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REVIEW ARTICLE

NICOTINE CHEWING GUM REMEDIAL APPROACH AGAINST SMOKING AND CHEWING HABITS

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ABSTRACT

Nowadays, with scientific and technological advancement in the pharmaceutical sciences, the researchers as well as scientists in research and development has been giving much more emphasis against bad habits of individuals namely smoking of cigarette and chewing of tobacco. Chewing gum containing nicotine and several ingredients not only help to quiet such habits but also in treating local mouth diseases through one or more approaches of drug delivery system. Moreover, Nicotine gum manufacturer, in India are very few, can measure at finger while habits of smoking and chewing gets increase at faster rate. Present review describes the best alternative in form of nicotine chewing gum against such bad habits. As available gum is 2 mg (appropriate for those who smoke 20 cigarettes a day or less) and 4 mg (appropriate for those who smoke more than 20 cigarettes a day) in market, whenever there is an urge to smoke, continue to use for up to three months to break the habit of smoking, and then gradually reduce the gum use and also reduces withdrawal symptoms including nicotine craving associated with quitting smoking of cigarette/chewing of gutka containing tobacco; hence indicated for smoking cessation therapy.

INTRODUCTION

Medicated (Nicotine) chewing gum is a novel drug delivery system containing masticatory gum base with pharmaco-logically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. Chewing gum is a pleasure that almost everyone enjoys[1].

Nowadays, the habit of individuals namely smoking of cigarette and chewing of tobacco going to increase at a faster rate and against it researchers as well as scientists in research and development has been giving much more emphasis to develop such a nicotine containing drug delivery with least dose which can act as a remedy or alternative for such habits[1-4].

Chewing gum containing nicotine and several ingredients not only help to quiet such habits but also in treating local mouth diseases through one or more approaches of drug delivery system[5-7]. Some forms of nicotine replacement therapy includes patches, gum, lozenges, mouth spray, oral strips and inhalator have been proven to help people quit smoking[8-10]. Cipla made nicotine chewing gum[11] its composition, pharmacokinetics, pharmacodynamics, indications, dosage and administrations, contraindications, precautions, warnings are given here

Ciplamed Nicotine chewing gum

NICOGUM Chewing Gum 2 mg (Nicotine polacrilex)

NICOGUM Chewing Gum 4 mg (Nicotine polacrilex)

Composition

NICOGUM 2 Chewing Gum

Each piece contains:

Nicotine Polacrilex USP (equivalent to Nicotine)... 2 mg

NICOGUM 4 Chewing Gum

Each piece contains:

Nicotine Polacrilex USP (equivalent to Nicotine)... 4 mg

Pharmacology

Pharmacodynamics

Nicotine, the primary alkaloid in tobacco products and a naturally occurring autonomous substance, is a nicotine receptor agonist in the peripheral and central nervous systems and has pronounced CNS and cardiovascular effects.

The principal mechanism of action of nicotine replacement therapy (NRT) is to partially replace the nicotine formally obtained from tobacco. It provides small and sustained quantities of nicotine without the harmful gases of smoking, to reduce the severity of withdrawal symptoms and

cravings. Amelioration of withdrawal symptoms is observed with relatively low blood levels of nicotine, which also provides for an alternative source of some reinforcing and cognitive effects. A second possible mechanism of benefit has been suggested to be the potential for nicotine medications to desensitize the nicotinic acetylcholine receptors (nAchRs). Such desensitization would result in a reduced effect of nicotine from cigarettes, such that if a person relapses to smoking while taking NRT, the cigarette would be less satisfying and the person less likely to resume. Hence, NRT also provide a coping mechanism, making cigarettes less rewarding to smoke. Clinical studies have shown that nicotine replacement products can help smoker abstain from smoking by relieving the withdrawal symptoms.

PHARMACOKINETICS

Absorption

Nicotine is a weak base with a p*K*a of 8.0. In its ionized state, such as in acidic environments, nicotine does not rapidly cross membranes. Nicotine from the chewing gum is released slowly and depends on the intensity of chewing. This nicotine is buffered to alkaline pH in the oral mucosa to facilitate absorption. Concentrations of nicotine in the blood rise gradually and plateau at about 30 minutes, with levels persisting and declining slowly over the next 2 hours. This slow increase in blood and, especially, brain levels results in low abuse liability of the gum. The absolute dose of nicotine absorbed systemically from nicotine gum is much less than the nicotine content of the gum, because some amount of nicotine is swallowed with subsequent first-pass metabolism. Nicotine is poorly absorbed from the stomach because it is ionized in the acidic gastric fluid. The bioavailability of nicotine from the gum ranges between 55–78%.

Type of nicotine Administration	Cmax (ng/ml)	Tmax (min)	Bioavailability (%)
Smoking (1 cigarette,5 min) (≈ 2 mg/cigarette)	15-30 (venous) 20-60 (arterial)	5-8 (venous) 3-5 (arterial)	80-90 (of inhaled nicotine)
Gum (30 min, total dose in gum)			
2 mg 4 mg	6-9 (venous) 10-17 (venous)	30 30	78 55

Table 1: Nicotine absorption pharmacokinetics of cigarette and gum after single dose Distribution

After absorption, nicotine enters the bloodstream where, at pH 7.4, it is about 69% ionized and 31% un-ionized. Binding to plasma proteins is less than 5%. The drug is distributed extensively to body tissues, with steady-state volume of distribution

averaging 2.6 of body weight. Nicotine binds to brain tissues with high affinity, and the receptor binding capacity is increased in smokers compared with non-smokers. Nicotine accumulates markedly in gastric juice and saliva. Nicotine also accumulates in breast milk (milk/plasma ratio: 2.9) and crosses the placental barrier easily.

Metabolism

Nicotine is metabolized primarily in the liver by the action of CYP450 enzymes. *In vitro* and *in vivo* studies show that CYP2A6 is the enzyme that is primarily responsible for the oxidation of nicotine and cotinine, a primary metabolite of nicotine. The second most active hepatic P450 enzyme in nicotine oxidation is CYP2B6, when investigated using hepatic tissues or expression systems *in vitro*, especially at high nicotine concentrations. About 90% of a systemic dose of nicotine can be accounted for as nicotine and metabolites in the urine. Based on studies with simultaneous infusion of labelled nicotine and cotinine, it has been determined that 70–80% of nicotine is converted to cotinine. About 4–7% of nicotine is excreted as nicotine *N*-oxide and 3–5% as nicotine glucuronide. Cotinine is excreted unchanged in the urine to a small degree (10–15%). The remainder is converted to metabolites, primarily *trans*-3-hydroxycotinine (33–40%), cotinine glucuronide (12–17%), and *trans*-3-hydroxycotinine glucuronide (7–9%). Extra hepatic nicotine metabolism in humans is probably of little importance for systemic nicotine clearance.

Moiety	Clearance (ml/min)	Renal clearance	Non renal clearance	Volume of Distribution (l/kg)	T 1/2(min)
Nicotine	1110-1500	35-90	1050-1460	2.2-3.3	100-150
Cotinine	42-55	3-9	36-52	0.69-0.93	770-1130
Trans-3-hydroxycotinine	82	50	32	0.66	396

Table 2: Pharmacokinetic parameters of nicotine, cotinine and trans-3-hydroxycotinine after intravenous administration

Excretion

Nicotine and metabolites are mainly excreted by glomerular filtration and tubular secretion, with variable reabsorption

depending on urinary pH. With uncontrolled urine pH, renal clearance averages about 35–90 ml/min, accounting for the elimination of about 5% of total clearance. About 1% of nicotine is excreted in the faeces, while some nicotine and cotinine is excreted in the sweat. Renal excretion of cotinine is a minor route of elimination, averaging about 12% of total clearance. In contrast, 100% of nicotine N-oxide and 63% of trans-3-hydroxycotinine are excreted unchanged in the urine.

Special Conditions

Elderly

Compared with young adults, clearance of nicotine is decreased in the elderly with total clearance being lower by 23% and renal clearance lower by 49%. Lower nicotine metabolism in the elderly may be because of reduced liver blood flow, as no decrease in CYP2A6 protein levels or nicotine metabolism in liver microsomes due to age has been detected. Volume of distribution of nicotine is lower in elderly subjects due to decrease in lean body mass.

Pregnancy and Menstrual Cycle

Results from a recently completed large-scale (N=290) twin study with intravenous infusions of both nicotine and cotinine clearly show that nicotine and cotinine clearances are higher in women compared with men, and oral contraceptive use further accelerates nicotine and cotinine clearances in women. Clearance is increased by 60% and 140% for nicotine and cotinine, respectively, in pregnancy compared with postpartum. The finding that, in pregnancy, cotinine clearance is increased more than nicotine clearance indicates that this increase in clearance is most likely caused by the induction of CYP2A6 and not by an increase in hepatic blood flow. These results suggest that CYP2A6 activity is induced by sex hormones; however, supporting experimental in vitro data are still lacking.

Pathological Conditions

The total metabolism by CYP2A6 is reduced in patients with alcoholic liver disease and viral hepatitis. Kidney failure not only decreases renal clearance of nicotine and cotinine, but also metabolic clearance of nicotine. Metabolic clearance of nicotine is reduced by 50% in subjects with severe renal impairment compared with healthy subjects.

Indications

NICOGUM chewing gum is indicated for smoking cessation therapy. It reduces withdrawal symptoms including nicotine craving associated with quitting smoking/chewed tobacco and gutka containing tobacco. The chewing gums

should be used whenever there is an urge to smoke. Continue use for up to three months to break the habit of smoking, and then gradually reduce the gum use.

NICOGUM chewing gum is available in two strengths, 2 mg and 4 mg

- 2 mg is appropriate for those who smoke 20 cigarettes a day or less.
- l4 mg is appropriate for those who smoke more than 20 cigarettes a day.

The smoker should stop smoking completely when he/she begins using the gum. In smokers currently unable or not ready to stop smoking abruptly, the gum may also be used as part of a programme to reduce smoking prior to stopping completely.

Under 18 years of age, the relative risks and benefits of pharmacotherapy need to be considered. No randomized controlled trials on the effectiveness of NRT in young smokers have been published until date.

Dosage and Administration

4 mg: As advised/told by the doctor

2 mg: 8-12 pieces a day. Do not use more than 24 pieces of gum a day. For recommended dosage schedule refer the following chart.

Weeks 1–6	Weeks 7–9	Weeks 10–12
One gum every 1–2 hours	One gum every 2–4 hours	One gum every 4–8 hours

Table 3: Sample dosage schedule

The treatment time is individual. Normally, treatment should continue for at least 3 months.

After 3 months, the user should gradually cut down the number of pieces chewed each day until they have stopped using the product.

Treatment should be discontinued when dose has been reduced to 1-2 pieces of gum per day. Adults (over 18 years of age) who use NRT beyond 9 months for smoking cessation are recommended to seek additional help and advice from a healthcare professional For Adolescents (12 to 18 years), due to the limited data available in this age group; the recommended duration of treatment is 12 weeks. If longer treatment is required, advice from a healthcare professional should be sought.

Steps to chew NICOGUM chewing gum

Use the following steps to ensure maximum benefit from the gum.

Step 1 - Chew the gum slowly until there is a nicotine taste.

Step 2 - Once you feel the nicotine taste, keep the gum in between the cheek and your teeth.

Step 3 - Nicotine is released from the gum which gets absorbed through the cheek.

Step 4 - Chew the gum again when the taste fades.

(If you experience strong or frequent cravings, you may use a second NICOGUM chewing gum within the hour. However, do not use more than 24 gums per day if you are using NICOGUM **2 mg** chewing gum and 15 gums per day if you are using NICOGUM **4 mg** chewing gum) Concomitant use of acidic beverages such as coffee or soda may decrease the buccal absorption of nicotine. Acidic beverages should be avoided for 15 minutes prior to chewing the gum.

Contraindications

NICOGUM chewing gum is contraindicated in patients with a hypersensitivity to nicotine polacrilex or any other components of the chewing gum.

Warnings and Precautions

Use with caution in the following conditions

Symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhoea, weakness, and rapid heartbeat occur. Keep out of the reach of children and pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum in paper and throw away in the trash. In case of overdose, get medical help or contact a physician right away. Smokers who wear dentures may experience difficulty in chewing the gum. The chewing gum may stick to, and may in rare cases damage dentures.

Cardiovascular Diseases NRT is safe in smokers with stable cardiovascular disease. Despite the vasoconstrictor effects of nicotine, studies have failed to demonstrate an increased risk with the use of NRT in patients with cardiovascular disease.

NICOGUM chewing gum presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or CVA and who are considered to be haemo-dynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NRT may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Drug Interactions

Pharmaco-dynamic interactions may alter the expected response or actions of other drugs. This should be kept in mind when prescribing NICOGUM chewing gum with drugs like sedatives, opioids, anti-hypertensive, insulin, theophylline, oral contraceptives, and caffeine. There has been no clinical trial performed to study the

interactions of various drugs with NICOGUM chewing gum; however, there have been some studies to show the effects of drugs on CYP2A6, the primary enzyme involved in nicotine metabolism. A few drugs have been shown to induce CYP2A6 in human primary hepatocyte culture. These include prototypical inducers like rifampicin, dexamethasone and phenobarbital, although there is wide inter-individual variability in response. Oral contraceptive use induced nicotine and cotinine clearances by 30% and 33%, respectively. Several compounds are inhibitors of CYP2A6-mediated nicotine metabolism in vitro, including methoxsalen, tryptamine and coumarin.

Renal Impairment

Kidney failure not only decreases renal clearance of nicotine and cotinine, but also metabolic clearance of nicotine. Metabolic clearance of nicotine is reduced by 50% in subjects with severe renal impairment compared with healthy subjects. It is speculated that accumulation of uremic toxins may inhibit CYP2A6 activity or down-regulate CYP2A6 expression in the liver. Hence, patients should be considered for the therapy only if the expected benefits are more than the risks involved and monitored closely.

Hepatic Impairment

The total metabolism by CYP2A6 is reduced in patients with alcoholic liver disease and viral hepatitis. As nicotine is metabolized primarily by the liver, patients should be considered for the therapy only if the expected benefits are more than the risks involved and monitored closely.

Pregnancy

NRT is not contraindicated in pregnancy. The decision to use NRT should be made on a risk-benefit assessment as early on in the pregnancy as possible with the aim of discontinuing use as soon as possible. During pregnancy, this medicine should only be used on the advice of healthcare provider. Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better. Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt. Nicotine passes to the fetus affecting breathing movements and has a dose-dependent effect on placental/fetal circulation. However the risk of using NRT

to the fetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide. Intermittent dosing products may be preferable as these usually provide a lower daily dose of nicotine than patches. However, patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Lactation

NRT is not contraindicated in lactation. Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. In breastfeeding mothers, this medicine should only be used on the advice of healthcare provider. Using intermittent dose NRT preparations, compared with patches, may minimize the amount of nicotine in the breast

Milk as the time between administrations of NRT and feeding can be more easily prolonged. Undesirable Effects Nicotine chewing gums can cause adverse reactions similar to those associated with nicotine administered by other means including smoking and these are mainly dose dependent. Most of the side effects which are reported by patients occur generally during the first 3- 4 weeks after initiation of therapy. Overall, NRT has a benign adverse event profile, with a relatively low rate of discontinuation due to adverse events. Possible adverse effects seen include mouth or throat irritation, sore mouth and throat, skin irritation, nausea/vomiting, gastrointestinal discomfort, coughing, headache, hiccups, dyspepsia, watering of eyes, headaches, dizziness, heart palpitations, sneezing, sleep disturbances and dream abnormalities, insomnia, rhinitis, vertigo, taste disturbances, and jaw-muscle aches, increased salivation. Other rare and uncommon adverse events include reversible atrial fibrillation, erythema, and urticarial, allergic reactions including angioedema.

Overdosage

If you have any symptoms of overdose, seek medical attention immediately. Symptoms of nicotine overdose may include**:** Abdominal pain, blurred vision, breathing abnormalities, cold sweat, confusion, diarrhoea, dizziness, drooling, fainting, hearing difficulties, heart palpitations, low blood pressure, nausea, pallor, rapid heartbeat, salivation, severe headaches, sweating, tremor, upset stomach, vision

problems, vomiting, and weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions Management of an overdose: All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration should be instituted if necessary. Activated charcoal reduces the gastrointestinal absorption of nicotine.Shelf-Life2 years.

Storage and Handling Instructions Store below 25^0C. Protect from light. Packaging Information NICOGUM **Chewing Gum** (fresh mint flavoured). Each sales pack contains 10 gum pieces.

CONCLUSION

Present review describes the best alternative in form of nicotine chewing gum against such bad habits. Scientific and technological advancement in the pharmaceutical sciences as well as the researchers should manufactured such a therapy with least cost which act an alternative to the common people who usually smoke or chew the tobacco products.

Moreover, some Pharmaceutical company's products are described here changing the scenario as the common person moves and convinced hence indicated for smoking cessation therapy.

FUTURE TRENDS

As numerous outcomes associated with a Nicotine chewing gum with none disadvantages. Hence pharmaceutical scientist or researchers in pharmaceutical industry should provide a positive approach in making such nicotine containing drug delivery iwhich boosts up its use in common public by awaking the adverse effects associated with chewing tobacco and smoking cigarettes.

Especially proper remedies containing nicotine drug delivery with least dose helps the youngsters either reduction or withdrawal of tobacco and will be the best remedy for such bad habits.

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