

A REVIEW ON CHOICE OF NICOTINE BUCCAL THIN FILM FOR NICOTINE REPLACEMENT THERAPY

Krishna Mohan Chinnala and Mayuri Konda*

School of Pharmacy, Nalla Narasimha Reddy Educational Society's Group of Institutions, Hyderabad, Telangana, India - 500 088.

*Corresponding Author: Mayuri Konda

School of Pharmacy, Nalla Narasimha Reddy Educational Society's Group of Institutions, Hyderabad, Telangana, India - 500 088.

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ABSTRACT

Smoking is injurious to health. Smoking termination (quit smoking) is the process of discontinuing smoking. Tobacco consists of nicotine, which is addictive and causes pulmonary diseases. Nicotine makes the process of quitting very prolonged and complex. Smoking is the foremost unnecessary basis of demise worldwide, and quitting smoking drastically reduces the risk of dying from tobacco-related diseases such as heart disease and lung cancer. The current established procedures for smoking cessation embrace wide variety of side effects, but as a comparison sublingual or buccal thin films are a better alternative due to negligible side effects and fast discharge of nicotine which also avoids first pass metabolism. Thin-film drug release has established as a better substitute to the conventional tablets, capsules and liquids dosage forms. Thin films are similar in size, outline and thickness to a postal stamp, thin-film strips are classically designed for oral route of administration, with the user placing the strip on or under the tongue (sublingual) or along side of the cheek (buccal). Utilization of oral films has attracted momentous consideration in therapeutic and nutraceutical applications. The current study is focusing usage of nicotine buccal thin films for the release of nicotine to aid in smoking cessation.

KEYWORDS: Nicotine, Thin Film, Smoking Cessation, Buccal, Polymer, Plastisizer.

INTRODUCTION

Nicotine

Nicotine is an alkaloid present in dried leaves and stems of *Nicotiana tobacum* and *Nicotiana rustica*, and it is present in concentrations of 0.5-8%. It is a natural constituent which acts as an insecticide in the leaves of tobacco. It is the major tobacco alkaloid present to the extent of 1.5% by weight in cigarettes available in market, and about 95% of total alkaloids.^[1] It is highly toxic and typical agonist at nicotinic cholinergic receptors; it stimulates neurons in central nervous system and block synaptic transmission. In low doses nicotine causes ganglionic stimulation and blockage at high doses. Acetylcholine, dopamine, serotonin, beta-endorphin and nor-epinephrine neurotransmitters are released through nicotine CNS-stimulation activity due to which blood pressure will be elevated and also tachycardia, peripheral vasoconstriction are observed.

Nicotine is colorless or pale yellow colored with fish like scent when warm and tastes acrid and burning. IUPAC nomenclature of nicotine is 3-(1-methylpyrrolidin-2-yl)pyridine with a chemical formula $C_{10}H_{14}N_2$ and molecular weight 162.23156g/mol. Nicotine gets solubilized in alcohol, chloroform, ether, petroleum

ether, kerosene, oils and miscible with water below 60°C.^[1]

Nicotine consists of pyridine and pyrrolidine ring and it is a tertiary amine, it possesses an asymmetric carbon atom, thus exists in two enantiomeric compounds. It is largely levorotatory (S)-isomer, and 0.1%-0.6% is dextrorotatory (R)-isomer.

Mechanism of action

Nicotine attaches to nicotine cholinergic receptors (nAChR) in the central nervous system; as (R)-nicotine is present in small quantities in cigarette smoke when compared to (S)-nicotine it acts as a weak agonist at cholinergic receptors. After inhalation of smoke from cigarette, nicotine is distilled and carried into the lungs along with smoke particles where it is rapidly absorbed into the pulmonary venous circulation, and through arterial circulation it moves to the brain.^[2] By diffusion it enters the brain tissue and binds to nAChRs. The ligand gated ion channel opens allowing the access of cations such as sodium and calcium, and these cations additionally trigger voltage dependent calcium channels for more entry of calcium ions. Activation of nAChRs by nicotine results in release of various neurotransmitters such as acetylcholine, endorphins, serotonin, GABA,

nor-epinephrine along with dopamine which plays a key role in CNS stimulation. Dopamine release is assisted by nicotine mediated glutamate release, and with continuing treatment it is released by inhibition of GABA release. In addition to this unceasing smoking reduces brain monoamine oxidase A and B, which would augment monoaminergic neurotransmitter levels (Dopamine and Nor-epinephrine) in synapses, and thus effects of nicotine are increased which leads to addiction.^[3] Dopamine release gives pleasurable occurrence which makes it more difficult for reinforcement from drug abuse and addiction.

Pharmacokinetics

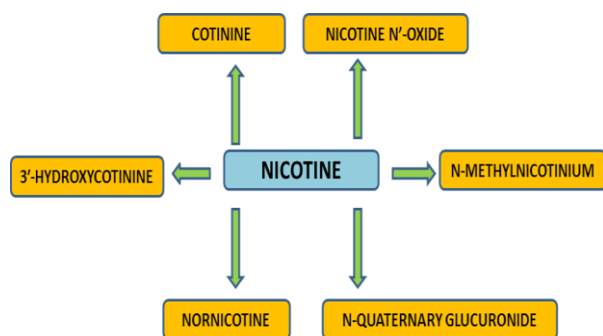


Figure 1: Metabolites of Nicotine.

Absorption

Nicotine is extracted through burning of tobacco and carried along with particulate matter to the respiratory system. Nicotine is a weak base with dissociation constant (pKa) of 8.0, this means that at pH 8.0, 50 percent of nicotine is ionized and 50 percent is non-ionized.^[3] In its ionized state, such as in acidic environments, nicotine does not rapidly cross membranes and absorption of nicotine is pH dependent.

Nicotine is swiftly absorbed when tobacco smoke reaches alveoli of lungs by which nicotine blood concentration increase rapidly within 10-20 seconds which is faster than intravenous administration and reaches to its peak after completion of smoking^[3]. This is probably due to large surface area of small airways and alveoli.

Nicotine is poorly absorbed from the stomach due to the acidity of gastric fluid, but is well absorbed in the small intestine, which has a more alkaline pH and a large surface area. Bioavailability of nicotine from the gastrointestinal tract (that is, swallowed nicotine) is incomplete because of pre-systemic (first pass) metabolism.

Nicotine is absorbed very well through skin, which makes it suitable for transdermal drug delivery system, but there is 1 hour lag time for the appearance of nicotine in bloodstream.

Distribution

Nicotine reaches the blood circulation at pH 7.4, where it is 69% ionized, 31% unionized and less than 5% is bound to plasma proteins. Volume of distribution is 2-3 L/Kg body weight, based on the study nicotine has highest affinity towards kidney, spleen, liver and lungs and low to adipose tissue. Nicotine has the higher receptor binding capacity in brain tissue of smokers when compared to non-smokers as smokers possess high nAChRs than non-smokers.^[4] Nicotine accumulates in gastric juice, plasma, saliva and also in breast milk due to ion trapping. It also crosses placental barrier and there is strong evidence that concentration of nicotine in amniotic fluid and fetal serum is high when compared to maternal serum.

Metabolism

Nicotine is metabolized in to number of metabolites by the liver in which six primary metabolites are; (figure 1)

1. Cotinine: It is a lactam derivative and in humans 70-80% of nicotine is converted into cotinine through two steps. The first step is mediated by CYP2A6 to form nicotine- $\Delta 1'(5')$ -iminium ion and 5'-hydroxynicotine, second step is facilitated by cytoplasmic aldehyde oxidase. Cotinine is further metabolized into 3'-hydroxycotinine, 5'-hydroxycotinine, 4-oxo-4-(3-pyridyl)-N-methylbutanamide, cotinine N-oxide, cotinine methonium ion, cotinine glucuronide, and nornicotine.
2. Nicotine N'-oxide: 4-7% on nicotine is metabolised into Nicotine N'-oxide through a flavin-containing monooxygenase 3 (FMO3), which forms two diastereomers, 1'-(R)-2'-(S)-cis and 1'-(S)-2'-(S)-trans-isomers. But only trans-isomer was detected in human urine samples, which indicate that some extent of N'-oxide may lead to recycling of nicotine.
3. N-methylnicotinium ion: It is also called as nicotine isomethonium ion which is formed by methylation of pyridine ring.
4. N-quaternary glucuronide: It is formed by glucuronidation catalyzed by uridine diphosphate-glucuronosyltransferase (UGT) enzyme(s) producing (S)-nicotine-N- β -glucuronide. 3-5% of nicotine is transformed to nicotine glucuronide and excreted in urine.
5. Nornicotine: A minute level of deuterium -labelled nornicotine is extracted in urine.
6. 3'-Hydroxycotinine: It is one of the key metabolite excreted through urine in humans and it is also eliminated as a glucuronide conjugate.^[4]

Excretion

Nicotine is extensively metabolized, primarily in the liver, but also to a small extent in the lung. Renal excretion of unchanged nicotine depends on urinary pH and urine flow, and may range from 2 to 35 percent, but typically accounts for 5 to 10 percent of total elimination.

Side effects

Cardiovascular: Increase in heart rate, blood pressure and PVC frequency has been reported. In patients with coronary artery disease, smoking may lead to coronary artery constriction. Tachycardia, arrhythmia, angina and myocardial infarction are associated with nicotine intake.

Respiratory: Pre-existing asthma patients experience bronchospasm while smoking and sore throat is also very familiar in smokers.

Gastro-intestinal: Nausea, dyspepsia, dry mouth and diarrhea are common side effects in 6% of patients. Some nicotine formulations may also cause flatulence, hiccups, increased saliva, dental disorders, stomatitis, glossitis and oral blistering.

Nervous system: 3% to 12% of patients were reported of headaches, sleep disturbances, unusual dreams, dizziness, irritability and tremor.

Musculoskeletal: Jaw pain, myalgias and arthralgias are associated with nicotine intake.

Hematologic: Increase in platelet aggregation and thrombus formation.

Blood circulation: Enlargement of aorta, atherosclerosis and platelet aggregation are common in case of highly habituated patients.

Hormonal (Endocrine): Insulin resistance and hyperinsulinemia.

Pregnancy: Pregnant women must avoid smoking because it may risk foetus life and after birth the infant may be diagnosed of diabetes-2, hypertension, respiratory defects and infertility.^[5]

Smoking

According to the World Health Organization tobacco kills nearly 4 million of population each year and the estimation is that 10 million smokers are going to be dead by 2030. Cigarette smoke consists of 4000 and over chemicals in which 69 are carcinogenic and 400 are toxins (Table No.1). Nicotine is the key ingredient emphasizes the smoking habit but do not cause mortality. Nicotine is addictive because it increases the levels of dopamine and it is responsible for pleasure feel. Tobacco consumption is a major cause of cancers. When people withdraw smoking habit, they face the nicotine withdrawal symptoms such as nervousness, irritability, insomnia, impatience, and increased appetite.^[6]

The toxicity of smoking is associated to added components of cigarette; it is mainly the pharmacologic action of nicotine that produces the obsession. Nicotine promotes satisfaction and reduces stress and nervousness. Smokers use it to adjust levels of provocation and to manage mood. Smoking improves

attentiveness, response time, and presentation of certain tasks. Aid from pulling out symptoms is probably the primary motive for this enhanced recital and heightened humor. Termination of smoking causes the materialization of withdrawal symptoms: irritability, dejected mood, agitation, and anxiety. The amount of these mood disturbances is comparable to that established in psychiatric outpatients.

Table 1: Chemicals found in tobacco smoke.

S.No	Chemical	Category
1	Acetone	Nail polish remover
2	Acetic acid	An ingredient in hair dye
3	Ammonia	Household cleaner
4	Angelica root extract	Causes cancer in animals
5	Arsenic	Rat poison
6	Benzene	An ingredient in rubber cement
7	Butane	Used in lighter fluid
8	Cadmium	It is an active constituent of battery acid
9	Carbon Monoxide	Present in car exhaust fumes
10	Cyanide	Deadly poison
11	DDT	A banned insecticide
12	Ethyl furoate	Causes liver damage in animals
13	Formaldehyde	Embalming fluid
14	Hexamine	Present in barbecue lighter fluid
15	Lead	Present in batteries
16	Naphthalene	An ingredient in mothballs
17	Maltitol	Sweetener for diabetics
18	Methanol	A key component in rocket fuel
19	Megastigmatrienone	Found in grape juice
20	Methoprene	Insecticide
21	Nicotine	Insecticide
22	Polonium	Cancer-causing radioactive element
23	Tar	Paving roads
24	Toluene	Paint manufacturing

Nicotine withdrawal

Nicotine withdrawal is connected with a depressing emotional condition, counting anxiety and the perception of increased strain. There is proof that the activation of the extra hypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor structure contributes to negative influence nicotine withdrawal. CRF activation produces anxiety behavior, and pharmacologic barrier of CRF1 receptors inhibits the anxiogenic effects of withdrawal.^[7]

Smoking termination (colloquially quit smoking) is the procedure of discontinuing tobacco smoking. Tobacco contains nicotine, which is addictive, which makes the process of quitting very prolonged and complicated. Smoking is the foremost unnecessary cause of demise worldwide, and quitting smoking drastically reduces the risk of dying from tobacco-related diseases such as heart disease and lung cancer^[8]. Seventy percent of smokers would will to quit smoking, and 50 percent details attempting to give up within the past time. Many diverse strategies can be used for smoking cessation, including quitting without assistance ("cold turkey" or cut down then quit), medications such as nicotine replacement therapy (NRT) or varenicline, and behavioral counseling. The greater part of smokers attempt to quit without

assistance, though only 3 to 6% of quit attempts without assistance are successful.^[9]

Use of medication and behavioral counseling both boost hit rates. Because nicotine is addictive, quitting smoking leads to symptoms of nicotine withdrawal such as craving, anxiety and irritability, depression, and weight gain.^[10]

The current established methods for smoking cessation include wide range of side effects (Table No. 2), but as a comparison sublingual or buccal thin films are a better choice due to minor side effects and fast release of nicotine which also avoids first pass metabolism.

Table 2: Smoking Cessation methods and side effects.

S.No	Method	Side Effects
1	Cold Turkey Method	No particular side effects but the method is not effective, it needs a support with medication.
Nicotine replacement therapy (NRT)		
2	Nicotine patches	Skin irritation, redness, itching, rash, Insomnia, vivid dreams, dizziness, racing heartbeat, headache, nausea, queasiness and muscle aches.
3	Nicotine Mouth Spray	Annoyance of the mouth and esophagus, increased saliva, nausea, dyspepsia, headache and hiccups.
4	Nicotine Lozenges	Nausea, hiccups, heartburn, flatulence, insomnia, dizziness, headache, cough, sore throat.
5	Nicotine gum	Hiccups and nausea, strong chewing can also cause jaw distress, bad taste, throat annoyance and a racing heartbeat
6	Nicotine Inhalator	Cough, irritation of mouth and throat, abdominal discomfort, nausea, hiccups and vomiting.
7	Nicotine strips	Mild nausea, throat irritation, hiccups and headache.
Stop smoking medication		
8	Zyban (bupropion)	Dry mouth, upset stomach, insomnia, headaches, difficulty concentrating, dizziness, drowsiness
9	Champix (varenicline)	Nausea and vomiting, headaches, insomnia, unusual dreams, increased appetite, constipation or diarrhea, swollen stomach, slow digestion, flatulence, dry mouth, tiredness, dizziness, drowsiness

Utilization of oral films has attracted significant consideration in therapeutic and nutra-ceutical applications.

Thin Film

Thin-film drug release has established as a superior substitute to the conventional tablets, capsules and liquids dosage forms. Thin films are similar in size, outline and thickness to a postal stamp, thin-film strips are classically designed for oral route of administration, with the consumer introduction of the strip on or under the tongue (sublingual) or along side of the cheek (buccal).^[11] These drug delivery alternatives permit the medication to circumvent the first pass metabolism by this means it makes the medication more bioavailable when compared to conventional dosage forms. Prolific inventors in the development of thin film drug delivery system include Richard Fuisz, Joseph Fuisz, Garry Myers and Robert Yang. These inventors have contributed over thirty patents in this area.



Figure 2: Buccal placement of thin film.

Advantages

Thin film offers numerous advantages above other modes of drug deliveries.

- The thin dissolving film has the potential for the advancement the onset of action, lesser the dosing,

and augments the efficacy and safety outline of the medicament.

- All tablet dosage forms, soft gels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to deprivation from stomach acid, bile, digestive enzymes and other first-pass effects. As a result, such formulations often require higher doses and usually have a delayed onset of action.
- Conversely, buccal and sublingual thin-film drug delivery can avoid these issues and yield quicker onsets of action at lower doses.
- Thin film is more stable, durable and quicker dissolving than other conventional dosage forms.
- Thin film provides improved dosing precision relative to liquid formulations as every strip is manufactured to contain a precise dose of the drug.
- Thin film can improve compliance due to the spontaneous nature of the dosage form and its intrinsic ease of administration. This behaviour is especially beneficial for pediatric, geriatric and neurodegenerative disease patients where appropriate and absolute dosing can be difficult.
- Thin film's ability to liquefy rapidly without the required for water provides an alternative to patients with swallowing problems and to patients suffer from nausea, such as those patients receiving chemotherapy.
- Thin film drug delivery has the probability to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations.

Disadvantages of Thin Films

1. High doses cannot be integrated.
2. Dose uniformity is a technical confront.
3. These films are moisture sensitive and expensive packing of oral film is required.

Standard composition of Oral Thin Films

Table 3: Standard Composition of oral thin films.

S. No	Category	Concentration (%)
1	Drug	1-25%
2	Hydrophilic Polymer	40-50%
3	Plasticizer	0-20%
4	Colors, Flavors, Fillers	0-40%

Choice of drug candidate includes the following characteristics:

- No bitter flavor or if it is then it must be covered.
- Good firmness in water and saliva.
- Dose should be as small as achievable up to 40 mg.
- It should be partly unionized at the pH of oral cavity.
- It must have the capacity to infuse the oral mucosal tissue.

Development of Oral Drug Strip

Polymer

The choice of film forming polymers is the mainly significant and critical consideration for the flourishing development of film formulation. The polymers can be formulated alone or in blend to present desired film properties.^[12] The polymers used in oral film formulation must be having the following parameters:

- Non-hazardous and nonirritant.
- Free of leachable impurities.
- Should not delay disintegration point of film.
- Should be tasteless.
- Should have fine wetting and stretch ability.
- Should have adequate peel, shear, and tensile force.
- Readily obtainable.
- Economical.
- Satisfactory shelf life.
- Should not assist in secondary infections in oral mucosa.

The physicochemical features of the polymer for film formulation play a critical role in determining the disintegration time of the thin film. Presently, both natural and synthetic polymers are used for preparation of fast dissolving oral film (Table No. 4).

Table 4: Classification of Polymers.

Polymer	Examples
Natural polymer	Pullulan, starch, gelatin, pectin, sodium alginate, maltodextrins, polymerized resin.
Synthetic polymer	Hydroxypropyl methylcellulose, sodium carboxy methylcellulose, polyethylene oxide, Hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, ethyl cellulose.

Plasticizer

Plasticizer is an important component of the thin films. Plasticizer helps to improve the elasticity of the strip and reduces the fragility. It considerably enhances the film properties by withdrawing the glass transition temperature of the polymer used. The choice of plasticizer will depend on its compatibility with the polymer and the kind of solvent engaged in the casting of the film. The pour of polymer will get improved with the application of plasticizer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are a few of the frequently used plasticizers.

Organoleptic additives

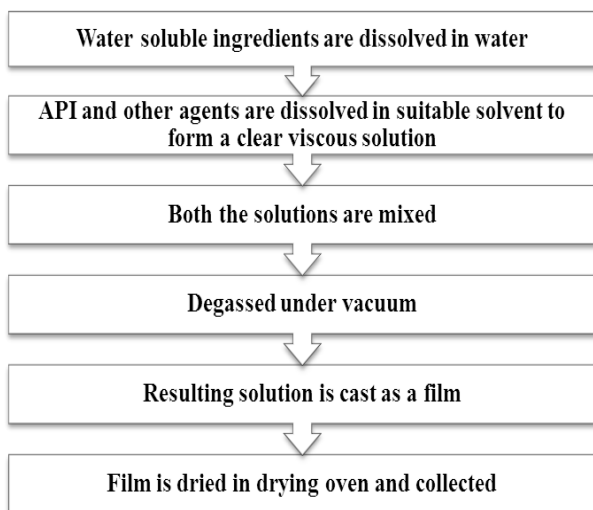
Sweetening, flavoring agents are added to mask the bitter taste of nicotine (Table No.5).

Table 5: Examples of Organoleptic additives.

Sweetening agents	Sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose, polyhydric alcohols such as sorbitol, mannitol and isomalt.
Flavoring agents	Synthetic flavor oils, oleo resins, peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary.
Coloring Agent	Titanium dioxide, silicon dioxide and zinc oxide.

Manufacturing Methods of thin films**Solvent casting method**

Fast dissolving films are preferably formulated using solvent casting method, whereby the water soluble ingredients are dissolved to structure a plain gelatinous solution and the drug along with diverse excipients is dissolved in an appropriate solvent then both the solutions are mixed and casted into the Petri plate and dried (Figure No.2).

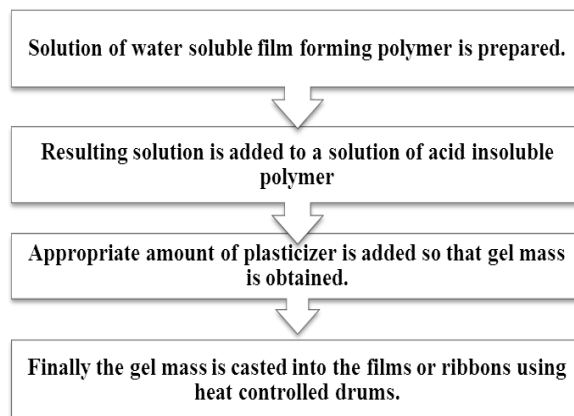
**Figure 3: Solvent casting method.**

An Oro-dispersible film of nicotine was successfully prepared through solvent casting technique using different grades of HPMC. In solvent casting technique, film forming polymer is usually soaked in an appropriate solvent for overnight^[13]. The type of API, which has to be incorporated in ODF, governs the selection of a suitable solvent depending on critical physico-chemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other Excipients is also brought under consideration before finalizing a formulation. During formulation, entrapment of air bubbles can hinder the uniformity of prepared films. Thus, desecration of the mixture is carried out with the help of a vacuum pump.

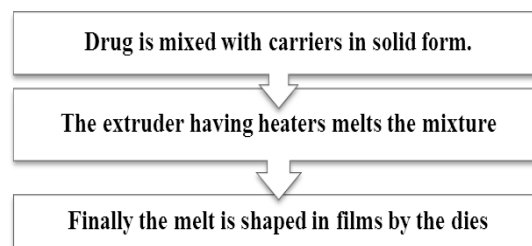
Semi-solid casting method

This technique is ideally embraced when acid insoluble polymers are to be used in the preparation of the films.

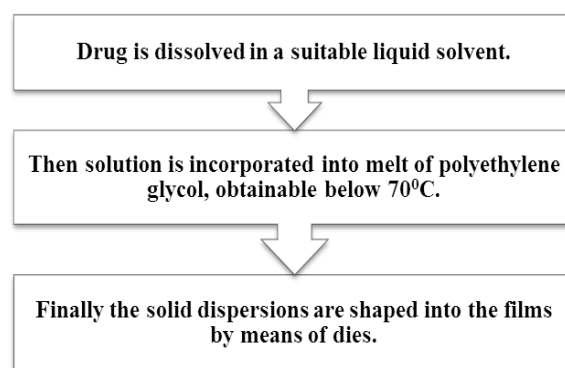
Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4 (Figure No.3).

**Figure 4: Semi-solid casting method.****Hot melt extrusion**

Hot melt extrusion is a technique in which a mixture containing drug, polymer and Excipients is extruded under high temperature to form a homogenous mass which is then casted to form smooth films.^[14] This is a solvent free process; however, the processing of thermo labile substances is a major drawback of this process due to the use of high temperature during extrusion (Figure.4).

**Figure 5: Hot melt extrusion method.****Solid dispersion extrusion**

Solid dispersion of domperidone using beta-cyclodextrin, PEG 400 and HPMC E15 was successfully prepared and films were casted using solid dispersion extrusion method (Figure No.5).

**Figure 6: Solid dispersion extrusion.**

Precautions while preparing solid dispersions

The selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol and polymeric form of drug precipitated in the solid dispersions may get affected by the liquid solvent used.

Rolling method

In this method the film is prepared by preparation of a pre-mix, the addition of an active and subsequent formation of a film (Figure No.6).

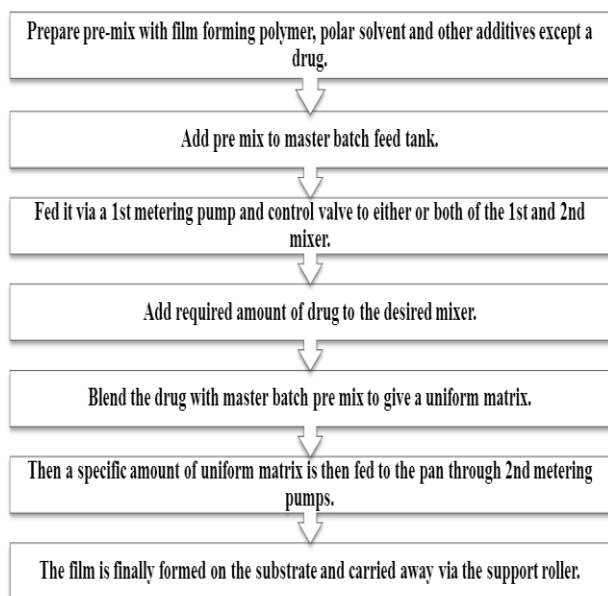


Figure 7: Rolling Method.

Spray technique

Drug substance, polymers and all other Excipients are dissolved in a suitable solvent to form a clear solution. This clear solution is then sprayed onto suitable material such as glass, polyethylene film of non-siliconized Kraft paper or Teflon sheet.

Evaluation

Organoleptic Evaluations

Formulated films are evaluated for organoleptic evaluations like Colour, odour and taste.

Weight Uniformity

Cut the cast film at different places and check the weight of each film was with the help of an electronic balance and then calculate average weight.

Thickness of Films

Thickness of a film is determined by means of calibrated digital micrometer and then consequently mean average is calculated. Generally, three readings from all the batches are determined and standard mean is calculated.

Folding Endurance

Folding endurance is a method to approximate the mechanical properties of a film. It is measured by repetitively folding a film at the same point until it breaks. Folding endurance value is number of times the

film is folded without breaking. Greater folding endurance value depicts the high mechanical strength of a film. A direct relation exists between mechanical strength and folding endurance of films.

Percentage Elongation

Upon exerting stress on a film, the sample stretches which is determined as strain. Strain is defined as change in length of film divided by its original/initial length of the film specimen. Percent elongation is related quantitatively to the quantity of plasticizer used in film preparation. Increased plasticizer quantity in the film generally results in increased elongation of the strip. It is determined by the following formula:

$$\text{Percentage elongation} = \frac{\text{Change in length}}{\text{Initial length}} \times 100$$

Disintegration Time

It can be performed by two methods for oral films

Slide frame method: one drop of distilled water was dropped by a Pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.^[15]

Petri dish method: 10 ml of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely. This test was done on randomly selected three films from each batch and average values were reported.^[16]

Surface pH

The surface pH of the films gets determined in order to study the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to maintain the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The 2 cm X 2 cm film was dissolved in 2 ml of distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and average values were reported.

Transparency

Transparency of a strip is determined by using a UV-spectrophotometer. This test is performed for visual appearance of the formulation. Film specimen are cut into rectangular shapes and placed on the internal side of the photometer cell. Transmittance of the film is worked out at 600 nm wavelength.

Swelling property

Replicated saliva solution is used to verify the swelling studies of films. Initial weight of film is determined and is placed in pre-weighed glass slide. This slide containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more

increase in weight. Degree of swelling is determined by these parameters:

$$\text{Degree of swelling} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}$$

Wt= weight of film at time interval t; W0 =weight of film at time 0.

Moisture uptake

Moisture uptake of a film is determined by first cutting the film with the dimension of 2X2 cm². Afterward these strips are exposed to environment with a relative humidity of 75% at room temperature for 7 days. Moisture uptake is determined as percent weight gain of the strips.

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Loss

Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterward, putting this film in desiccators for three days. Dessicator contains calcium carbonate^[12]. After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In-Vitro Drug Release

The in vitro dissolution study is carried out in stimulated saliva solution pH 6.4 phosphate buffer using USP paddle (Type II) apparatus at 37±0.5°C^[16]. Samples withdrawn at regular time interval are analyzed by UV-Visible spectrophotometer. By this method cumulative drug release and cumulative percentage of drug retained were calculated. The studies were carried out at 37°C with stirring speed of 75 rpm in 900 mL of pH 6.4 phosphate buffer dissolution medium. 5 ml of samples were withdrawn at predetermined time intervals of 5,10,15,20 minutes and replaced with the same volume of buffer. The samples were collected and the absorbance was determined using UV-visible spectrophotometer. Cumulative percentage drug release can be calculated by using the following formula:

$$\text{Concentration of drug } (\mu\text{g/ml}) = (\text{slope} \times \text{absorbance}) \pm \text{intercept}$$

Amount of drug released mg/ml

$$= \frac{\text{Concentration} \times \text{Dissolution bath volume} \times \text{dilution factor}}{1000}$$

Cumulative percentage release (%)

$$= \frac{\text{Volume of sample withdrawn (ml)}}{\text{bath volume (v)}} P(t-1) + Pt$$

$$\text{Dilution Factor} = \frac{\text{Solute volume}}{\text{Final volume}}$$

CONCLUSION

Nicotine is the main ingredient of cigarette, which has the tendency of addiction; this makes the base for the smokers hard to prevent smoking. Nicotine is a stimulator which not only gives pleasure but also affects many parts of the body, including lungs, airways and also brain. Variety of smoking cessation treatments are existing in the market such as gums, patches, lozenges, sprays, inhalers etc..., but majority of the treatments show side effects. In order to overcome the side effects nicotine thin films are used which provide fast and effective craving relief. The film is small, flavored, transparent dosages form which dissolves in mouth and when administered sub-lingual it avoids first pass metabolism. Thus thin films are considered as suitable dosage form for nicotine fast delivery which would also avoid first pass metabolism.

REFERENCES

1. Neal L. Benowitz, Janne Hukkanen, and Peyton Jacob, III: Nicotine Chemistry, Metabolism, Kinetics and Biomarkers, *Handb Exp Pharmacol*, 2009; 192: 29–60.
2. Elisabeth Stahl, Anne Lindberg, Sven-Arne Jansson, Eva Ronmark, Klas Svensson, Fredrik Andersson et al. Health-related quality of life is related to COPD disease severity. *Health and Quality of Life Outcome*, 2005; 53-56.
3. Svensson CK: Clinical pharmacokinetics of nicotine, *Clin Pharmacokinet*, 1987; 12(1): 30-40.
4. Feyerabend C, Ings RM, Russel MA: Nicotine pharmacokinetics and its application to intake from smoking, *Br J Clin Pharmacol*, 1985; 19(2): 239-47.
5. Aseem Mishra, Pankaj Chaturvedi, Sourav Datta, Snita Sinukumar, Poonam Joshi, and Apurva Garg: Harmful effects of nicotine, *Indian J Med Paediatr Oncol*, 2015; 36(1): 24–31.
6. Robert C Smith MD, Ph.D, Abhay Singh MD, Mauricio Infante MD, Amaresh Khandat MD and Angelica Kloos BA: Effects of Cigarette Smoking and Nicotine Nasal Spray on Psychiatric Symptoms and Cognition In Schizophrenia, *Neuropsychopharmacology*, 2002; 27: 479–497.
7. Neal L. Benowitz: Nicotine Addiction, *N Engl J Med*, 2010; 362(24): 2295–2303.
8. Anne Emilie Smith, Dana A. Cavallo, Amanda McFetridge, Thomas Liss, and Suchitra Krishnan-Sarin: Preliminary examination of tobacco withdrawal in adolescent smokers during smoking cessation treatment, *Nicotine Tob Res*, 2008; 10(7): 1253–1259.
9. C.Silagy, D.Mant, G.Fowler, M.Lodge. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *The Lancet*, 1994; 343(8890): 139-142.
10. Neal L Benowitz MD, Steven G Gourlay. Cardiovascular Toxicity of Nicotine: Implication for Nicotine Replacement Therapy. *American College of Cardiology Foundation*, 1997: 7; 29.

11. Cilurzo F, Cupone I, Minghetti P, Selmin F, Montanari L. “Fast dissolving films made of maltodextrins”. *Eur J Pharm Biopharm Nov*, 2008; 70 (3); 895-900.
12. Ding A, Nagarsenker M. “Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity”. *AAPS Pharm Sci Tech*, Feb. 2008; 9(2); 349-56.
13. Chen MJ, Tirol G, Bass C, Corniello CM, Watson G, Sanchez I. “Castable edible pharmaceutical films”. *Drug Del Tech June*, 2008; 8(6): 35-41.
14. Ali S, Quadir A, “High molecular weight povidone based films for fast dissolving drug delivery applications”, *Drug Del Tech*, June, 2007; 7(6): 36-43.
15. B Bhupinder, J Sarita, K Mandeep, S Harmanpreet. Orally Fast Dissolving Films: Innovations in Formulation and Technology. *Int. J. Pharma. Sci. Review Res*, 2011; 9(2); 50-7.
16. T Nishi, B Mayank, S Neha, Y Ghanshyam and K Pragati. Overview “A Novel Approach of Fast Dissolving Films and Their Patients”. *Advan. Biol. Res*, 2013; 7(2); 50-8.