

RESEARCH & DEVELOPMENT / QUALITY

Re.: Transdermal Nicotine

I. Background

Since the mid-70's pharmacological support in breaking the smoking habit by giving doses of nicotine has been under discussion and has led to the launch of two types of product.

1. Chewing gum containing nicotine
(In Germany Nicorette, Boehringer Mannheim)
2. Nicotine plasters
(In Germany Nicotinell TTS, Ciba Geigy; Nikofrenon, Hefa-Frenon Arzneimittel GmbH)

Other types of plaster are being clinically tested or have already been registered worldwide (e.g. Nicolan, Elan; sold in USA by Warner-Lambert).

In their pharmacological effects both forms of application differ quite clearly from nicotine intake via smoking.

Nicotine intake is slow and continuous - with chewing gum containing nicotine over a period of approx. 20-30 minutes after which intake slowly ceases (1) - with plaster over a period of 4-7 hours until a plateau is reached (2). The nicotine concentrations measured in the blood fluctuate interindividually and are somewhat lower than those found among smokers (3,4).

In contrast to this, smoking induces very rapid nicotine intake which means that maximum concentrations in the blood are achieved within 10 minutes and then subside again quickly (1).

The slow increase in nicotine concentration and the longer period during which it remains high mean that the nicotine receptors in the central nervous system adapt/are blocked; this in turn means that the stimulating effects achieved by smoking cannot be achieved with these products (5). On the other hand, the almost constantly high nicotine level suppresses withdrawal symptoms.

II. Comparison of chewing gum / plaster (5,6)

1. Pharmacodynamics

a) Gum

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Gradual increase and decrease in nicotine concentration during the day; during the night the nicotine level subsides. As it is discontinuous, the nicotine remains effective from day to day.

b) Plaster

Gradual increase and formation of a plateau which remains almost constant. The nicotine level does not subside overnight (24-hour plaster).

2. Advantages:

a) Gum

The smoker can organize intake to suit himself. Active control over intake and the condition it produces.

b) Plaster

Simple form of application. Independent of any situation, and invisible.

3. Disadvantages:

a) Gum

Problems with flavour and chewing. In some cases nausea and headaches. The danger of addiction.

b) Plaster

In some cases skin irritation, in isolated cases nausea and sweating. Theoretically the danger of total nicotine intolerance.

III. Therapeutical effect:

The effect of therapies to break the smoking habit using plasters or chewing gum is disputed. In the short term (a few weeks) far higher abstinence rates are observed. After 1-2 years, however, these have adapted themselves to the rates of placebo or control groups which means that most investigations do not establish success rates which are significantly better.

For this reason an additional behaviour therapy is recommended in almost all applications (2,7,8,9).

IV. STOWIC - Product:

The product is a plaster which is manufactured using an innovative combination release membrane/matrix for the active substance.

Compared with other products this is intended to achieve a more even release rate for the active substance which is less dependent on its initial concentration (Pat. WO 89/07959).

Nicotine is given as the example but the principle is said to be applicable to other active substances, too.

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As the principle of nicotine application does not differ from that of other products (Enc. 1), the pharmacological effect of the product with all its advantages and disadvantages is equivalent to that of the other nicotine substitute products.

The somewhat faster absorption of nicotine which Stowic emphasises and thus the more rapid achievement of a plateau should not be seen as a product advantage compared with smoking because of the generally differing pharmacodynamics.

Use over a period of only 16 hours is also recommended for the products of other competitors (e.g. Kabi Pharmazia).

The improved dermatological sensitivity and lower production costs cannot be conclusively appraised with the currently available information.

Nicotine application in the treatment of Alzheimer's and Parkinson's disease is under discussion worldwide and is being clinically tested in some cases (10). As far as is known today, success is only possible if the development of nicotine intolerance is avoided. Accordingly, nicotine has to be applied short-term in small doses (e.g. inhalation, nasal sprays) (11).

The transdermal application of other pharmaceutical products is documented in several patents and is the object of numerous research projects being carried out by the pharmaceutical industry.

V. Alternatives:

The rapid, peaking intake of nicotine which the smoker clearly wants cannot be achieved with nicotine application via chewing gum or plaster (Enc. 2).

To overcome this disadvantage other forms of nicotine intake are necessary.

For this reason intensive work is being carried out on developing nasal sprays and inhalators (Favor type). Some are already undergoing clinical tests (6).

The disadvantage of rapid nicotine intake similar to that achieved with a cigarette is seen in the danger of people possibly becoming dependent on it. Successes in breaking the smoking habit are therefore seen in a combination of slow and fast-working nicotine release systems tailored to individual needs.

Enc. 3 (from 6) provides an overview of nicotine substitute systems which are already available or are being tested.

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VI. Literature:

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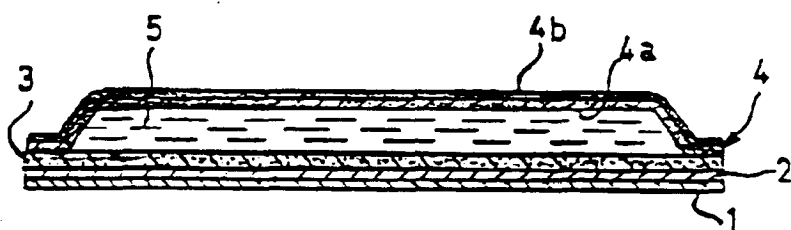
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Appendix 1

WO 89/07959

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STOWIC - Product



1 = release liner

2 = adhesive layer

3 = microporous membrane

4a = polyester face

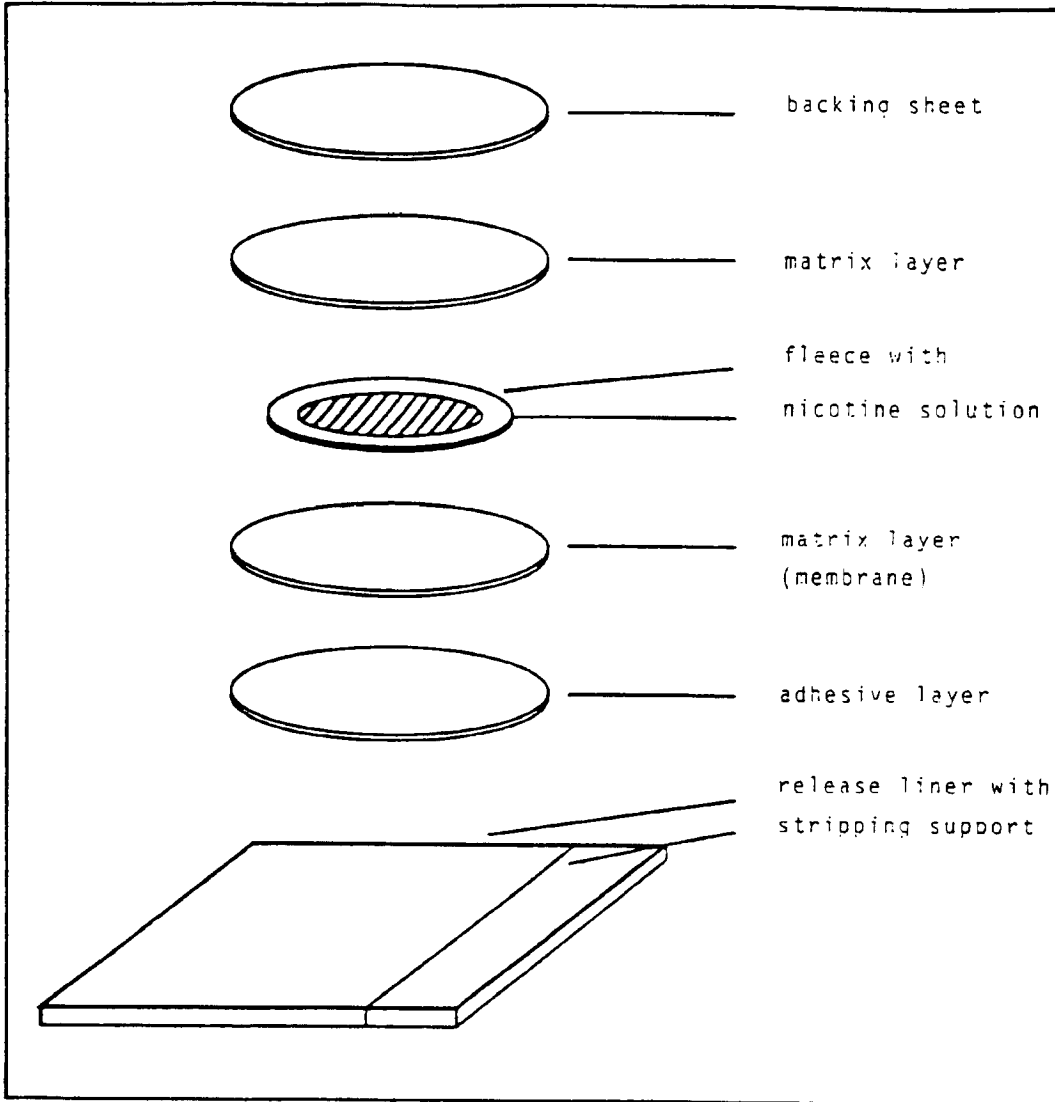
4b = aluminised layer

5 = nicotine formulation

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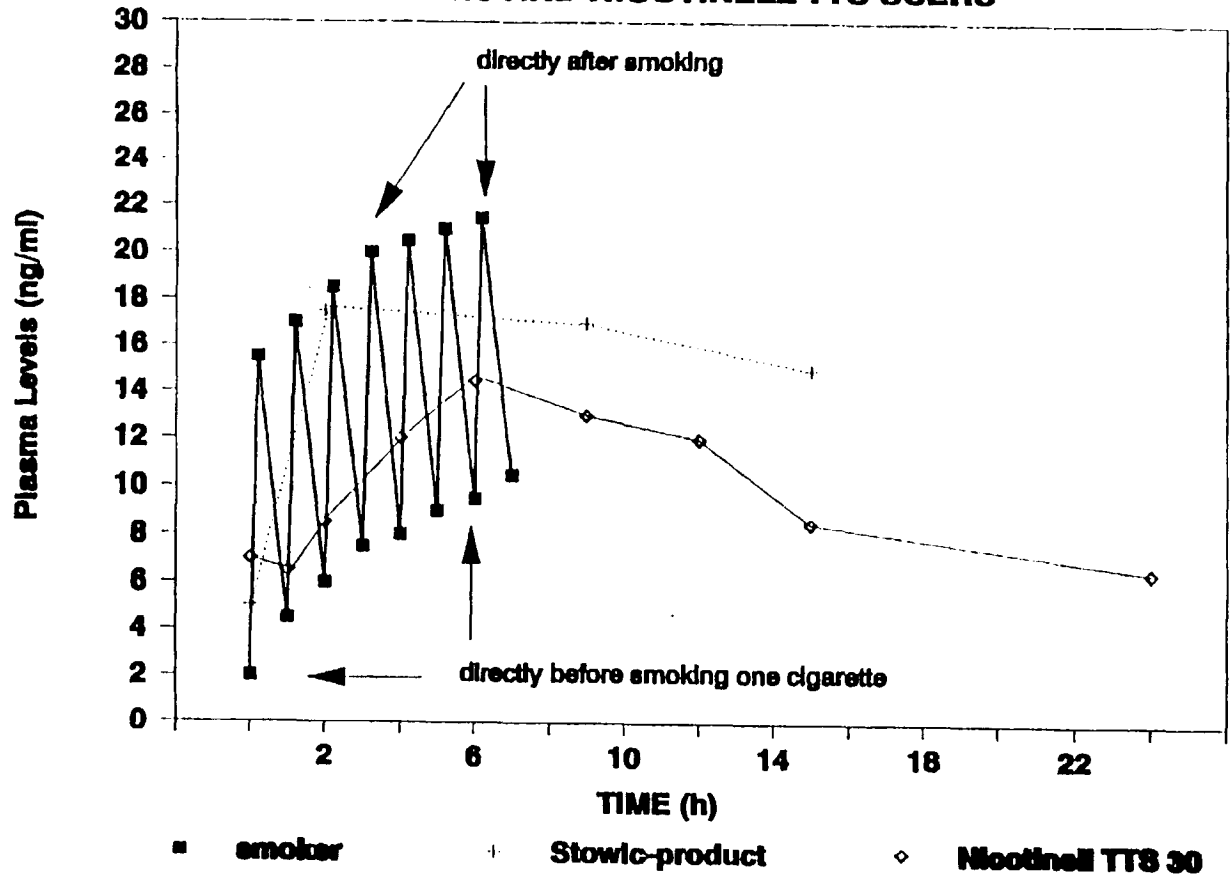
Appendix 1

Construction of Nicotine11 TTS



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PLASMA LEVELS OF NICOTINE IN SMOKERS AND NICOTINELL TTS USERS



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RATE OF ABSORPTION SPECTRUM

TOBACCO PRODUCTS NEW DELIVERY SYSTEMS

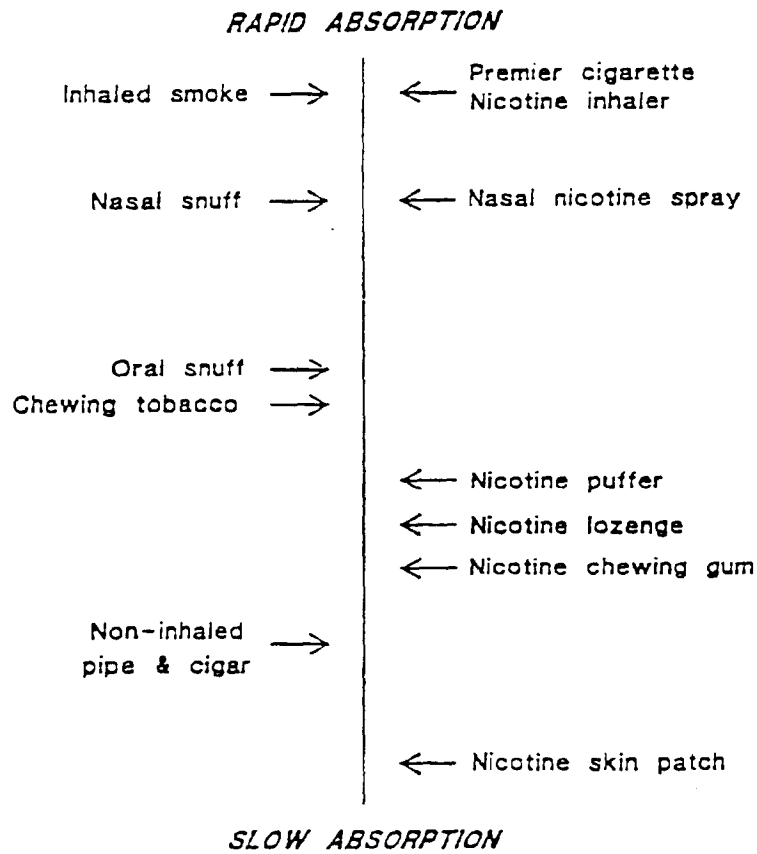


Figure 1. Tobacco products and new nicotine delivery systems can be positioned roughly on a spectrum based on the rate of nicotine absorption obtained from their use.

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