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Mechanism and Fate of Nicotine Based Transdermal Drug Delivery Systems

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ABSTRACT

In general, nicotine-based transdermal drug delivery systems are found to be safe and efficient support in smoking termination. Studies have shown that nicotine replacement therapy has significantly reduced the sternness of withdrawal symptoms and conquer the habit of smoking. The safety concerns of all these products have been established in more or less all parts of the populace. Currently, four nicotine-based/incorporated transdermal delivery systems are available in the market, and even though they transport analogous daily doses of nicotine they vary notably in their nicotine release rates and pharmacokinetic behavior and therefore cannot be measured bioequivalent or compatible. The consequences of these differences in clinical applications are yet to be recognized, and further assessments using similar study protocols are required for direct similarities. Apart from this, three varying types of dosage forms are presently obtainable commercially for nicotine replacement therapy such as chewing gums, nasal sprays, and transdermal patches. In the present review, we have focused on the mechanism, consequences, and significant uses of transdermal based drug delivery systems of nicotine.

INTRODUCTION:

Nicotine (NT) is found as a chief therapeutic component in tobacco, which acts as a prime source in maintaining cigarette smoking [l-3]. On basis of such pieces of information, few experiments regarding the reduction of smoking frequency and termination have led to establishing a pure form of NT in place of NT attained from tobacco. It has been observed that replacement with pure NT could be helpful in the reduction of ingestion of carcinogenic substances, available in the smoke components and also harmful volatile compounds including carbon monoxide, hydrogen cyanide, and formaldehyde [4]. Various studies have been performed regarding the consequences of different routes of administration of NT such as oral, intravenous (i.v), buccal, and it has been observed that all the routes significantly suppressed cigarette smoking to some extent. The conventional type of tobacco and its intake through smoking in women during the pregnancy stage has always been a matter of concern and affected the public worldwide. Countries like Ireland, Uruguay and Bulgaria have been reported to exhibit the highest number of women affected by tobacco smoking, whereas countries like Tanzania and Sri Lanka have been reported to have the lowest. Apart from this, the ratio of women affected by tobacco smoking in Asiatic countries is also found to be quite significant i.e. approximately 30% [5,6]. More than four thousand types of different chemical entities have been found in the cigarette smokes obtained through conventional tobaccos and some around a hundred of these chemical entities have shown severe toxic effects towards the health [7]. During pregnancy, if a women frequently intakes tobacco through smoking or either source then could lead to severe health issues including infertility, miscarriage, premature delivery of newborn, intrauterine growth constraints, and abrupt infant death syndrome [8,9]. Apart from direct smoking, post natal secondhand smoking is associated with several health disorders in women such as delay in the development of the infant, behavioral issues such as mood swings, irritations, aggressions and many others [10, 11]. One of the cases has been reported where patients in the age group of 6-12 were reported to have neuro-sensorial hearing loss due to infection in the cochlear portions of the ear and the major cause of these issues was secondhand smoking [12]. Thus, it is very important to control the mishaps caused in pregnant women or the local public due to either tobacco smoking or secondhand smoking with the highest priority and should be involved in scheduled practices of prenatal controls.

First-line approaches for the termination of NT such as individual counseling and behavioral therapies are safe and effective [13]. NT-based delivery systems involve those approaches

that are useful for replacing the effects of NT. These delivery systems include sublingual tablets, transdermal patches, gums, sprays, inhalers, etc. Apart from these approaches, another technique i.e. electronic-NT delivery systems (E-NDS) have been found very significant. In this method NT is directly delivered within the body with fewer toxic substances as compared to the toxic tobacco leaves [14]. In existing guidelines, NRT which is utilized at the pregnancy stage has remained to be as controversial; however, it is recognized as a less injurious substitute as compared to the conventionally available tobacco smoking [15]. In earlier 2010, in countries like China, United States, and European countries, electronic NDS or electronic cigarettes were introduced as a substitute for tobacco-based cigarettes [16]. In 2016, the Food and Drug Administration (FDA) mentioned electronic NDS as tobacco-mediated products. The electronic NDS is comprised of a microprocessor, a battery, a heating component, and a fluid-entailing reservoir. The amount of NT and a transporter fluid (mostly 1, 2-propanediol) are presented in the reservoir. Both NT and transporter fluid substances are initially heated leading to the production of the mixed vapors and finally breathe in by the user. In recent days, new devices such as the JUUL electronic cigarette comprised of a prefilled liquid cartridge, a battery, and a temperature regulating tool. Furthermore, they utilized NT-based salts to imitate the NT "hit" of conventional cigarettes [17]. Electronic-based NDS are occasionally utilized to assist smoking termination, but their enduring efficiency and protection remain indistinct [18]. Usage of electronic-based NDS demonstrated an almost 7-fold greater risk to initiate smoking conventional cigarettes amongst the adolescents, but it remains uncertain if this enhancement could cause by the electronic-based NDS utilize itself or by an improved motivation to experimentation with proscribed materials [19]. In 2015, a survey was conducted amongst pregnant women and it was found that almost 45% of these women considered electronic-NDS as less injurious for the newborns rather than the traditional tobacco-based cigarettes [20, 21].

Pharmacokinetics NT and NT-based delivery systems

In 1970, the first pharmacokinetic study related to the NT was conducted in humans, and afterward, a huge number of studies were conducted which showed that the potential therapeutic activities of NT [22]. In the pharmacokinetic analysis of NT in blood, various parameters such as C_{max} (maximum level NT found in the blood), T_{max} (time at which maximum level of NT is found in the sample) and AUC (area under the curve) plays a crucial role in detecting the total NT in a sample at the respective time. As soon as NT reaches the body, it gets absorbed via diverse mucous cell membranes based on the pH. It has been

noticed that NT, as a weak base (pKa = 7.9), does not cross-over the membranes in an acidic environment because of its ionized state. Though, at the physiological blood pH (7.4), almost 35% of NT is non-ionized and could significantly cross through the plasmatic membranes [23]. Therefore, it has been found that the most potential and competent route of absorption of NT in the human body is through direct smoking because through smoking NT gets directly entered into the circulatory system through the large alveolar-capillary boundaries and arrives in the brain within few seconds [24]. NT circulations after oral, nasal, or transdermal absorption generate, in disparity to breathing, a steady enhancement in the concentrations of NT within the brain [25]. NT is usually metabolized to cotinine within the liver, primarily by the cytochrome P450 2A6 enzyme (CYP2A6) and to a minor amount by cytochrome P450 2B6 enzyme (CYP2B6) and cytochrome P450 2E1 enzyme (CYP2E1) [26]. It is very interesting to note that the rate of metabolism of NT is quicker in women as compared to men, and even much sooner in pregnant women [27].

NT-based transdermal drug delivery systems

NT-based transdermal drug delivery systems have shown considerable improvement in the effective delivery of NT in the body through various membranes. Some of the significant works have been discussed. Linakis et al. utilized the population pharmacokinetic methods for demonstrating this inconsistency, mainly when it pertains to the assimilation of NT from the transdermal patches. In this study, randomly a population of 25 candidates was selected who were further treated with transdermally applied doses of nicotine. Results of this study showed that the pharmacokinetic profiles of NT were best explained with a one-compartment model with assimilation dependent upon a Weibull distribution and first-order elimination [28]. Godage et al. developed and established a novel method of solid-phase micro extraction-liquid chromatography-tandem mass spectrometry method for the finest estimation of NT and its four main metabolites (cotinine, norcotinine, norNT, and anabasine) from the plasma samples collected from the rabbit models. Dual fiber extraction techniques were attained to assure the utmost recovery of the analytes. Apart from this, a tandem mass spectrometry technique was attained to detect and quantify in the positive electrospray ionization (ESI+) mode concerning all the target analytes. Results showed that the method was very helpful in the significant identification of all the components in the rabbit plasma samples. As compared to all other derivatives, NT was found to be the most in the plasma samples [29]. Ahrens and Thiel examined the potential consequences of the cholinergic agonist NT modulates in healthy human candidates. It was suggested that NT did not

significantly affect the treated human volunteers in balancing stability and flexibility [30]. La count et al. developed a combined approach including experimental and computational models for assessing the effects of heat over the delivery of NT from transdermal delivery systems in vitro. Results showed that with the increase in the temperature of the skin surface, a 2-fold increase was observed in the average NT flux. ANOVA statistical analysis of the *in-vitro* permeation statistics recognized transdermal delivery systems dissimilarities, further confirmed by the requirement of a two-layer model to explain one of the transdermal delivery systems. The amalgamation of *in-vitro* permeation analysis in the presence of a computational model offered a parameter-mediated mass and heat transport approach to assess the effects of heat over NT-based transdermal delivery systems [31]. The effect of NT-based transdermal patches was also tested and found significant in delivering NT at the targeted sites [32].

CONCLUSION:

NT addiction has always been found as a major issue amongst all groups of society and has affected the lives of a huge population of the world. As a consequence, NT replacement therapies, including transdermal-based NT patches, have been found so significant and have been widely spread and utilized. Also, the pharmacokinetic profiling of transdermal-based delivery systems of NT has been widely explained using non-compartmental methods, and even need to be explored more shortly for assessing the fate and real mechanism of NT in the body delivered through various transdermal based delivery systems.

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