



Tobacco: Its Conventional and Modern Dosage Forms in Medication

Tütün: Konvansiyonel ve Modern İlaç Dozaj Şekilleri

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ABSTRACT

Tobacco is one of the most planted products in worldwide and the whole *Nicotiana tabacum L.* plant, its leaves, flowers, seeds or roots, and individual chemical compounds have medicinal uses such as sedative, diuretic, or expectorant. From the past to the present, tobacco has been used in various dosage forms including oral/transdermal films, sublingual tablets, mouth/nasal spray, and inhaler. In addition, Tobacco is a very valuable plant with uses in medicine and bioengineering applications. In this review, it was aimed to give information about the tobacco plant and its medicinal uses and also the pharmaceutical dosage forms as well as novel delivery systems of nicotine compound of tobacco via comprehensively search method of the literature by using Pubmed, ScienceDirect, ISI Web of Knowledge, and Google Scholar databases for articles published in peer-reviewed journals from mostly 2016 to 2021. It is also aimed to draw attention to the pharmaceutical use of tobacco plant instead of potential harmful uses. In conclusion, there is need to be carried out new studies to enlighten the exact mechanisms of tobacco and its major compound of nicotine on other diseases such as schizophrenia, Parkinson's disease, and prose memory and attention than smoking cessation therapy and evaluate its safety and develop more effective novel pharmaceutical dosage forms.

Keywords: Tobacco, nicotine, pharmaceuticals, dosage forms

ÖZ

Tütün, dünya çapında en çok ekilen ürünlerden biridir ve tüm *Nicotiana tabacum L.* bitkisi, yaprakları, çiçekleri, tohumları veya kökleri ve tek tek kimyasal bileşikleri, yatıştırıcı, idrar söktürücü veya balgam söktürücü gibi tıbbi kullanımlara sahiptir. Geçmişten günümüze tütün, oral/transdermal filmler, dil altı tabletleri, ağız/burun spreyi ve inhaler dahil olmak üzere çeşitli dozaj formlarında kullanılmıştır. Ayrıca tütün, tıp ve biyomühendislik uygulamalarında kullanımları olan çok değerli bir bitkidir. Bu derlemede, Pubmed, ScienceDirect, ISI Web of Knowledge ve Google Scholar veri tabanlarında çoğunlukla 2016-2021 yılları arasındaki hakemli dergilerde yayınlanan makaleler kullanılarak kapsamlı literatür taraması yöntemi ile tütün bitkisi ve tıbbi kullanımları ve ayrıca farmasötik dozaj formları ve tütünün nikotin bileşiğinin yeni salım sistemleri hakkında bilgi verilmesi amaçlanmıştır. Ayrıca tütün bitkisinin potansiyel zararlı kullanımları yerine farmasötik kullanımına dikkat çekilmesi amaçlanmıştır. Sonuç olarak, tütünün ve ana bileşeni olan nikotinin sigara bırakma tedavisinden başka şizofreni, Parkinson hastalığı, Alzheimer hastalığı ve dikkat bozukluğu gibi diğer hastalıklardaki etki mekanizmalarının aydınlatılmasına, güvenliğinin değerlendirilmesine ve daha etkili yenilikçi farmasötik dozaj şekillerinin geliştirilmesine ihtiyaç vardır.

Anahtar Sözcükler: Tütün, nikotin, farmasötikler, dozaj şekilleri

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Introduction

Tobacco is one of the most planted agricultural products obtained from the leaves of the plants of the genus of *Nicotiana* of the Solanaceae family (nightshade family). The other known names of tobacco are Tamak, Siah (Marma), Tabaci, and Tabacca. It is economically, agriculturally, and socially a valuable plant (1,2). Tobacco grows all over the world but it is mainly native to tropical and subtropical America (1,2). There are more than 600 tobacco species worldwide and many of them such as *Nicotiana affinis*, *Nicotiana rustica*, *Nicotiana Sanderae*, *Nicotiana alata grandiflora*, *Nicotiana acuminata*, *Nicotiana Bigelovii*, *Nicotiana longiflora*, *Nicotiana noctiflora*, *Nicotiana suaveolens*, *Nicotiana sylvestris*, *Nicotiana Tabacum*, *Nicotiana wigandoides* are cultivated. However, *Nicotiana tabacum* and *Nicotiana rustica* are the species used for medicinal purposes (3).

The pharmacological activities of tobacco mostly come from the active compound of nicotine found especially in the *Nicotiana tabacum* species (1). *Nicotiana tabacum* is a perennial herbaceous and annual little branched plant. It grows up to 2 meters and has high large green leaves and long white-pinkish flowers (Figure 1). All parts of the plant are sticky because of the yellow-colored exudate containing nicotine (1).

There are many groups of compounds in the tobacco plant, such as alkaloids, essential oils, polyphenols, triterpenes, aromatic substances, fatty alcohols, and phytosterols (4-10). The important secondary metabolites found in some of the parts of tobacco are summarized in Table 1. The alkaloid constituents in tobacco are nicotine, nicotine, nicotimine, anabasine, anatabine, anattaline, and nornicotine which are found in the leaves of the tobacco plant (3,11). Among these, nicotine is the most active drug, which stimulates the central nervous system and causes addiction like heroin and cocaine. It is present in the moisture of tobacco



Figure 1. *Nicotiana tabacum* a) Leaves b) Flowers c) Seeds (<https://www.cabi.org/isc/datasheet/36326>)

leaf at different concentrations. Whereas the bright variety leaf contains 2.5% to 3% nicotine, the burley type tobacco contains 3.5% to 4% nicotine and the oriental type contains less than 2% nicotine (12). The chemical structures of the major constituents of nicotine, nicotinic acid and nornicotine of tobacco are given in Figure 2.

Tobacco is usually used worldwide in cigars and cigarettes, snuff, and pipe, and chewing gums (1,2). In modern times, tobacco is mostly used as a cigarette but there are many pharmacological activities of leaves, flowers, seeds, or roots. Nevertheless, the chemical compounds in cigarettes lead people to have serious cardiovascular or pulmonary diseases and different cancers. By the 20th century, it was presumed that chronic tobacco use was leading to serious health problems based on substance abuse and addiction (1,13). In this review, medicinal uses of the tobacco plant, and conventional and modern pharmaceutical dosage forms of its major compound of nicotine were summarized. It is also aimed to draw attention to the pharmaceutical use of tobacco plant instead of potential harmful uses.

Methods

Comprehensively search method of the literature by using Pubmed, ScienceDirect, ISI Web of Knowledge, and Google Scholar databases for articles published in peer-reviewed journals from mostly 2016 to 2021 and rare and older articles for the history part of tobacco were used. Because the initial search of the study was carried out at the beginning of 2021, the authors decided to search for literature published during the most recent 5 completed years. The search contained either the phrase “Tobacco dosage forms”, or the words “nicotine” along with “medication” or “dosage form” in any searchable field (i.e., title, abstract, or keywords). Four hundred sixty seven titles and abstracts were screened and 325 full-text articles were evaluated for assessment. Two hundred seventeen articles were excluded according to the eligibility criteria and remaining 108 articles were included. We followed a guideline named PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) when writing the review article (14). The authors decided together to choose the suitable articles based on their title and abstract and shared them equally. The risk of bias in the study was independently assessed by 3 review authors using Cochrane Collaboration’s tool (15). These domains were rated: sequence generating, allocation concealment, blinding of outcome assessment, incomplete



Figure 2. The chemical structures of nicotine, nicotinic acid and nornicotine of Tobacco plant (<https://pubchem.ncbi.nlm.nih.gov/>)

Table 1. The important secondary metabolites found in some of the parts of tobacco (4-10)

Leaves of the tobacco plant	Alkaloids; nicotine, nicotine, nicotimine, anabasine, anatabine, anatabine, and nornicotine Glucosides, tahacinin, tahacilin and isoquercitrin, 1-quinic, chlorogenic, caffeic, and oxalic acids
Roots	Anatabine and (+) nornicotine
Flowers	Quercetin-3,3'-dimethyl ether, quercetin-3-methyl ether, gibberellins-nicotiana α , β and γ and gibberellins A and A3
Seeds	Cycloartanol, cycloartenol 24-daturadiol, solavetivone, cholesterol, cholest-7-enol, 24-methylenecholesterol, campesterol, stigmasterol, sitosterol, 28-isofucosterol, lanosterol, 31-norlanosterol, lanost-8-enol, obtusifoliol, 31-norcycloartenol, cycloeucalenol, granisterol, citrostadienol, β -amyrin, lupeol, cycloartanol and 24-methylenecycloartanol

outcome data, selective outcome reporting and other sources of bias. Then, the overall risk of bias of each included study was evaluated as either: low (all criteria were of low risk), unclear (at least one criterion was evaluated to be of unclear risk but no criterion of high risk), or high (at least one criterion with high risk of bias).

Medicinal Uses of Tobacco

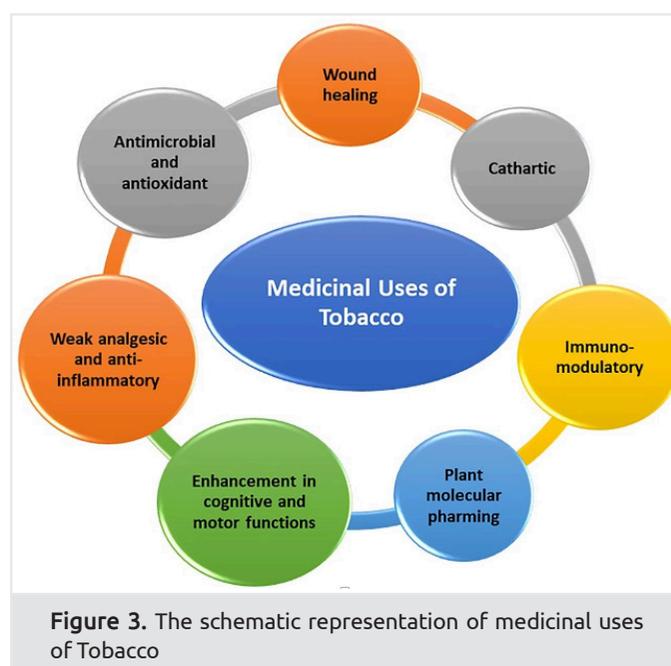
The whole tobacco plant, its leaves, flowers, seeds or roots, and individual chemical compounds have medicinal uses. It is used medicinally as a sedative, diuretic, expectorant, discutient, sialagogue, and internally only as an emetic when it is the only option. It is also a local irritant on the mucous membrane when chewed, causes sneezing as snuff, and acts as a cathartic when injected into the rectum. Tobacco smoke is good for strangulated hernia and obstinate constipation when injected into the rectum, tobacco leaf rolled into a suppository or in the form of enema of the leaves. It is also beneficial in the treatment of retention of urine, spasmodic urethral stricture, hysterical convulsions and worms, and inflammation of the peritoneum, tympanitis, and tetanus. For the treatment of croup and spasms of the rima glottides, tobacco is formulated as a plaster including snuff and lard and applied to the throat and breast. The leaves of tobacco are beneficial as an ointment for cutaneous diseases and used for obstinate ulcers, painful tremors, and spasms when combined with belladonna or stramonium leaves. In addition, the concentrated juice of tobacco relieves neuralgia. Its other external applications are for poisonous reptiles and insects bites, hysteria, pain, laryngeal spasm, gout, growth of hair, tetanus, ringworm, ulcers, and wounds. However, tobacco causes nausea, vomiting, sweats, drowsiness, and muscular weakness in high doses (16-18). The medicinal uses of tobacco are represented in Figure 3.

The main active compound of tobacco species, nicotine, interacts with nicotinic acetylcholine receptors which are transmembrane ion channels. These receptors are found in the autonomic and central nervous systems and at the neuromuscular junctions. When nicotine act with these receptors, different neurotransmitters are released. Nicotine enhances attention and the ability to concentrate on particular stimuli. So that, nicotine patches have been investigated for the treatment of mild cognitive impairment for a while (19-23).

In addition, nicotine is thought to have analgesic effects and efficacy against obesity (1). However, nicotine has various side

effects, especially in the digestive and circulatory systems. It causes palpitation, vascular contraction and arterial degeneration thus increase the risk of heart attack and stroke. When applied externally, it causes poisoning and might be even fatal (17,18,24).

It is shown that tobacco has some antimicrobial properties against various microorganisms. Sesquiterpenoid compounds and their glucosides obtained from tobacco have antibacterial activities (25). Nicotine and zinc complex are found to be more potent than zinc metal against different Gram (+) and Gram (-) bacteria (26). Aqueous and methanol extracts of the leaves of *Nicotiana plumbaginifolia* Viv (wild tobacco) exhibited good antibacterial activity on five human pathogenic bacteria: *Bacillus cereus*, *Bacillus fusiformis*, *Salmonella typhimurium* *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (18). In a study, silver nanoparticles were synthesized using tobacco leaf extract and showed antimicrobial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Pseudomonas vulgaris*, *Bacillus subtilis*, and *Staphylococcus typhi* (27). Tobacco has also antifungal activity due to the isoforms of chitinases and 1,3-glucanases against *Fusarium solani* germlings (28). *Nicotiana tobacum* also has antimicrobial activity against *Mycobacterium tuberculosis* (29). Also, tobacco leaves have antioxidant activity due to the flavonoids and phenolic

**Figure 3.** The schematic representation of medicinal uses of Tobacco

compounds contained in the plant (30,31). In a study, it was shown that bioactive extracts of the stem of *Nicotiana tabacum* also had antibacterial activity and antioxidant activity due to the presence of flavonoids in the stem (32). Besides, tobacco plant has antihelmintic activity against *Marshallagia marshalli* due to the alkaloids contained (18,33).

Tobacco plant affects peripheral and central nervous systems. The major compound of tobacco, nicotine, depresses all autonomic ganglia, evokes discharge of catecholamines in low doses, and prevents their release in higher doses. Nicotine stimulates the prejunctional sites in the central nervous system and results in a release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, and growth hormone. It is a weak analgesic in low doses, causes tremors to convulsions at toxic doses, and occasionally induces vomiting. The activation of the sympathomimetic response by nicotine contributes to the activation of chemoreceptors of the aortic and carotid bodies, causing vasoconstriction, tachycardia, and increased blood pressure. It limits the amount of blood reaching internal organs. Also, the activation of parasympathetic ganglia and cholinergic nerve endings by nicotine contributes to the increased tone and motor activity of the bowel (2).

Nicotine has anti-inflammatory effects after exposure following adipose, pulmonary, renal, and hepatic injuries. In recent studies, it has also been shown that tobacco has immunomodulatory effects by decreasing tumor necrosis factor- α and interleukin (IL)-1 levels that promote inflammation and increasing IL-6, IL-10, and transforming growth factor- β levels that reduce inflammation. In addition, nicotine stimulates angiogenesis and wound healing. Thereby, it may have an impact on peripheral nerve regeneration and functional recovery following injuries (2,34,35).

Nicotine affects exocrine glands leading to an initial stimulation of salivary and bronchial secretions and then followed by inhibition. The tobacco plant decreases red blood cell count, hemoglobin level, and platelet count. Also, it causes retarded increase in body weight due to the negative effects of the plant on the normal human metabolism and has anti-nociceptive activity through both central and peripheral nociceptive mechanisms (17).

Although tobacco smoking provokes many fatal diseases, there are some reports that cigarette users have a lower incidence of Parkinson's disease, Alzheimer's disease, and some psychiatric disorders such as schizophrenia, anxiety, and depression (36).

More recently, the tobacco has been used for plant molecular pharming, which is the cell culture and bioengineering application of using plants to produce human therapeutic agents. Tobacco is one of the plants, which has the ability for mass production of pharmaceuticals with less cost than traditional methods due to its short life cycle of 3 months from seed to seeding. Even more, tobacco is the first transgenic plant and usually referred as the "white mouse" of the plants due to its property of being amicable to genetic modifications for recombinant protein

production. In addition, it produces a plenty of biomedically important secondary metabolites such as alkaloids, flavonoids, terpenoids and phenylpropanoids. Firstly, human growth factor was generated with plant-by-plant pharming in tobacco plant. Then, immunoadhesin (DPP4-Fc) protein was obtained from tobacco plant and used against the virus of MERS-CoV infecting lung cells. In addition, many vaccines against malaria, anthrax, hepatitis and influenza were produced in tobacco. Recently, a plant defensin (NaD1), a cationic antimicrobial peptide, was obtained from the flowers of *Nicotiana glauca* and showed good antifungal activity against pathogenic fungi (2,4,37,38).

Despite the medicinal effects of tobacco, it is one of the major public health problems and tobacco smoking is the most common addictive behavior worldwide. Nicotine leads to addiction similar to heroin and cocaine. In addition, tobacco is responsible for more than 3 million deaths a year worldwide. After inhalation of tobacco smoke, nicotine reaches most of the organs in the body too fast. Especially, it increases blood pressure and may cause thrombosis and atherosclerosis in smokers. There are many attempts to stop tobacco smoking worldwide. In nicotine replacement therapy, many other toxic compounds of tobacco smoke such as polycyclic aromatic hydrocarbons and N-nitroso compounds, acrolein, benzene, formaldehyde, ammonia, acetone, acetic acid, and carbon monoxide are separated (3,12,16,39).

Pharmaceutical Dosage Forms of Tobacco

There are many nicotine delivery forms on the market to help quit tobacco smoking. Such forms include chewing gums, sublingual/buccal tablets, capsules, lozenges, oral films, transdermal/mucoadhesive patches, mouth spray, nasal spray, and inhaler (40,41). The aim of stopping smoking is to reduce the death and diseases related to tobacco use. Smokers usually have nicotine withdrawal syndrome after quitting smoking and this condition may be prevented or its effects may be minimized using medicinal nicotine delivery systems. Also, there are many novel nicotine delivery systems in the literature, which have been developed either for nicotine replacement therapy/nicotine vaccination or for medicinal uses of nicotine on the cardiovascular system, the central nervous system diseases, and others (40,42-47). This section reviews conventional and newly developed dosage forms of medicinal nicotine according to their application routes. Also, novel nicotine delivery systems are summarized in Table 2.

Oromucosal Nicotine Delivery Systems

Nicotine replacement therapy can help people to quit smoking by releasing only nicotine, which is found in cigarettes. Medicated chewing gum is an oromucosal dosage form for obtaining systemic drug delivery. The Food and Drug Administration approved the use of nicotine chewing gum as a smoking cessation aid in 1984 and its non-prescription sale in 1995. It is available on the market as either 2 or 4 mg per gum. Nicotine gums release nicotine in a controlled manner but most of the drug is released within the first half an hour. Then, nicotine is absorbed through the buccal mucosa to obtain plasma concentration

Table 2. Novel nicotine delivery systems

Application route	Dosage form/delivery system	Reference
Oromucosal	Medicated chewing gum	(50)
		(51)
		(52)
	Lozenge	(54)
		(64)
		(65)
	Tablet	(58)
		(59)
		(60)
		(61)
		(62)
	Oral soluble film	(63)
	Buccal patch	(66)
Wafer	(67)	
Mouth spray	(71)	
	(72)	
	(73)	
	(74)	
	(75)	
Solid lipid nanoparticles	(76)	
Electrospun nanofibers	(77)	
Microparticles	(70)	
Transdermal	Transdermal patch	(79)
		(82)
		(83)
	Molecularly imprinted polymers	(92)
	Microneedles	(93)
Carbon nanotubes	(94)	
	(95)	
Nasal	Nasal gel	(101)
	Nasal spray	(101)
		(104)
		(105)
Powder	(103)	
Pulmonary	Dry powder inhaler	(107)
		(108)
		(109)

levels, which are half of the levels after tobacco smoking. When formulating medicated chewing gums, some excipients are included in the formulation such as gum base, filler, softeners, sweetening agents, flavoring agents, and emulsifiers (45,48-50). The unpleasant taste of nicotine and burning sensation were reduced by adding mint flavor to the gum formulations (51). In another study, the unpleasant taste of nicotine chewing gums was enhanced by using aspartame as sweetener, cherry and eucalyptus as flavoring agents, and sugar as a coating agent. In addition, the chewing gums released 79-83% of nicotine within the first 20

minutes (52). In addition, in some cases, even faster nicotine delivery might be desirable for faster craving relief. In a study, the developed gum formulations released nicotine in the first 10 minutes (53).

Nicotine polacrilex lozenges are over-the-counter nicotine replacement therapy products, which are found as 2 or 4 mg on the market. The nicotine lozenges usually dissolve faster than nicotine polacrilex gums, thereby deliver more nicotine and have more plasma concentrations. However, in a study comparing the safety of 4 mg nicotine lozenges and 4 mg nicotine gums, it was found that the lozenges were similarly well tolerated as the gums and had no worsening effect on the patients with cardiovascular diseases (54).

In order to investigate another usage of nicotine rather than nicotine replacement therapy, patients who received 2-mg nicotine included chewing gum (2 mg/gum) or normal chewing gum and then they were compared in terms of gastrointestinal recovery and prevention of prolonged postoperative ileus after colorectal surgery. It was found that the pain in the first three postoperative days was relieved but there was a need to carry out more studies to reveal the effects of nicotine gum on bowel recovery after surgery (55).

The buccal route has always been the most advantageous route for nicotine administration since the drug can reach the systemic circulation without being degraded by gastrointestinal and hepatic first-pass metabolism (56,57). Sublingual/buccal tablets are other conventional dosage forms designed for nicotine delivery into the oral cavity. In this context, nicotine-β-cyclodextrin complex loaded tablets were prepared. When nicotine-β-cyclodextrin complex dissolved, free nicotine was released from the tablet formulation and penetrated through the oral mucosa (58). In another study, buccal bioadhesive tablets of nicotine were developed. Carbomer and sodium alginate were used as bioadhesive polymers in combination with hydroxypropyl methylcellulose and magnesium carbonate was added into the formulations as a pH-increasing agent. It was observed that these formulations released the drug during 8 h period (59). Indeed, 20% w/w Carbopol and 20% w/w hydroxypropyl cellulose tablets were developed as biphasic buccal adhesive tablets. The bilayer tablets which contained an adhesive controlled release layer and a fast release layer provided an initial burst release of nicotine followed by the controlled release for a period of up to 4 h (60). Moreover, in another study, various biocompatible polysaccharide polymers such as xanthan gum, karaya gum, guar gum, and glycol chitosan were evaluated as mucoadhesive controlled release excipients in mucoadhesive tablet formulations for buccal drug delivery. The strongest adhesion was obtained with glycol chitosan and guar gum was a poor mucoadhesive where xanthan gum and karaya gum had strong mucoadhesive properties (61). Kanjanabat et al. (62) prepared nicotine-magnesium aluminum silicate complex-loaded sodium alginate matrix tablets for buccal delivery. Magnesium aluminum silicate is a mixture of montmorillonite and saponite clays and forms complexes with nicotine via ionic interactions and thus controls nicotine delivery. The results also indicated that sodium alginate

had an important role in enhancing the mucoadhesive properties of the tablets.

Fast-dissolving oral delivery systems are solid dosage forms that dissolve rapidly in the oral cavity (less than 1 min) without drinking or chewing (63). Rather than chewing gums, lozenges and oromucosal tablets or buccal patches offer rapid delivery of nicotine into the mouth and thus provide a faster craving relief (64-66). Du et al. (64,65) compared a product of 2.5 mg nicotine oral soluble film with 2 mg nicotine lozenge and 2 mg nicotine gum, which were available on the market. The results confirmed that nicotine film enabled faster craving relief than the other dosage forms due to the rapid delivery of the full dose of 2.5 mg nicotine in 2 to 3 minutes. Cilurzo et al. (63) developed fast-dissolving films made of low dextrose equivalent maltodextrins loaded with 0.5 mg nicotine and mint or milk as a flavor in the formulation. The developed films disintegrated within 10 s and neither mint nor milk flavor did not affect the tensile properties of the films.

The free base of nicotine is volatile and prone to oxidative degradation (67). There are many studies in the literature to overcome these challenges of nicotine. In a study, tri-layered buccal mucoadhesive nicotine base or polacrilex patch formulations consisting of a thin dry tablet and a bi-layered mucoadhesive film were developed. The trilayered patch formulations enabled rapid initial drug release especially for nicotine base in 30 min and fast-to-slow permeation rates (66). Also, Pongjanyakul et al. (68-70) prepared sodium alginate–magnesium aluminum silicate and chitosan-magnesium aluminum silicate films loaded with nicotine. The films presented mucoadhesive properties and strong potential as buccal nicotine delivery systems. Whereas films are extensively used in buccal drug delivery systems and prepared by a solvent evaporation method, wafers are other drug delivery systems, which are prepared by the freeze-drying method. Hydroxypropyl methylcellulose and sodium alginate film and wafer formulations are prepared to improve nicotine stability. An anionic polymer of sodium alginate forms strong electrostatic interaction with the cationic nature of the mucin and thereby demonstrates mucoadhesive property. Hydroxypropyl methylcellulose also contributes to the design of a controlled nicotine delivery system (67). In the subsequent studies, the physicochemical properties of nicotine-loaded hydroxypropyl methylcellulose and sodium alginate films and wafers were stabilized with magnesium aluminum silicate. The formulations released showed high permeation flux for both porcine and the buccal tissue and enhanced the functional physical properties such as hydration, swelling, and release (71).

For faster nicotine replacement therapy, another nicotine delivery dosage form is mouth spray. There have been studies in the literature, which are evaluating the efficacy of the spray formulations. Nicotine mouth spray was found to be very potent and preferred over the nicotine gum and inhaler. However, some local side effects such as mouth irritation, nausea, and hiccup were seen by mouth spray formulation containing 1 mg nicotine per actuation (72). Kraiczi et al. (73) evaluated the pharmacokinetics of nicotine at three different doses of the mouth spray (4 mg, 2

mg, and 1 mg per actuation) and compared the nicotine uptake from the spray versus nicotine lozenge and gum. Nicotine was absorbed faster for all doses of nicotine of the mouth spray than either lozenge or gum and maximum plasma concentration was reached in a shorter time with the spray. In the clinical studies, Tonnesen et al. (74) demonstrated that 1 mg nicotine mouth spray was efficacious and safe for smoking cessation with a rate of 2.48 compared to placebo regarding abstinence at 1 year. In another clinical study, 1 mg nicotine mouth spray plus nicotine patch showed significant enhancement in prolonged abstinence during 6 months (75).

When nicotine is administered as a solution such as a mouth spray, it is distributed in the mouth by the effect of saliva and mostly swallowed. In order to decrease the adverse effects of nicotine after entering the gastrointestinal tract and obtain a localized delivery in the oral cavity, nicotine may be incorporated into a nanocarrier system. The small size of the dosage form results in fast nicotine release due to the enhanced specific surface area and therefore fast oromucosal absorption. Ding et al. (76) prepared an oromucosal formulation of lipid-drug-conjugates containing solid lipid nanoparticles, which were prepared with Kolliwax® S, and stearic acid as a counter-ion and hydrogenated sunflower oil (HSO) as lipid particle matrix were used. In addition, the high encapsulation efficiency of nicotine, which was a hydrophilic drug, was obtained in the carrier. Thereby, the developed formulation retained nicotine in the oral cavity and enabled fast absorption. In another study, α -lactalbumin/polyethylene oxide electrospun nanofibers containing nicotine were prepared for oromucosal nicotine replacement therapy. Nanofibers released nicotine faster than two relevant marketed formulations of lozenge and sublingual tablet due to their high surface area property (77). Nicotine base can interact with a negatively charged clay, magnesium aluminum silicate, electrostatically and form microparticles. In a study, high molecular weight chitosan was adsorbed to the surfaces of these microparticles and obtained a positive surface charge. Thereby, mucoadhesive properties of the particles were enhanced and nicotine had high oromucosal permeation (70).

Transdermal Nicotine Delivery Systems

The transdermal delivery system carries drugs through the skin into the blood circulation at a predetermined rate. It is accepted as an alternative route to oral and intravenous delivery. The advantages of this route are lower systemic exposure and thus lower systemic targeted delivery, and lower systemic toxicity than oral/oromucosal routes. Nicotine can easily permeate and absorb through the skin, reach blood vessels and then pass the blood-brain barrier when applied topically. Transdermal nicotine delivery systems are mostly used in smoking cessation programs. In this route, nicotine is released from transdermal dosage forms in a sustained manner (78). The amount of nicotine, which is equivalent to that delivered by a single cigarette, is absorbed transdermally in 3-4 h. Also, nicotine absorption may be enhanced by using skin penetration enhancers in novel nanocarrier systems (79-81).

There are available transdermal patches on market, which are releasing nicotine with polymer matrix diffusion (82,83). Nicotine included 15, 30, and 45 mg doses nicotine-patches on the market were evaluated in terms of safety profiles and it was shown that the use of high doses of transdermal nicotine was safe in dependent smokers and could reduce exposure to the other toxicants of tobacco (84). In another study, 21 mg transdermal nicotine patch was examined on the hypertensive smokers and it was found that transdermal nicotine was safe for short-term exposure in mildly hypertensive smokers (42). Moreover, transdermal patches were found to minimize weight gain which was mostly seen in people who successfully quit smoking (85).

In the past, proliposomes of nicotine were prepared and applied in the form of patches. Sustained nicotine release was achieved since proliposomes acted as a release rate controlling dosage form (86). In a study, a transdermal patch was prepared by forming an inclusion complex between nicotine and β -cyclodextrin. Cross-linked polyvinyl alcohol was used as a rate-controlling membrane in the patch and a zero-order controlled release system was obtained (87). In another study, polyethylene membrane was used as a rate-controlling barrier and carbomer was used as the gel reservoir, which provided sustained release of nicotine with an easy application (88). Also, transdermal patches of nicotine were successfully prepared by using the polymers in the concentrations of 4%, 1.4%, 0.5%, and 0.8% of Eudragit® E100, HPMC E5, PEG4000, and PVP K30, respectively (89). In another study, a drug-in-adhesive patch of nicotine was prepared successfully using an ion-pair strategy, enabling a dual release of nicotine which was a promising strategy to regulate drug release profiles from the patch (90). Pichayakorn et al. (91) used a heat-sealing technique for the developed reservoir-type nicotine transdermal patches, which were composed of a concentrated nicotine solution embedded between a backing layer and deproteinized natural rubber as a controlling layer membrane. The transdermal patches were stable under storage in a tightly sealed container at 4 °C or ambient. Molecularly imprinted polymers are one of the carriers that can be used for the controlled transdermal delivery of nicotine. In a study, molecularly imprinted polymers of nicotine were synthesized by a free radical polymerization method using methacrylic acid as the monomer and ethylene glycol dimethacrylate as the cross-linker (92). More recently, Panda et al. (93) prepared nicotine-loaded microneedles using a mold casting method with polyvinylpyrrolidone as the water-soluble polymer. The microneedles presented immediate nicotine release within the first hour and enabled a potential pain-free and minimally invasive treatment option for nicotine replacement therapy.

Indeed, carbon nanotube membranes in the form of a switchable transdermal drug delivery device were developed. These devices enabled programmable delivery rates with minimal skin irritation and no skin barrier disruption (94) and improved smoking cessation treatments (95). In a study, a new computer-operated delivery system for time-controlled pulsatile transdermal delivery

of nicotine was evaluated in phase I clinical trial. The device was programmed to deliver two pulses of drug within 16 hours with three delivery rates and was found to be efficient in smoking cessation for an individualized therapy (96). Moreover, Gulati et al. (97) developed a switchable carbon nanotube membrane device for transdermal nicotine delivery that could be programmed to deliver variable doses matching those of nicotine patches (7, 14, and 21 mg/24 h) and nicotine gums (2 mg/4 mg). It could adjust nicotine dosing between craving and withdrawal blood plasma levels for smoking cessation therapy.

Other than nicotine replacement therapy, transdermal nicotine patches were evaluated for the treatments of central system disorders. The patches enabled improvement in diseases such as schizophrenia, Parkinson's disease, and prose memory and attention (43,44,98). In a study, transdermal nicotine delivery (15 mg/16 h) in the patch form was found as effective and safe in acute pain relief after laparoscopic cholecystectomy surgery (99).

Nasal and Pulmonary Nicotine Delivery Systems

The nasal route for nicotine delivery enables faster action via passing to the systemic circulation than other routes of nicotine administration (oral or transdermal) (100). The first nicotine formulation was developed in the form of a gel consisting of a 0.1 mL droplet of 2 mg of nicotine in a 2% aqueous solution and a cellulose derivative was used to increase the viscosity. In order to enhance absorption, decrease nasal irritation with the gels, and increase acceptability, nicotine was formulated as a nasal spray (101). Later, proliposome formulations of nicotine were prepared for intranasal administration to obtain prolonged delivery to the systemic circulation (102). Another nasal formulation, in the form of nicotine-Amberlite resin complex powder was developed thus a combined pulsatile and sustained plasma nicotine profile for smoking cessation was obtained (103). Also, it was shown that nicotine sprays might modestly enhance attention and spatial working memory in schizophrenic patients who were chronic smokers (104). In another study, 3 mg nicotine nasal spray was found to decrease pain during the 5 days after third molar surgery (105).

The pulmonary drug delivery route is the direct access of drug to the target area with lower doses. Drugs are absorbed in a very short time after inhalation. Because the lungs have high permeability and large absorptive surface area (approximately 70-140 m²) and a good blood supply (106). Wang et al. (107,108) developed nicotine hydrogen tartrate nanoparticles in the form of inhalable micro-aggregates of biodegradable chitosan for pulmonary delivery of nicotine from dry powder inhaler formulations. Nicotine hydrogen tartrate was released from the formulations with a burst release in the first 8 h and then with a prolonged release. More recently, the activity of controlled release nicotine from dry powder inhaler formulations was assessed via the locomotor activity of C57BL/6 mice. The results revealed that the inhaled nanoparticles were a preclinical option for developing novel inhalation formulations as a potential anti-smoking therapeutic (109).

Conclusion

Tobacco is a very important plant that is grown worldwide and has many medicinal uses from the past to the present day despite having many toxic effects on the body when used as a cigar/cigarette or e-cigarette. Various dosage forms were developed and took place on the market of tobacco or its compounds. Besides its medicinal uses as a sedative, diuretic, expectorant, and antimicrobial, tobacco is also used for plant molecular pharming to produce human therapeutic agents, which makes it a much more valuable plant in terms of cell culture and bioengineering applications. Indeed, the major compound of nicotine is mostly used in smoking cessation therapy in a variety of dosage forms for different routes of administration such as oral, sublingual, transdermal, nasal, or inhaler. The recent studies indicate that nicotine is not only used in smoking cessation therapy and also is a potential compound for the treatments of central system disorders such as schizophrenia, Parkinson's disease, and prose memory and attention, and also in acute pain relief after surgeries. In conclusion, there is a need to carry out new studies to enlighten the exact mechanisms of tobacco and its major compound of nicotine on these diseases, evaluate its safety, and develop more effective novel pharmaceutical dosage forms.

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