5
% Drug release	1	38.53	26.45	15	20.72	32.05
	2	58.23	47.24	27.78	33.98	55.52
	3	74.25	58.01	33.6	44.27	61.89
	4	81.82	80.15	62.22	64.22	80.84
	5	97.55	93.53	83.96	85.24	89.53

All values expressed as mean ± SD (n=3), F = Formulation batch

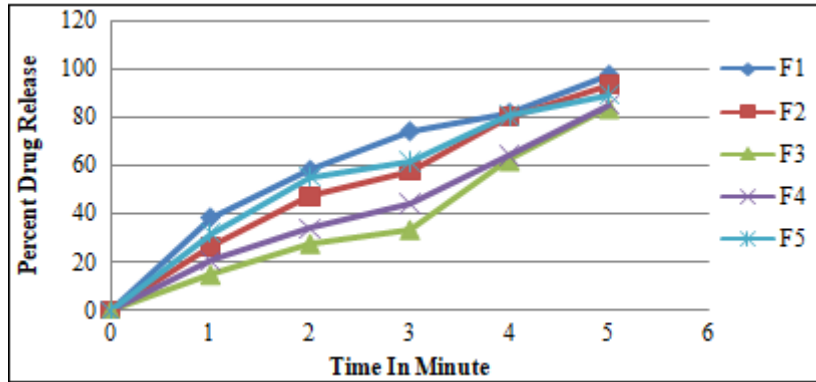


Figure 16: In-vitro dissolution study/profile Nicotine of batches F1-F5

Table 12: Evaluation Parameter of Nicotine Buccal Film

Formulation	Weight Uniformity (mg)	Thickness (mm)	Folding Endurance	Surface pH	Disintegration (Sec)	% Drug content
F1	15.33 ± 0.002	0.058±0.01	250±2.5	6.79±0.12	38.00±1.00	98.14
F2	10.33±0.001	0.05±0.01	209±1.2	6.39±0.16	43.00±1.00	97.57
F3	12.16±0.002	0.08±0.02	235±1.1	6.72±0.30	54.66±0.5	96.62
F4	18.12±0.001	0.09±0.04	240±2.1	6.68±0.22	62.66±1.0	93.85
F5	19.10±0.003	0.098±0.02	220±2.5	6.66±0.15	48.66±1.0	95.27

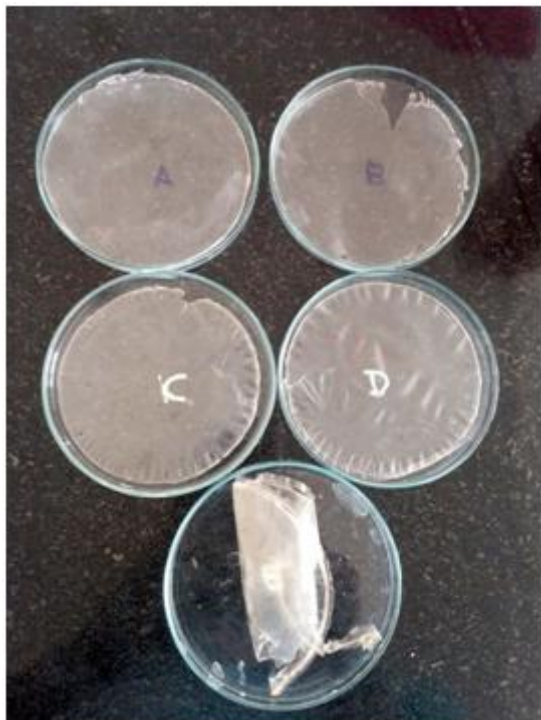


Figure 17: Nicotine Buccal Films F1 to F5 formulations



Figure 18: Nicotine Buccal Film F1

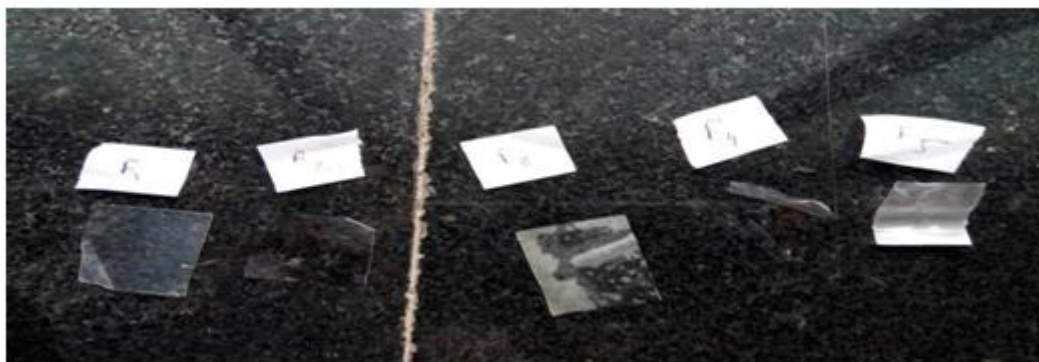


Figure 19: Nicotine Buccal Films 2cmx2cm F1 to F5 formulations

7. Discussion

In the present research work Design and characterization of polymeric Fast dissolving film for buccal delivery of Nicotine were prepared. Nicotine Fast dissolving film were prepared using HPMC K 15 and HPMC E 5 in different concentrations by solvent casting technique, the prepared fast dissolving film were evaluated for various parameters.

Physical appearance and surface texture of fast dissolving film:

These parameters were checked simply with visual inspection of Fast dissolving film and by feel or touch. The observation suggests that the Fast dissolving film are having smooth surface and they are elegant enough to see.

Weight uniformity of fast dissolving film:

It was observed that all the batches were uniform in weight with no significant difference in the weight of individual formulation from the average value. The weight variation was found to be in the range of 0.082 ± 0.002 to 0.1666 ± 0.003 mg for films prepared.

Thickness of fast dissolving film:

The thickness of films varied between 0.05 ± 0.01 to 0.098 ± 0.02 . The standard deviation values were low indicating uniformity in thickness.

Folding Endurance of Fast dissolving film:

The folding endurance of the Fast dissolving film was determined by repeatedly folding a small strip of the Fast dissolving film at the same place till it broke and the result of average folding endurance of all Fast dissolving film formulation is provided in Table no.12. The maximum & minimum folding endurance were found to be 278 ± 2.51 & 235 ± 2.50 respectively.

Surface pH of fast dissolving film:

The Surface pH of all the films exhibited uniformity in their values & were found to be between 6.39 ± 0.16 to 6.79 ± 0.12 representing its compatibility with buccal pH. Results are shown in table 12.

Disintegration Test:

It was observed that in vitro disintegration time varies from 38.00 ± 1.00 to 62.66 ± 1.00 sec for all formulations. In vitro disintegration time of the films is shown in table 12.

Drug interaction studies of fast dissolving film:

Spectrum No1. Pure drug:

The infrared spectrum of Nicotine recorded in a KBr pellet on Perkin Elmer Infrared Spectrophotometer. From the Infrared frequencies & the respective assignments given drug is compatible.

Spectrum No2. Drug & HPMC K-15:

The infrared spectrum of HPMC K-15 recorded in a KBr pellet on Perkin Elmer Infrared Spectrophotometer. From the Infrared frequencies & the respective assignments given drug are compatible.

In vitro Drug Release of fast dissolving film:

All the Fast dissolving films of Nicotine prepared were subjected to in vitro drug release studies for a period of 01-05 min.

It showed that drug gets rapidly released from all formulations. Maximum in vitro release was found to be 97.55 % over a period of 5 min in batch F1 while minimum in-vitro release was found to be 83.96 % in batch F3. The results for drug release studies are shown in Table no. 11. The graph was plotted between % drug release & time & shown in Figure 17.

8. Result

- 1) The films prepared were elegant in appearance and of smooth surface.
- 2) The weight of films were found to be uniform.
- 3) The thickness of films were found to be uniform.
- 4) The films were found satisfactory in evaluation of drug content.
- 5) The films has better flexibility.
- 6) The surface pH was uniform & suitable for buccal use.
- 7) There were no drug-polymers and drug-excipient interaction between the drug and Polymers used in the formulations.
- 8) Similarly, the fast dissolving films are also subjected to drug content uniformity study and it lies in between 93.85 to 98.14 % which suggest that uniform dispersion throughout the fast dissolving film.
- 9) A good % drug release was observed for formulation F1- F5 in time 1-5min. Among all of them F1 gives the best results in respect to all dissolution as well as evaluation parameters.
- 10) Thus F1 film containing Nicotine (2 mg) in HPMC K 15 (400mg) is considered being the best choice. These films were found to be appropriate for smoking cessation therapy.
- 11) This formulation will show enhanced Patient compliance due to ease of use.

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