(19) DANMARK

(10) DK/EP 2361081 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/24 (2006.01)* *A 61 P 25/34 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-08-15**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-06-29**

(86) Europæisk ansøgning nr.: **09820843.2**

(86) Europæisk indleveringsdag: **2009-10-13**

(87) Den europæiske ansøgnings publiceringsdag: **2011-08-31**

(86) International ansøgning nr.: **SE2009051163**

(87) Internationalt publikationsnr.: **WO2010044736**

(30) Prioritet: **2008-10-14 SE 0802189**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR**

(73) Patenthaver: **McNeil AB, P.O.Box 941, 25109 Helsingborg, Sverige**

(72) Opfinder: **LINDELL, Katarina, Skarhult 1325, S-241 93 eslöv, Sverige**
THYRESSON, Kristina, Sakförarevägen 28, S-226 57 Lund, Sverige
BUNICK, Frank, 47 Long Ridge Road, Randolph, New Jersey 07869, USA
LUBER, Joe, 750 East Cherry Rd., Quakertown, Pennsylvania 18951, USA
HUGERTH, Andreas, Trollsjövägen 107, S-237 33 Bjärred, Sverige
NICKLASSON, Fredrik, Leifs Vag 82, S-237 31 Bjarred, Sverige

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark**

(54) Benævnelse: **FLERDELT INTRAORAL DOSERINGSFORM OG ANVENDELSE DERAF**

(56) Fremdragne publikationer:
WO-A1-01/37814
WO-A1-91/06288
WO-A1-91/09599
WO-A1-2005/121312
WO-A2-00/13662
US-A- 5 879 710
US-A1- 2008 187 589
DELVAUX M ET AL: "L'aide a l'arret du tabagisme: la reussite au long terme Aspects psychologiques et pharmacologiques", REVUE MEDICALE DE LIEGE, LIEGE, BE, vol. 61, no. 1, 1 January 2006 (2006-01-01), pages 27-30, XP003026378, ISSN: 0370-629X
GARG S ET AL: "Development and evaluation of a buccal bioadhesive system for smoking cessation therapy", DIE PHARMAZIE, GOVI VERLAG PHARMAZEUTISCHER VERLAG GMBH, ESCHBORN, DE, vol. 62, no. 4, 1 January 2007 (2007-01-01), pages 266-272, XP003026379, ISSN: 0031-7144, DOI: 10.1691/PH.2007.4.6144
DELVAUX M. ET AL: 'L'aide a l'arret du tabagisme: la reussite au long terme Aspects psychologiques et

Fortsættes ...

pharmacologiques' REVUE MEDICALE DE LIEGE vol. 61, no. 1, 2006, pages 27 - 30, XP003026378
GARG S. ET AL: 'Development and evaluation of a buccal bioadhesive system for smoking cessation therapy' PHARMAZIE vol. 62, no. 4, 2007, pages 266 - 272, XP003026379
GILLES PONCHEL: 'Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials' ADVANCED DRUG DELIVERY REVIEWS vol. 13, no. 1-2, 1994, pages 75 - 87, XP023861787
EP-A2- 1 107 730
EP-A2- 1 190 721

DESCRIPTION

Field of the Invention

[0001] The present invention relates to a multi portion intra-oral dosage form where at least one portion is rapidly disintegrating and at least one portion is slowly disintegrating, whereby the disintegration time for the slowest disintegrating portion is at least two times longer than for the most rapidly disintegrating portion. Of certain interest is use of sensory markers/signals as conceptual aids for the subject.

[0002] Also described are a method and a system for delivering active agents, such as nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof as well as use and production of said formulations.

Background of the Invention

[0003] Tobacco dependence and reduction thereof is a desirable goal. In recent years, with the recognition of the harmful effects of tobacco smoking, there have been numerous campaigns and programs by governmental agencies and various health groups and other interested organisations to disseminate information about the adverse health effects resulting from tobacco smoking. Moreover, and as a result of this recognition of the harmful effects, there have been many programs directed to attempts in reducing smoking incidence.

[0004] Nicotine is an organic compound and is the principal alkaloid of tobacco. Nicotine is the chief addictive ingredient in the tobacco used in cigarettes, cigars, snuff and the like. Nicotine is also an addictive drug, and smokers characteristically display a strong tendency to relapse after having successfully stopped smoking for a time. Nicotine is the world's second most used drug, after caffeine from coffee and tea.

[0005] The main problem with tobacco smoking is its enormous implications on health. It is estimated that smoking related diseases cause some 3 - 4 million deaths per year. According to Centers for Disease Control and Prevention, cigarette smoking among adults - United States, 1995. MMWR 1997; 46:1217 - 1220 around 500,000 persons in USA die each year as a result of tobacco use. In fact, excessive smoking is now recognised as one of the major health problems throughout the world. This grim consequence of tobacco smoking has urged many medical associations and health authorities to take very strong actions against the use of tobacco.

[0006] Even though tobacco smoking is decreasing in many developed countries today it is hard to see how the societies could get rid of the world's second most used drug. The incidence of smoking is still rising in many countries, especially in less developed countries.

[0007] The most advantageous thing a heavy smoker can do is to stop smoking completely or at least to reduce his/her smoking. Experience shows, however, that most smokers find this extremely difficult since, mostly, tobacco smoking results in a dependence disorder or craving. The World Health Organization ("WHO") has in its International Classification of Disorders a diagnosis called Tobacco Dependence. Others like the American Psychiatric Association call the addiction Nicotine Dependence. It is generally accepted that these difficulties to stop smoking result from the fact that those heavy smokers are dependent on nicotine. The most important risk factors related to health are, however, substances that are formed during the combustion of tobacco, such as carcinogenic tar products, carbon monoxide, N-nitrosamines, aldehydes, and hydrocyanic acid.

Effects of nicotine

[0008] Nicotine is an addictive poisonous alkaloid $C_5H_4NC_4H_7NCH_3$, derived from the tobacco plant. Nicotine is also used as an insecticide. The administration of nicotine (for example, in the form of smoking a cigarette, cigar or pipe) can give a pleasurable feeling to the smoker. However, smoking has health hazards and it is, therefore, desirable to formulate an alternative way of administering nicotine in a pleasurable and harmless manner that can be used to facilitate withdrawal from smoking and/or used as a replacement for smoking.

[0009] When smoking a cigarette, nicotine is quickly absorbed into the smoker's blood and reaches the brain within around ten seconds after inhalation. The quick uptake of nicotine gives the consumer a rapid satisfaction, or kick. The satisfaction usually lasts during the smoking time of the cigarette and for a period of time thereafter. The poisonous, toxic, carcinogenic, and addictive nature of smoking has provided strong motivation to develop methods, compositions and devices, which can be used to break the habit of smoking cigarettes.

Nicotine replacement products.

[0010] One way to reduce smoking is to provide nicotine in a form or manner other than by smoking and some products have been developed to fulfil this need. Nicotine containing formulations are currently the dominating treatments for tobacco dependence. Formulations comprising nicotine metabolites, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures thereof, with or without nicotine, have also been found useful for this purpose.

[0011] The successes in achieving reduction in the incidence of smoking have been relatively poor using presently known products. The present state of the art involves both behavioural approaches and pharmacological approaches. More than 80 % of the tobacco smokers who initially quit smoking after using some behavioural or pharmacological approach to singly reduce smoking incidence generally relapse and return to the habit of smoking at their former rate of smoking within about a one year's period of time.

[0012] As an aid for those who are willing to stop smoking there are several ways and forms of nicotine replacement products available on the market. Several methods and means have been described for diminishing the desire of a subject to use tobacco, which comprises the step of administering to the subject nicotine or a derivative thereof as described in e g U.S. Patent Number 5,810,018 (oral nicotine-containing spray), U.S. Patent Number 5,939,100 (nicotine-containing micro spheres) and U.S. Patent Number 4,967,773 (nicotine-containing lozenge).

[0013] Nicotine-containing nose drops have been reported (Russell et al., British Medical Journal, Vol. 286, p. 683 (1983); Jarvis et al., Brit. J. of Addiction, Vol. 82, p. 983 (1987)). Nose drops, however, are difficult to administer and are not convenient for use at work or in other public situations. Ways of administrating nicotine by way of delivering directly into the nasal cavity by spraying is known from U.S. Patent Number 4,579,858, DE 32 41 437 and WO93/12764. There may be local nasal irritation, however, with use of nasal nicotine formulations. The difficulty in administration also results in unpredictability of the dose of nicotine administered.

[0014] The use of skin patches for transdermal administration of nicotine has been reported (Rose, in Pharmacologic Treatment of Tobacco Dependence, (1986) pp. 158-166, Harvard Univ. Press). Nicotine-containing skin patches that are in wide use today can cause local irritation and the absorption of nicotine is slow and affected by cutaneous blood flow.

[0015] Also, inhaling devices resembling a cigarette are known for uptake of nicotine vapours as suggested in U.S. Patent Number 5,167,242. Said means and methods address the problems associated with addiction to nicotine.

[0016] One successful product that is used as a smoking substitute and/or as a smoking cessation aid and which is based on nicotine, is the chewing gum Nicorette®. This product was one of the first nicotine replacement forms that was approved by the Food and Drug Administration (FDA) and is still one of the most used nicotine replacement products. Nicorette® chewing gum has been on the market in about 60 countries for several years. In this chewing gum the nicotine is present in the form of a complex with an insoluble cation-exchanger (polacrilex) that is dispersed in a gum base. The nicotine is slowly released from the gum due to chewing and will reach similar plasma levels as when smoking a cigarette after about 30 minutes depending on the chewing technique, i e slow or active. Patents related to this product are e g U.S. Patent Number 3,877,468, U.S. Patent Number 3,901,248 and U.S. Patent Number 3,845,217.

[0017] Other successful nicotine replacement products are Nicorette® Microtab and its successor Microtab Lemon. These tablets are sublingual tablets and provides slow release of nicotine that aids a subject to achieve a nicotine plasma profile similar (bioequivalent) to that of the Nicorette® chewing gum.

[0018] Pharmaceuticals intended for oral administration are typically provided in solid form as tablets, capsules, pills, lozenges, or granules. Rapidly disintegrating tablets are often employed in the administration of pharmaceuticals where it is impractical to provide a tablet for swallowing whole, for instance with paediatric patients. Several workers in the field have explored rapidly disintegrative tablets (e g, U.S. Patent Nos. 6,106,861 and 6,024,981 and PCT Application No. WO 99/47126).

[0019] Applicant's invention relates for example to an intra-oral multi portion dosage form that combines the use of e g a rapidly disintegrating portion comprising a pharmaceutically active agent with a slower disintegrating hard portion, e g a lozenge. The dosage form, thus, may provide both the benefit of fast delivery of pharmaceutically active compound/s contained within the rapidly disintegrating portion with the benefit of slow/extended release from the slowly disintegrating portion that may comprise another or the same pharmaceutically active compound/s. The dosage form may be but are not limited to a lozenge, a tablet, a capsule, an oral film, a sublingual tablet, a troche, a lolly pop, a hard boiled candy, a chocolate lens, a micro bead, a jelly, a jelly bean, a semi solid, a center filled dosage form, a combination thereof or any other intra-oral dosage form.

[0020] Furthermore, the dosage form facilitates the use of sensory markers/signals or organoleptic sensations as a sensory aid to indicate to the subject the content of different layers, e g menthol or cinnamon in the rapidly disintegrating portion and evergreen mint flavour in the slowly disintegrating portion. In further embodiments it can also be envisaged that a sensory signal is conveyed to the subject e g when the pharmaceutically active compound/s has started /will start to be released there from or when approximately one-quarter of the active has been released etc.

Prior art

[0021] US 5,879,710 discloses a specific mucoadhesive double layer formulation for administration of melatonin.

[0022] US 5,236,713 discloses a laminated preparation for intermittently releasing an active agent.

[0023] WO 1992/01445 discloses an osmotic device for controlled delivery of nicotine base through an oral mucosa membrane.

[0024] US 20060073189A1 discloses monolayer oral preparations for biphasic delivery of nicotine.

[0025] US 5,681,583 discloses a double-layer tablet to be swallowed for administration of an active material, whereby one layer releases the active quickly, while the other layer releases the active more gradually. A tablet to be swallowed is intended for uptake of an active in the GI tract, which is totally different from a dosage form for intraoral uptake of an active.

[0026] US 20030118648A1 discloses a pharmaceutical composition comprising a moulded triturate portion surrounded by a compressed annular tablet comprising a pharmaceutically active ingredient.

[0027] WO2001/037814 discloses a tablet that is attachable to the buccal mucosa, where it releases a substance in a multiphasic manner, typically with an initial burst release followed by controlled release over a longer period. '814 though does not comprise any proof of utility for this concept.

[0028] US 6,248,760 discloses a multi-layered nicotine-containing tablet where a non-toxic matrix layer comprises an antacid, but does not contain nicotine.

Detailed Description of the Invention

Definitions

[0029] The below definitions apply *mutatis mutandis* on expressions being similar to those being defined below.

[0030] The term "organoleptic sensation" is herein intended to mean a feature of the embodiment that is discernable to the taste, mouth feel, smell, hearing and/or vision of the subject such as, but not limited to, flavor, cooling, burning, warming, tingling, bubbling, foaming, effervescing, heating, mouth watering, crunchiness, stickiness, physical form, texture e g hardness, softness, roughness, and engravings.

[0031] The term "nicotine mimicking component" is herein intended to mean a component that in some respects may be considered to share or resemble any organoleptic feature of nicotine irrespective of the form of nicotine.

[0032] The term "intra-oral dosage form" is herein intended to mean dosage form intended for administration into the systemic

blood circulation by means of absorption of an active principle, i.e. a pharmaceutically active compound, by any tissue of the oral cavity.

[0033] The term "oral formulation" or similar is herein intended to mean all formulations being suitable to be placed in the oral cavity for delivering nicotine essentially to the tissue of the oral cavity.

[0034] The term "complete reduction" or "complete" is herein intended to mean complete or substantially complete reduction.

[0035] The term "controlled release" is intended to mean a release of nicotine from an oral formulation in the oral cavity of the subject, whereby active sucking or other manipulation of the oral formulation is controlling the amount of nicotine released.

[0036] The term "disintegration" is intended to mean disintegration of a portion into particles and subsequent solubilization as well as dissolving of a portion or melting of a portion and the spreading of a liquid.

[0037] The term "portion" is intended to mean a separate entity of a dosage form. Examples of a portion is e.g. a tablet layer, a hard boiled candy layer, a melt layer, a film, a liquid, a capsule, a coating, and a wine gum.

[0038] The term "slow release" is intended to mean that e g nicotine is released from the oral formulation upon sucking or other manipulation over a period of time for example, several minutes to an hour.

[0039] The term "unit formula" is intended to mean one multi portion intra-oral formulation unit.

[0040] The term "transient" is intended to mean a non-permanent change, upon which the relevant state, e g biological or physiological state, after a certain period of time will return to its value or behaviour prior to said change.

[0041] The terms "buccal" and "buccally" are herein intended to pertain to all of or any part of the tissue of the oral cavity.

[0042] The term "coating" or "coating layer" or similar is here intended to mean a layer which totally encloses a solid or semi-solid object, e g a solid or semi-solid pharmaceutical dosage form. A multiportion intra-oral dosage form according to the present invention may or may not be coated.

Summary of the Invention

[0043] The present invention relates to a multi portion intra-oral dosage form as described in claim 1 where at least one portion is rapidly disintegrating and at least one portion is slowly disintegrating, whereby the disintegration time for the slowest disintegrating portion is at least two times longer than for the most rapidly disintegrating portion.

[0044] Of certain interest is use of sensory markers/signals as conceptual aids for the subject, where at least one portion may comprises a component for creating an organoleptic sensation. Also contemplated are a method and a system for delivering nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof as well as use and production of said formulations. Nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form and/or a nicotine-mimicking compound may be included in one or several portions of the dosage form.

[0045] An object of the present invention is thus to provide an efficient and effective product to deliver nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof and/or a nicotine-mimicking compound and optionally component/components for creating an organoleptic sensation to a subject so as to obtain a transmucosal uptake of nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in the oral cavity of the subject. Therefore, the present invention provides the dosage form according to claim 1. Thus, described herein is a method for delivering for example nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form to a subject comprising administering to a subject an oral formulation containing nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form into the oral cavity of the subject and if needed allowing the nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form in the oral formulation to be released in the saliva in the oral cavity

and absorbed into the systemic circulation of the subject as well as a method for producing said oral formulation.

[0046] Also described is a method for obtaining reduction of the urge to smoke or use tobacco containing material and/or for providing a sense of smoking satisfaction without smoking, comprising the steps of replacing at least partly the tobacco containing material with the above said oral formulation, administering to a subject an oral formulation containing nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form into the oral cavity of the subject and if needed allowing the nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form of the oral formulation to be released in the saliva in the oral cavity and absorbed by the subject.

[0047] Also described is a system for delivering nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form to a subject, comprising said oral formulation and at least one other means for obtaining reduction of the urge to smoke or use of tobacco as well as a system for obtaining reduction of the urge to smoke or otherwise use tobacco and/or for providing a sense of smoking satisfaction without smoking, comprising an oral formulation as described above and at least one other method for obtaining reduction of the urge to smoke or otherwise use tobacco. Said system may be a system wherein the at least other method is selected from the group consisting of administration of nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form to a subject through for example, but not limiting to, mouth sprays, nasal sprays, transdermal patches, inhaling devices, lozenges, tablets and parenteral methods, subcutaneous methods, and transmucousal methods; or other use of tobacco.

[0048] In addition, the production of a formulation comprising nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nomicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form for use in therapy is described, wherein the therapy is treatment of a disease selected from the group consisting of tobacco or nicotine dependence, Alzheimer's disease, Crohn's disease, Parkinson's disease, Tourette's syndrome, ulcerous colitis and post-smoking-cessation weight control.

[0049] Other features and advantages of the present invention will be apparent from the detailed description of the invention and from the claims.

Pharmaceutically Active Agent

[0050] The pharmaceutically active agent included within the rapidly disintegrating portion/s or within the slowly disintegrating portion/s may be a smoking cessation compound such as, but not limited to, nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in any form, varenicline, bupropion, nortriptyline, doxepin, fluoxetine, imipramine, moclobemide, and/or cytisine and pharmaceutically acceptable salts, inclusion complexes and prodrugs thereof. +

[0051] The one or more pharmaceutically active agent(s) may also be chosen from

o the antiinflammatory agents diclofenac, ketorolac, indometacin, tornoxicam, piroxicam, tenoxicam, ketoprofen, celecoxib and roficoxib;

o the muscle relaxants orphenadrine and baclofen;

o the drugs affecting bone mineralization alendronic acid and risedronic acid;

o the analgesics propoxyphene, buprenorfin, ketobenidon, hydromorphone, tramadol, morphine, and tapentadol;

o the antimigraine preparations: dihydroergotamine, ergotamine, eletriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan;

o the anti-Parkinson drugs pramipexole, ropinirole and selegiline;

o the anxiolytics alprazolam, diazepam, lorazepam and oxazepam;

o the hypnotics flunitrazepam, midazolam, nitrazepam, triazolam, zaleplone, zopiclone, zolpiderm, clometiazole and propiomazine;

o the psychostimulant caffeine;

o the drugs against substance dependence bupropione, lobeline, naltrexone and methadone;

o the gastric ulcer remedy famotidine;

o the antispasmodic hyoscyamine;

o the antiemetics metoclopramide, ondansetron, scopolamine, hyoscine, perfenazine, prochloperazine and haloperidol;

o the antidiabetic agent rosiglitazone;

o the cardiovascular agents etilefrin, glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate;

o the antihypertensive agent hydralazine;

o the diuretics furosemide and amiloride;

o the beta-receptor blocking agents propranolol and timolol;

o the calcium channel blocker amlodipine;

o the ACE-inhibitors kaptopril, lisinopril and fosinopril;

o the serum lipid reducing agent simvastatin;

o the antipsoriatic acitretin;

• the antiasthmatic terbutaline;

• the antitussives codeine and noscapine;

• the antihistamines clemastine, chlorpheniramine, cyproheptadine, loratadine and acrivastine: the antidepressant and anti-sexual dysfunction drug dapoxetine;

• the anti-sexual dysfunction drugs sildenafil (Viagra), tadalafil, vardenafil, cabergoline and pramipexole,

• the antiepileptic topiramate, and

• the oral and/or gastrointestinal and/or general health promoting agent Lactobacillus reuteri.

where the therapeutic area given shall be regarded as a non-limiting example of a suitable therapeutic area for the stated drug(s).

[0052] In the present invention the dual portion lozenge drug delivery system may be used for delivering nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof to a subject for treating e g tobacco dependence. The drug delivery system provides a potentially advantageous drug delivery system for delivery of nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof, where the rapidly disintegrating portion facilitates a rapid release of nicotine and/or metabolites thereof, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof in the saliva in the oral cavity and subsequent absorption into the systemic circulation of a subject followed by a prolonged release and absorption into the systemic circulation from the slower disintegrating portion/s. A number of nicotine replacement forms are available but the present drug delivery system provides new means for producingsmoking cessation products and increasing the compliance and potentially also reducing the initial nicotine craving as well as the craving over time and hence reducing the urge to use tobacco-containing material.

[0053] The portion/s may also comprise for example, but not limited to, zinc, chlorhexidine, L. reuteri, nystatin, amphotericin, miconazole, phenylephrine, dextromethorphan, pseudoephedrine, acetaminophen, ibuprofen, ketoprofen, loperamide, famotidine, calcium carbonate, simethicone, pseudoephedrine, chlorpheniramine, methocarbomal, chlophedianol, ascorbic acid, menthol, thymol, methyl salicylate and eucalyptol, pectin, dyclonine, benzocaine, and pharmaceutically acceptable salts and derivatives thereof.

Nicotine

[0054] With nicotine it is intended to include nicotine, 3-(1-methyl-2-pyrrolidinyl)-pyridine, with its base form, including synthetic nicotine as well as nicotine extracts from tobacco plants, or parts thereof, such as the genus Nicotiana alone or in combination; or pharmaceutically acceptable salts, inclusion complexes, isomers and prodrugs thereof.

[0055] In preferred embodiments, the nicotine in any form is selected from the group consisting of the free base form of nicotine, a nicotine salt, a nicotine derivative, such as a nicotine cation exchanger, a nicotine inclusion complex or nicotine in any non-covalent binding, nicotine bound to zeolites, nicotine bound to cellulose or starch micro spheres, and mixtures thereof.

[0056] Numerous nicotine salts are known, and may be used, e g the salts presented in Table 1, preferably monotartrate, hydrogen tartrate (also called bitartrate or bitartrate dihydrate), citrate, malate, and/or hydrochloride.

Table 1. Examples of possible acids useful for nicotine salt formation

Acid	Molar ratio* of acid:nicotine
Formic	2:1
Acetic	3:1
Propionic	3:1
Butyric	3:1
2-Methylbutyric	3:1
3-Methylbutyric	3:1
Valeric	3:1
Lauric	3:1
Palmitic	3:1
Tartaric	2:1
Citric	2:1
Malic	2:1
Oxalic	2:1
Benzoic	1:1
Gentisic	1:1
Gallic	1:1
Phenylacetic	3:1
Salicylic	1:1
Phthalic	1:1
Picric	2:1
Sulfosalicylic	1:1
Tannic	1:5
Pectic	1:3
Alginic	1:2
Hydrochloric	2:1
Chloroplatinic	1:1
Silicotungstic	1:1
Pyruvic	2:1
Glutamic	1:1
Aspartic	1:1
* recommended at the time of production	

[0057] The inclusion complex may include cyclodextrin complexation, such as complexation of the active pharmaceutically compound with cyclodextrin where preferably the cyclodextrin used is chosen among α-, β- and γ-cyclodextrin, the hydroxypropyl derivatives of α-, β- and γ-cyclodextrin, sulfoalkylether cyclodextrins such as sulfobutylether β-cyclodextrin, alkylated cyclodextrins

such as the randomly methylated β-cyclodextrin, and various branched cyclodextrins such as glucosyl- and maltosyl-β-cyclodextrin.

[0058] Some suitable cation exchangers are given in below Table 2 and are further disclosed in U.S. 3,845,217. Preferred are nicotine cation exchangers of polyacrylates, such as the Amberlite collection from Rohm & Haas.

Table 2 Examples of cation exchangers

Name	Type of crosslinked polymer	Manufacturer
Amberlite IRC 50	Divinylbenzene-methacrylic acid	Rohm & Haas
Amberlite IRP 64	Divinylbenzene-methacrylic acid	Rohm & Haas
Amberlite IRP 64M	Divinylbenzene-methacrylic acid	Rohm & Haas
BIO-REX 70	Divinylbenzene-acrylic acid	BIO-RAD Lab.
Amberlite IR 118	Styrene-divinylbenzene	Rohm & Haas
Amberlite IRP 69	Styrene-divinylbenzene	Rohm & Haas
Amberlite IRP 69M	Styrene-divinylbenzene	Rohm & Haas
BIO-REX 40	Phenolic	BIO-RAD Lab.
Amberlite IR 120	Styrene-divinylbenzene	Rohm & Haas
Dowex 50	Styrene-divinylbenzene	Dow Chemical
Dowex 50W	Styrene-divinylbenzene	Dow Chemical
Duolite C 25	Styrene-divinylbenzene	Chemical Process Co
Lewatit S 100	Styrene-divinylbenzene	Farbenfabriken Bayer
Ionac C 240	Styrene-divinylbenzene	Ionac Chem.
Wofatit KP S 200	Styrene-divinylbenzene	I.G. Farben Wolfen
Amberlyst 15	Styrene-divinylbenzene	Rohm & Haas
Duolite C-3	Phenolic	Chemical Process
Duolite C-10	Phenolic	Chemical Process
Lewatit KS	Phenolic	Farbenfabriken Bayer.
Zerolit 215	Phenolic	The Permutit Co.
Duolite ES-62	Styrene-divinylbenzene	Chemical Process
BIO-REX 63	Styrene-divinylbenzene	BIO-RAD Lab.
Duolite ES-63	Styrene-divinylbenzene	Chemical Process
Duolite ES-65	Phenolic	Chemical Process
Ohelex 100	Styrene-divinylbenzene	BIO-RAD Lab.
Dow Chelating Resin A-1	Styrene-divinylbenzene	Dow Chemical Company
CM Sephadex C-25	Dextran	Pharmacia Fine Chemicals
SE Sephadex C-25	Dextran	Pharmacia Fine Chemicals

Amount and distribution of the nicotine in the oral formulation

[0059] The term nicotine is below intended to include nicotine metabolites, such as cotinine, nicotine N'-oxide, nornicotine, (S)-nicotine-N-β-glucuronide and mixtures, isomers, salts and complexes thereof unless the context indicates that just nicotine as such is meant,

[0060] The nicotine in any form according to the invention is formulated to provide the subject with a dose to achieve an effect. The effect may be to provide a sense of smoking satisfaction without smoking. Another effect of the administered nicotine in any form may be a reduction of the urge to smoke or use tobacco.

[0061] The effect may also be a combination of reduction of said urge and providing a sense of smoking satisfaction without

smoking. The amount of the nicotine should be sufficient to provide such an effect in a subject. This amount may, of course, vary from person to person.

[0062] According to the invention, embodiments of the oral formulation comprise embodiments wherein nicotine in any form is present in an amount of 0.05 - 12 mg calculated as the free base form of nicotine per unit dose of the oral formulation. This may in different embodiments include 0.05, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 , 11 or 12 mg calculated as the free base form of nicotine per unit dose, preferably in an amount of 0.1 - 6 mg, more preferably in an amount of 1 - 6 mg, and most preferably in an amount of 2 - 5 mg calculated as the free base form of nicotine per unit dose.

[0063] The nicotine in any form may be distributed in the oral formulations in different embodiments. Different distributions of the nicotine throughout the oral formulations will imply administration of the nicotine to the subject in different ways. This may, then, provide several possibilities to adjust the composition of the oral formulation according to different needs of different subjects depending on the urge to smoke or use tobacco of the subject. In the below Examples are disclosed different such embodiments.

Buffering agents

[0064] The rapidly disintegrating portion(s) and/or the slowly disintegrating portion(s) may also comprise a suitable system of buffering agent/s to facilitate nicotine administration. Absorption of nicotine from the oral cavity to the systemic circulation is dependent on the pH of the saliva, pH of the blood plasma and the pKa of nicotine, which is about 7.8. Thus, the level and type of buffering agent/s or combination thereof will affect the pH of the saliva and hence the absorption of nicotine in a free base form, which is the form predominantly absorbed through the mucosa. The buffering is designed so as to achieve a transient buffering of the saliva of a subject during melting, disintegration or dissolution of the oral formulation. As the change is transient, the pH will return to its normal value after a certain period of time.

[0065] The buffering agent may be but are not limited to buffering agents from the group consisting of carbonate (including bicarbonate or sesquicarbonate), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol, and also referred to as tromethamine, tris(hydroxymethyl aminomethane and TRIS), glycinate, different phosphate systems such as trisodium phosphate, disodium hydrogen phosphate; and tripotassium phosphate, dipotassium hydrogen phosphate, glycerophosphate or citrate of an alkali metal (such as potassium or sodium, or ammonium), e g trisodium and tripotassium citrate, different hydroxides, amino acids, e g as per below Table 3, and mixtures thereof.

Table 3 Examples of useful amino acids.

compound	CAS number	pKa value (in interval 8 - 9,6)	Solubility in water, g/kg
Arginine	74-79-3	9,00	182,6a)
Aspargine	70-47-3	8,73	25,1
Glutamic acid	56-86-0	9,58	8,61 a)b)
Glutamine	56-85-9	9,00	42
Glycine	56-40-6	9,58	250,9
Histidine	71-00-1	9,09	43,5
Isoleucine	73-32-5	9,60	34,2
Leucine	61-90-5	9,58	22,0
Lysine	56-97-1	9,16	Very soluble a)b)
Methionine	63-68-3	9,08	56
Phenylalanine	63-91-2	9,09	27,9
Serine	56-45-1	9,05	50,2
Threonine	72-19-5	8,96	98,1
Valine	72-18-4	9,52	88,5
Cysteic acid	13100-82-8	8,70	Very soluble
N-Glycylglycine	556-50-3	8,10	No information
Ornithine	70-26-8	8,78	Very soluble

a) reported as buffer in non-nicotine-containing pharmaceutical formulations.
b) low or uncertain value on solubility in water.

[0066] The captioned data on the amino acids are taken from "Handbook of Chemistry and Physics", 85th edition; Table 7-1 ("20 standard amino acids that are the basic constituents of proteins") and Table 7-2 ("Amino acids and related compounds of biochemical importance").

Other additives to the oral formulation

[0067] Other additives may be added optionally to the oral formulation. Optional additives comprise at least one or more additives selected from the group consisting of solvents, such as ethanol and water; co-solvents, such as propylene glycol; stabilisers, such as preservatives, e g antioxidants; softeners, such as sorbitol and glycerine; thickening agents, such as colloidal silicon dioxide; binding agents, such as xanthan gum; filling agents, such as mannitol, isomalt, cocoa powder and Crospovidone; solubilizers, such as Polysorbat 80 and Atmos 300; rubbers, lipid barriers, such as sucrose fatty acid esters and hydrogenated vegetable oils; film forming agents, such as porcine gelatine, Pullulan, carrageenan, pectin, locust bean gum and xanthan gum; emulsifiers, such as pectin, soy lecithin, glycerol monostearate, castor oil and poloxamer; glidants, such as colloidal silicon dioxide; lubricants, such as magnesium stearate; coating agents, such as castor oil and sorbitol; melting vehicles, such as vegetable oils; sweeteners, flavors, aromatics, cooling agents, enhancers, colouring agents, vitamins, minerals, fluorine, breath fresheners, tooth whitening agents and mixtures thereof. According to the invention, at least one of such additives is optionally added to the product.

[0068] Enhancers may be added essentially to increase the transmucosal uptake of nicotine from the oral cavity.

[0069] Sweeteners are added essentially to improve the taste. Sweeteners comprise one or more synthetic or natural sugars, i e any form of carbohydrates suitable for use as sweetener, as well as so called artificial sweeteners such as saccharin, sodium saccharin, aspartame, e g NutraSweet®, acesulfame or Acesulfame K, potassium acesulfame, thaumatin, glycyrrhizin, sucralose, dihydrochalcone, alitame, miraculin, monellin, stevside and neotame.

[0070] Suitable sweeteners may be selected from the group consisting of sugar alcohols, such as sorbitol, xylitol, single sugars including sugars extracted from sugar cane and sugar beet (sucrose), dextrose (also called glucose), fructose (also called leavulose), and lactose (also called milk sugar); sorbitol, mannitol, glycerol, xylitol, erythritol, maltitol syrup (or hydrogenated starch hydrolyzate), isomalt, lactitol; and mixtures of sugars including glucose syrup, e g starch hydrolysates, containing a mixture of dextrose, maltose and a range of complex sugars, invert sugar syrup, e g sucrose inverted by invertase (also called sucrase or sacchrase) containing a mixture of dextrose and fructose, high sugar content syrups such as treacle and honey containing a mixture of particular leavulose, dextrose, maltose, lactitole, sucrose, resins, dextrin and higher sugars; and malt or malt extracts.

[0071] The flavor and aroma additives may comprise one or more synthetic or natural taste-masking, flavoring or aromatizing agents and may be added as liquids and/or as powder. Flavor and aroma agents may be selected from essential oils including distillations, solvent extractions, or cold expressions of chopped flowers, leaves, peel or pulped whole fruit comprising mixtures of alcohols, esters, aldehydes and lactones; essences including either diluted solutions of essential oils, or mixtures of synthetic chemicals blended to match the natural flavor of the fruit, e g strawberry, raspberry and black currant; artificial and natural flavors of brews and liquors, e g cognac, whisky, rum, gin, sherry, port, and wine; tobacco, coffee, tea, cocoa, and mint; fruit juices including expelled juice from washed, scrubbed fruits such as lemon, orange, and lime; spear mint, pepper mint, wintergreen, cinnamon, cacoe/cocoa, vanilla, liquorice, menthol, eucalyptus, aniseeds, nuts (e g peanuts, coconuts, hazelnuts, chestnuts, walnuts, colanuts), almonds, raisins; and powder, flour, or vegetable material parts including tobacco plant parts, e g genus Nicotiana, in amounts not contributing significantly to the level of nicotine, and ginger.

[0072] Colouring additives may be selected from dyes being approved as a food additive.

[0073] Stabilizing additives may be selected from the group consisting of antioxidants including vitamin E, i e tocopherole, ascorbic acid, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole, edetic acid and edetate salts ; and preservatives including citric acid, tartaric acid, lactic acid, malic acid, acetic acid, benzoic acid, and sorbic acid. Preferred embodiments comprise an antioxidant as the stabiliser, and even more preferably the antioxidant vitamin E and/or butylated hydroxytoluene (BHT).

Compressible Excipients

[0074] In one embodiment, at least one rapidly disintegrating tablet portion includes one or more compressible excipients. In one embodiment the at least one rapidly disintegrating intra-oral tablet portion comprises at least 40% by weight of such compressible excipients. With "compressible excipient" is here meant an ingredient that can be compressed into a tablet shape without the addition of other binding agents. In certain embodiments, the compressible excipient is in the form of a hydrate, and may be selected from organic compounds such as dextrose monohydrate, maltodextrin, lactose monohydrate, and dextrin, as well as inorganic compounds including dibasic calcium phosphate dihydrate, dibasic sodium phosphate dihydrate, dibasic sodium phosphate heptahydrate, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate monohydrate and monobasic sodium phosphate dihydrate. In one embodiment, the rapidly disintegrating tablet portion includes a compressible excipient selected from the group consisting of isomalt, dextrose monohydrate, maltodextrin, lactose monohydrate, dextrin, mannitol, lactitol, sorbitol, xylitol, erythritol, sucrose, and lactose.

[0075] In one embodiment, the compressible excipient(s) are in the form of particles having an average particle diameter of from about 50 to about 500 microns, such as from about 75 to about 400 microns.

[0076] In one embodiment, the rapidly disintegrating tablet portion includes from about 5 to about 90 percent, such as from about 15 to about 75 percent, by weight of one or more compressible excipients. In one embodiment, the disintegrative tablet portion includes at least 40 percent by weight of the one or more compressible excipients, based on the total weight of the disintegrative tablet portion.

Water-Swellable Excipients

[0077] In the present invention, the rapidly disintegrating tablet portion further includes one or more water-swellable excipients as defined in the claims. With "water swellable excipient" is here meant a material that is designed to swell or wick liquid upon contact with a liquid medium and to aid in the disintegration of the compressed tablet. The water-swellable excipient may be selected from superdisintegrants such as crospovidone, croscarmellose, sodium starch glycolate, cellulose compounds such as microcrystalline cellulose, starches, alginic acid and inorganic clays such as bentonite, attapulgite, and magnesium aluminum silicate. In one embodiment, the water-swellable excipient is at least partially hydrated and selected from the group consisting of sodium starch glycolate, crospovidone, croscarmellose, microcrystalline cellulose, starches, hydroxypropyl cellulose, and alginic acid.

[0078] In one embodiment, the amount of water-swellable excipient(s) in the rapidly disintegrating tablet portion is from about 0.1 to about 5 percent by weight, such as from about 0.5 to about 3 percent by weight of the total weight of the rapidly disintegrating tablet portion.

[0079] In one embodiment, the compressible excipient(s) is present in a greater amount than the water-swellable excipient(s). In one embodiment, the ratio of compressible excipient(s) to water-swellable excipient(s) in the disintegrative tablet portion is from about 1:1 to about 150:1, such as from about 10:1 to about 100:1, such as from about 25:1 to about 75:1.

Effervescent Couple

[0080] In one embodiment, the disintegrative tablet portion further includes one or more effervescent couples. In one embodiment, effervescent couple includes one member from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium carbonate, magnesium carbonate, sodium carbonate and one member selected from the group consisting of citric acid, malic acid, fumaric acid, tartaric acid, phosphoric acid, alginic acid.

[0081] In one embodiment, the combined amount of the effervescent couple(s) in the disintegrative tablet portion is from about 0.1 to about 20 percent by weight, such as from about 2 to about 10 percent by weight of the total weight of the disintegrative tablet portion.

Additional information on ingredients

[0082] A rapidly disintegrating tablet portion may include conventional ingredients, including other fillers, which include water-soluble compressible carbohydrates such as dextrose, sucrose, Mannitol, sorbitol, maltitol, xylitol, lactose, and mixtures thereof; other conventional dry binders like polyvinyl pyrrolidone and the like; sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharin; lubricants, such as magnesium stearate, stearic acid, talc, and waxes; preservatives; flavors; disintegrants, antioxidants; acidulants, such as but not limited to citric acid, malic acid, tartaric acid, ascorbic acid, and fumaric acid; surfactants; and coloring agents

[0083] A slowly disintegrating portion or portions may comprise an excipient selected from, but not limited to, the group consisting of isomalt, sucrose, dextrose, dextrose monohydrate, corn syrup, lactitol, lycasin, mannitol, sorbitol, erythritol, xylitol, starches, gelatinized starches, maltodextrin, lactose, lactose monohydrate, dextrin, and mixtures and/or derivatives thereof. The slowly disintegrating portion/s may comprise an excipient selected from but not limited to the group consisting of isomalt, sucrose, dextrose, corn syrup, lactitol, and lycasin, and mixtures and/or derivatives thereof.

[0084] Especially the rapidly disintegrating portion/s may comprise an effervescent couple comprising e g one member selected from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium carbonate, magnesium carbonate, and sodium carbonate and one member selected from the group consisting of citric acid, malic acid, fumaric acid, tartaric acid, and alginic acid.

Examples

[0085] The skilled person may on the basis of the following examples envisage also other embodiments of the present invention. Batch sizes for the manufacture of the below formulations may be modified according to the actual need and to the actual production facilities.

Example 1

[0086] Preparation of a dual portion tablet where the rapidly disintegrating portion contains 0.5 mg nicotine (NRC) together with menthol flavor and the slowly disintegrating portion contains 1.5 mg nicotine (NRC) with a lemon flavor

Method

[0087] The ingredients listed in below Table A 1 and Table A2 are sieved and thereafter blended, each separately, according to methods known in the art e g using a double cone blender. The two portions of blended material are then compressed into tablets by means of direct compression. The powder compression may for example be performed using a double-sided rotary tablet press with individual fill stations and where each of the two layers, i.e. the rapidly disintegrating tablet portion and the slowly disintegrating portion, are subjected to pre-compression and main compression, respectively, to form a dual portion lozenge.

Table A1: Components of the rapidly disintegrating tablet portion.

Ingredients	Percent (w/w)	Mg/portion
Nicotine resin complex (20% nicotine)	0.625	2.5*
Crospovidone	0.75	3
Microcrystalline Cellulose (Avicel PH100)	5	20
Dextrose Monohydrate	90.74	362.96
Trometamol	1.875	7.5
Menthol	0.25	1
Coloring agent	0.01	0.04
Magnesium Stearate	0.75	3
TOTAL	100.0	400
* Equivalent to 0.5 mg dose of nicotine.		

Table A2: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	mg/portion
Nicotine resin complex (20% nicotine)	0.75	7.5
Sorbitol	95.75	957.5
Trometamol	1.0	10
Sodium Carbonate	0.5	5
Lemon flavor	1	10
Magnesium Stearate	1	10
TOTAL	100.0	1000.0
* Equivalent to 1.5 mg Dose of nicotine.		

Example 2

[0088] Preparation of a dual portion tablet where the slowly disintegrating portion has a rough geometric pattern or form or shape and the rapidly disintegrating portion has a smooth surface.

Method

[0089] The same method as in Example 1, but for the shape of the punches used.

Table B1: Components of the rapidly disintegrating portion.

Ingredients	Percent (w/w)	mg per tablet
Nicotine bitartrate dihydrate	0.77	3.08*
Crospovidone	0.75	3
Microcrystalline Cellulose (Avicel PH100) 100101)	5	20
Dextrose Monohydrate	85.32	345.28
L-Arginine	5.4	21.6
Lemon	1	4
Coloring agent	0.01	0.04
Magnesium Stearate	0.75	3
TOTAL	100.0	400
* Equivalent to a 1.0 mg dose of nicotine.		

Table B2: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	Mg/hard candy portion
Nicotine resin complex (20% nicotine)	1	10*
Isomalt	91.68	926.8
L-Arginine	4.32	43.2
Mint	1	10
Magnesium Stearate	1	10
TOTAL	100.0	1000.0
* Equivalent to a 2.0 mg dose of nicotine.		

Example 3

[0090] Preparation of a dual portion tablet where the tablet upon contact with the saliva shows that the rapidly disintegrating

portion is softer and may be experienced as flaky/crumbly as it disintegrates and the slowly disintegrating portion is harder and do not crumble/flake.

Method

[0091] The same method and the same formulation as in Example 1 and 2 are used, but without added flavor. Hereby the difference in flakiness/crumbliness between the portions becomes more noticeable than in Examples 1 and 2.

Example 4

[0092] Preparation of a triple portion tablet with two rapidly disintegrating portions, where one portion comprises 1 mg nicotine and the other portion comprises cinnamon flavor, and one slowly disintegrating portion, which comprises 3 mg nicotine.

Method

[0093] Manufacturing principles according to the preceding examples are used.

Table C1: Components of the first rapidly disintegrating tablet portion containing 1.0 mg nicotine.

Ingredients	Percent (w/w)	mg/portion
Nicotine resin complex (20% nicotine)	1.25	5*
Crospovidone	0.75	3
Microcrystalline Cellulose (Avicel PH100)	5	20
Dextrose Monohydrate	91.345	360.46
Trometamol)	1.875	7.5
Menthol	0.25	1
Coloring agent	0.01	0.04
Magnesium Stearate	0.75	3
TOTAL	100.0	400
* Equivalent to 1.0 mg dose of nicotine.		

Table C2: Components of the second rapidly disintegrating tablet portion containing cinnamon flavor.

Ingredients	Percent (w/w)	mg/portion
Crospovidone	0.75	3
Microcrystalline Cellulose (Avicel PH100)	5	20
Dextrose Monohydrate	91.345	360.46
Trometamol	1.875	7.5
Cinnamon	1.5	6
Coloring agent	0.01	0.04
Magnesium Stearate	0.75	3
TOTAL	100.0	400

Table C3: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	mg/portion
Nicotine resin complex (20% nicotine)	1.5	15
Sorbitol	96.5	965
Trometamol	1.0	10
Sodium Carbonate	0.5	5
Lemon flavor	1	10

Ingredients	Percent (w/w)	mg/portion
Magnesium Stearate	1	10
TOTAL	100.0	1000.0
* Equivalent to 3.0 mg dose of nicotine.		

Example 5

[0094] Preparation of a double portion tablet as in Example 1, but where a pre-compressed slowly disintegrating portion has the shape of a torus in which the powder of the rapidly disintegrating portion is filled where after main compression is performed.

Example 6

[0095] Preparation of a double portion tablet with 2 mg nicotine containing a slowly disintegrating boiled sugar portion and a rapidly disintegrating tablet portion.

Method

[0096] The method for preparing the slowly disintegrating boiled sugar portion is as follows: Sieve the dry materials given in above Table D1. Add purified water, isomalt and maltitol solution to a stainless steel beaker. Mix and heat to ca 170°C during continuous mixing until the water is evaporated. Discontinue heating and cool to 135-140 °C. Add nicotine bitartrate dihydrate and mix until fully dispersed. Add buffer components and mix at 120 °C until dispersed thereafter add flavor and mix until uniform. While in the flowable state, deposit the hard candy portion blend into a circular stainless steel molds with dual flat faces. The resulting boiled sugar portion is allowed to cool and harden at room temperature for approximately 15 minutes. The hard candy portion is then placed into a rubber mold. Approximately 30 milligrams of powdered polyethylene glycol (PEG) 3350 is evenly dispersed along one surface of the hard candy portion.

Table D1: Components of the slowly disintegrating boiled sugar portion blend.

Ingredients	Percent (w/w)	mg/hard candy portion
Nicotine bitartrate dihydrate (32.55% Nicotine)	0.538	5.376*
Isomalt	76.46	764.6
Maltitol 75 % solution	19.5	195
Sodium carbonate anhydrous	1	10
Sodium Bicarbonate	0.5	5
Flavoring agents	2	20
Purified water	-	-
TOTAL	100.0	1000.0
*Equivalent to a 1.75 mg does of nicotine.		

[0097] A flat-faced compressed tablet is manufactured according to Example 1 with components as per below Table D2.

Table D2: Components of the rapidly disintegrating tablet portion.

Ingredients	Percent (w/w)	mg per tablet
Nicotine bitartrate dihydrate (32.55% Nicotine)	0.192	0.768*
Crospovidone	0.75	3
Microcrystalline Cellulose (Avicel PH 100) 100101)	5	20
Dextrose Monohydrate	88.8	355.19
Sodium carbonate anhydrous	2.5	10

Ingredients	Percent (w/w)	mg per tablet
Flavoring agent	2	8
Coloring agent	0.01	0.04
Magnesium Stearate	0.75	3
TOTAL	100.0	400
* Equivalent to a 0.25 mg dose of nicotine.		

[0098] The rapidly disintegrating tablet portion is adjoined to the boiled hard candy portion as follows: A flat-faced compressed tablet as per above is placed on top of the hard candy portion, and the resulting dosage form is placed into an oven providing a temperature being so high that the PEG 3350 melts and creates an adhesion between the compressed tablet and the hard candy portion. The resulting dual portion tablet is then allowed to cool at room temperature for 30 minutes and removed from the rubber mold.

Example 7

[0099] Preparation of a double portion tablet with 2 mg nicotine, containing a slowly disintegrating hard boiled candy portion and a rapidly disintegrating melt tablet portion.

Method

[0100] The slowly disintegrating hard boiled candy portion is prepared according to Example 6.

[0101] To prepare the melt tablet portion with composition as per below Table E1a part of the hydrogenated soybean oil is first melted. Then the solid components, i e the cocoa powder, mannitol, acesulfame-K, and the flavoring agents, if solid, are added and mixed. A reduction of particle size of the solid components is performed by milling in a roll-refiner. If the solid components have already got the required particle size, e g by milling before the mixing with the oil, roll refining is dispensed with. After treatment in the roll-refiner the mixture is mixed with the rest of the melted fatty components or remelted, if solidified, and mixed with the rest of the melted hydrogenated soybean oil. A mixing of the melt is performed in a suitable mixer. The liquid components, i e the soy lecithin and the flavoring agents (if liquid), are added at this stage. The two portions, hard boiled candy and melt tablet, are then combined by dispensing the melt on top of the cooled and hardened hard boiled candy portion in a suitable mold. The melt is then allowed to solidify by cooling at 8-15 °C for 2 hours. The complete dual portion dosage form is then broken from the mold and suitably packaged.

Table E1: Components of the melt tablet portion.

Ingredients	Percent (w/w)	mg/melt tablet portion
Hydrogenated soybean oil	40,0	80,0
Cocoa powder	38,3	76,6
Mannitol	20,0	40,0
Acesulfame-K	0,4	0,8
Flavoring agents	1,0	2,0
Soy lecithin	0,7	1,4
TOTAL	100,0	200,0

Comparative Example 8

[0102] Preparation of seamless softgel concentric triple portion intra-oral capsules.

Table F1: Components of the triple portion capsules.

Ingredients	Percent in portion (w/w)	mg/capsule
Ingredients in Centre Core		
Portion:		
	2.2	2.0
Nicotine free base	91.8	83.5
Medium chain triglycerides	5.5	5.0
Flavors and sweeteners Colloidal silicon dioxide	0.5	0.5
Ingredients of Inner Shell		
Portion:	58.0	24.7
	38.0	16.2
Sucrose fatty acid ester Hydrogenated vegetable oil Sodium carbonate anhydrous	4.0	1.7
Ingredients of Outer Shell	77.0	6.5
Portion:	18.0	1.5
	3.0	0.3
Gelatin	2.0	0.2
Sorbitol		
Flavors and sweeteners		
Glycerin		
Weight Ratio:		
Core/Inner shell/Outer shell	64/30/6 %	
Total Capsule weight:		142.1 mg

Method

[0103] Seamless softgel capsules are manufactured by formation of droplets consisting of two or more concentric layers with ingredients as per above Table F1. The droplets are formed by feeding different liquids through concentric nozzles. The outermost nozzle feeds a hydrophilic solution consisting of gelatin and additives e g plasticizers. The one or more inner nozzles feed a lipophilic liquid (e g oils, triglycerids) wherein one or more active substances may be dispersed. The lipophilic centre and hydrophilic perimeter of the formed droplets ensure a good phase separation between shell and core contents. The formed capsules are then subjected to sequential processing steps such as cooling, drying, washing and selection of size and shape.

Example 9.

[0104] Preparation of a Sugar-free Chewing Sweet

[0105] A chewy dual portion dual portion formulation where the rapidly disintegrating portion contains 1 mg nicotine (NRC) together with menthol flavor and the slowly disintegrating portion contains 2 mg nicotine (NRC) with a lemon flavor may be prepared by essentially using the method described in US 6,372,271B1. Optionally a stabilising layer may be added to the soft caramel mixture.

Preparation of the Soft Caramel Mixture For the Centre

Method

[0106] ISOMALT.RTM. (Type M), maltitol syrup and water are heated at 125-135°C, preferably 131°C, in a boiler. Add the gelatine solution. Add vegetable fat, emulsifier, citric acid, ISOMALT.RTM. (Type PF) in the given sequence, while mixing at high speed for 2 to 3 minutes until an homogenous mixture is obtained. Add fruit flavouring, mix, and empty the boiler. Homogenise using a suitable homogeniser. Cool the mixture to 42 to 48°C Pulling time for the mixture for the centre: 1 to 15 minutes, preferably 8 minutes. The preparation of the soft caramel mix can be carried out in a batch cooker or continuous cooking equipment. Pulling of the mixture is carried out with standard pulling machines or continuous pulling machines or, in the case of aeration, with standard aerators.

[0107] *Forming of the Mixture:* Processing of the mixture is carried out in the normal way, in which the forming of the fillings is performed by an embossing machine. The surface temperature of the rope before the stamping operation is not greater than 35°C After stamping, the fillings pass through a cooling tunnel. Afterwards, the temperature is 10 to 30°C, preferably 25°C

[0108] *Pregumming*: Immediately after leaving the cooling tunnel, the fillings are collected in containers and pregummed. For this purpose, a 50% Quick Coat solution (gum arabic, Wolff & Olsen, Hamburg) with 10% titanium dioxide is prepared, which is applied in one amount to the fillings so that the filings are well-moistened, then the applied solution is sprinkled with Quick Coat powder until the fillings are dry. This process is repeated up to two or three times so that the fillings are stabilized against changes in volume and do not stick together.

Table G1: Composition of the rapidly disintegrating portion

Ingredients	Percent (w/w)	mg/portion
Nicotine resin complex (20% nicotine)	0.75	15*
ISOMALT .RTM. (Type M)	24.20	484
Maltitol syrup (75% TS)	49.70	994
ISOMALT .RTM. (Type PF)	8.40	168
Vegetable fat (34-36.degree. Sp)	5.80	116
Water	5.00	100
Gelatin 120 Bloom (40%)	3.55	71
Trometamol)	0.5	10
Sodium Carbonate	0.25	5
Emulsier	0.75	15
Citric acid (monohydrate)	0.70	14
Lemon flavor	0.40	8
TOTAL	100.0	2000
* Equivalent to a 3.0 mg dose of nicotine.		

[0109] *Sweet Coating:* Preparation of the Solution. ISOMALT.RTM. (Type M) is mixed in warm water and heated to 70 to 80°C until the solution is free of crystals. Preparation of the Suspension: The solution prepared as previously described is cooled to 60°C Aspartame, acesulfame K, gum arabic solution, TiO_2 and ISOMALT.RTM. (Type PF) are added and stirred until a homogeneous mixture is obtained. The temperature of the suspension is maintained at 60°C during the process.

Table G2: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	mg/portion
Nicotine bitartrate dihydrate	0.88	3.08*
ISOMALT .RTM. (Type M)	40.23	140.80
Water	29.00	101.5
ISOMALT .RTM. (Type PF)	22.15	77.53
Gum arabic (solution 1:1)	4.10	14.35
Trometamol)	2.14	7.49

Ingredients	Percent (w/w)	mg/portion
TiO_2	1.00	3.5
Menthol	0.4	1.4
Acesulfame K	0.05	0.175
Aspartame	0.05	0.175
TOTAL	100.0	350
* Equivalent to a 1.0 mg dose of nicotine.		

[0110] A stabilizing layer consisting of a soft caramel mixture may also be included.

Example 10.

[0111] Preparation of a tablet containing 2mg nicotine and $10x10^6$ cfu Lactobacillus reuteri ATCC PTA-5289

[0112] Preparation of a dual portion tablet where the rapidly disintegrating portion contains Lactobacillus reuteri for improved oral health together with fruit flavor and the slowly disintegrating portion contains 2.0 mg nicotine (NRC) with a mint flavor

Method

[0113] The same method as in Example 1 is used.

Table H1: Components of the rapidly disintegrating tablet portion.

Ingredients	mg or amount / portion
Lactobacillus reuteri ATCC PTA-5289	$10x10^6$ cfu
Crospovidone	3
Microcrystalline Cellulose (Avicel PH100) 100101)	20
Dextrose Monohydrate	360
Fruit flavor	1
Coloring agent	0.04
Magnesium Stearate	3

Table H2: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	mg/portion
Nicotine resin complex (20% nicotine)	1	10*
Sorbitol	95.5	955
Trometamol	1.0	10
Sodium Carbonate	0.5	5
Mint flavor	1	10
Magnesium Stearate	1	10
TOTAL	100.0	1000.0
* Equivalent to a 2.0 mg dose of nicotine.		

Example 11.

[0114] Preparation of a tablet containing Terbutaline sulfate 5mg and Loratadine 10mg

Table A1 : Components of the rapidly disintegrating tablet portion.

Ingredients	Percent (w/w)	Mg/portion
Terbutaline sulfate	1.67	5
Crospovidone	3.33	10
Mannitol	93.15	279.46
Menthol	0.33	1
Sweetner	0.50	1.5
Coloring agent	0.01	0.04
Magnesium Stearate	1.00	3
TOTAL	100.00	300

Table A2: Components of the slowly disintegrating portion.

Ingredients	Percent (w/w)	mg/portion
Loratadin	1	10
Sorbitol	97	966.5
Citric acid	0.35	3.5
Lemon flavor	1	10
Magnesium Stearate	1	10
TOTAL	100.0	1000.0

[0115] Preparation of a dual portion tablet where the rapidly disintegrating portion contains terbutaline sulfate as a beta-adrenergic agonist bronchodilator together with menthol and the slowly disintegrating portion contains Loratadine with a lemon flavor.

Method

[0116] The same method as in Example 1 is used.

[0117] Also many other embodiments than those presented in the captioned examples are encompassed by the present invention.

[0118] One such other embodiment is e g a chewy preparation with a hard coating. The centre of such a preparation may be a soft caramel mixture comprising nicotine resin complex, isomalt, maltitol syrup, vegetable fat, gelatine, emulsifier, buffer and flavour. This soft centre may be manufactured using conventional technology. The centre is subsequently hard coated with a coating solution comprising nicotine bitartrate dihydrate, isomalt, gum arabic, buffer, sweetener, and flavour. It should be noted that one form of nicotine is used in the centre and another form of nicotine is used in the coating. Optionally a a thin stabilizing layer, consisting of a soft caramel mixture, may placed between the soft centre and the hard coating.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US5810018A [0012]
- US5939100A [0012]
- US4967773A [0012]

- US4579858A [0013]
- DE3241437 [0013]
- WO9312764A [0013]
- US5167242A [0015]
- US3877466A [0016]
- US3901248A [0016]
- US3845217A [0016] [0058]
- US6106861A [0018]
- US6024981A [0018]
- WO9947126PCT [0018]
- US5879710A [0021]
- US5236713A [0022]
- WO199201445A [0023]
- US20060073189A1 [0024]
- US5681583A [0025]
- US20030118648A1 [0026]
- WO2001037814A [0027]
- US6248760B [0028]
- US6372271B1 [0105]

Non-patent literature cited in the description

- Centers for Disease Control and Prevention, cigarette smoking among adults - United StatesMMWR, 1995, vol. 46, 1217-1220 [0005]
- **RUSSELL et al.**British Medical Journal, 1983, vol. 286, 683- [0013]
- **JARVIS et al.**Brit. J. of Addiction, 1987, vol. 82, 983- [0013]
- **ROSE**Pharmacologic Treatment of Tobacco DependenceHarvard Univ. Press19860000158-166 [0014]
- Handbook of Chemistry and Physics [0066]

Patentkrav

1. Flerdelt intraoral doseringsform omfattende en komponent til behandling af tobaksafhængighed, hvilken er nikotin og/eller metabolitter deraf, valgt fra cotinin, nikotin-N'-oxid, nornikotin- og (S)-nikotin-N-β-glucuronid og blandinger, isomerer, salte og komplekser deraf i en hvilken som helst form,
hvor mindst en del af den flerdelte intraorale doseringsform hurtigt desintegrerer og mindst en del langsomt desintegrerer, hvor henfaldstiden for delen med den langsomste desintegration er mindst to gange længere end for delen med den mest hurtige desintegration, og hvor hver del omfatter mindst et element valgt fra følgende elementer:

en farmaceutisk aktiv komponent, en nikotin-efterlignende komponent, en pH-buffer komponent, en pH-regulerende komponent, et smagsstof, en barrierekomponent, en farvekomponent, en klæbemiddelkomponent, et smagsmaskeringsmiddel, et tandafblegningsmiddel, et åndeforfriskningsmiddel, et oralt sundhedsfremmende middel, et anti-cariesmiddel, og et anti-inflammatorisk middel; og

hvor mindst én hurtigt desintegrerende del yderligere omfatter en vand-kvældbar excipiens valgt fra natriumstivelsesglycolat, crospovidon, croscarmellose, mikrokrystallinsk cellulose, stivelser, hydroxypropylcellulose, og alginsyre.

2. Flerdelt intraoral doseringsform ifølge krav 1, hvor en farmaceutisk aktiv komponent er en komponent til behandling af tobaksafhængighed.

3. Flerdelt intraoral doseringsform ifølge krav 1 eller 2 der ikke er et tyggegummi eller triturat.

4. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav,
omfattende en buffer og/eller et pH-justerende middel, hvilket ved administration til et individ midlertidigt forhøjer pH af individets spyt med 0,2 – 3,5 pH enheder, fortrinsvis med 0,5-2,0 pH enheder.

5. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 2 - 4, hvor mindst en af de hurtigt og langsomt desintegrerede dele omfatter en komponent til at danne en mærkbar organoleptisk følelse; hvor fortrinsvis den organoleptiske følelse/følelser er i form af én eller flere af sanseindtryk af eller en ændring i sanseindtrykket af smag, afkøling, forbrænding, varme, opvarmning, knasning, prikning, sprudlende, skumning, brusning, mundvand, fysisk form, klæbrighed, og tekstur, fx hårdhed, blødhed, ruhed og gravering; hvor fortrinsvis den organoleptiske følelse/følelser er således at den/de gør det let for et individ der anvender doseringsformen at differentiere mellem forskellige dele deraf; og hvor fortrinsvis den organoleptiske følelse er et sanseindtryk af smag eller en ændring i sanseindtrykket af smag.

6. Flerdelt intraoral doseringsform ifølge krav 5, hvor en organoleptisk følelse leveres fra en del som et signal til at informere et individ der anvender doseringsformen at en vis fraktion af, eksempelvis mere end tre fjerdedele af, alt af eller næsten alt af, en farmaceutisk aktiv bestanddel der indledningsvis er til stede i delen er blevet frigivet derfra.

7. Flerdelt intraoral doseringsform ifølge krav 5 eller krav 6, hvor en organoleptisk følelse leveres fra en del som et signal til at informere et individ der anvender doseringsformen at en farmaceutisk aktiv bestanddel der er til stede i delen er påbegyndt at blive frigivet derfra.

8. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor

I. de hurtigt og langsomt desintegrerede dele omfatter det samme farmaceutisk aktive middel, eller

II. de hurtigt og langsomt desintegrerede dele omfatter forskellige farmaceutisk aktive midler, eller

III. de hurtigt og langsomt desintegrerende dele, uden hensyn til deres respektive henfaldstid, har de samme eller forskellige farmaceutiske aktive midler, og/eller

IV. doseringsformen giver mulighed for at inkludere ikke-kompatible bestanddele, såsom smagskomponenter, buffere og farmaceutisk aktive midler der ikke er kompatible, ved formulering af sådanne bestanddele i separate dele.

9. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor henfaldstiden for den langsomst desintegrerende del er 3 - 10 gange længere, fortrinsvis 3 - 5 gange længere, end for den hurtigst desintegrerende dele.

10. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor de hurtigt integrerende del(e) omfatter et brusemiddel.

11. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor den mindst ene hurtige desintegrerende del mindst delvist dækker den mindst ene langsomt desintegrerende del.

12. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor de langsomt integrerende del(e) mindst delvist dækker overfladen af den hurtigt desintegrerende dele.

13. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, i form af en pastil, en tablet, en oral film, en sublingual tablet, en troche, en slikkepind, et bolsje, en chokoladelinse, en mikrokugle, gele, et gelebolsje, en vingummi, et halvfast stof, en centerfyldt doseringsform eller en kombination deraf.

14. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, hvor hver desintegrerende del er sammensat af to eller flere underdele, hver underdel omfattende et farmaceutisk aktivt middel, hvor det farmaceutisk aktive middel i mindst én af disse underdele er overtrukket.

15. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav omfattende en komponent til behandling af tobaksafhængighed, der er valgt

fra gruppen bestående af et nikotin-salt, den frie baseform af nikotin, et nikotinderivat, såsom en nikotin-kationombytter, et nikotin-inklusionskompleks eller nikotin i en hvilken som helst ikke-kovalent binding, nikotin bundet til zeolitter, nikotin bundet til cellulose eller stivelsemikrokugler, et nikotin-pro-drug, og/eller blandinger deraf; hvor nikotin-inklusionskomplekset fortrinsvis er et cyclodextrinkompleks, hvor cyclodextrinen der anvendes er valgt blandt α-, β- og γ-cyclodextrin, hydroxypropylderivater af α-, β- og γ-cyclodextrin, sulfoalkylethercyclodextriner såsom sulfobutylether-β-cyclodextrin, alkylerede cyclodextriner såsom tilfældigt methyleret β-cyclodextrin, og forgrenede cyclodextriner såsom glucosyl- og maltosyl-β-cyclodextrin; og hvor nikotinkationombytteren fortrinsvis er en polyacrylatkationombytter; og hvor nikotin-saltet fortrinsvis er monotartrat-, hydrogentartrat-, citrat-, malat- og/eller hydrochloridsalt; hvor nikotin-og/eller metabolitter deraf er til stede i en mængde på 0,05 - 12 mg, fortrinsvis i en mængde på 0,1 - 6 mg, mere fortrinsvis i en mængde på 1 - 6 mg, og mest fortrinsvis i en mængde på 2 - 5 mg beregnet som den frie baseform af nikotin pr. enhedsdosis.

16. Flerdelt intraoral doseringsform ifølge et hvilket som helst af de foregående krav, omfattende en komponent til behandling af tobaksafhængighed der er valgt fra én eller flere af vareniclin, bupropion, nortriptylin, doxepin, fluoxetin, imipramin, moclobemid, og/eller cytisin.

17. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 til anvendelse for at opnå en hurtig og/eller vedvarende og/eller fuldstændig reduktion af trangen til røg eller anvendelse af tobak.

18. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16, hvor mindst én hurtigt desintegrerende del omfatter en komprimerbar excipiens valgt fra isomalt, dextrosemonohydrat, maltodextrin, lactosemonohydrat, dextrin, mannitol, lactitol, sorbitol, xylitol, erythritol, saccharose, og lactose, og blandinger eller derivater deraf; hvor fortrinsvis den hurtigt desintegrerende del omfatter mindst 40 vægtprocent af en komprimerbar excipiens valgt fra isomalt, dextrose monohydrate, maltodextrin, lactosemonohydrat, dextrin, mannitol, lactitol, sorbitol, xylitol, erythritol, saccharose, og lactose, og blandinger deraf; hvor

fortrinsvis den komprimerbare expiens er i form af partikler med en gennemsnitlig partikeldiameter på ca. 50 til ca. 400 mikrometer.

19. Flerdelt intraoral doseringsform ifølge krav 18, hvor vægtforholdet af den komprimerbare expiens til den vand-kvældbare excipiens er fra ca. 10:1 til ca. 500:1.

20. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16, hvor mindst én hurtigt desintegrerende del yderligere omfatter en pH-buffer komponent og/eller en pH-justerende komponent valgt fra et carbonat inkluderende bicarbonat eller sesquicarbonat, glycinat, phosphat, glycerophosphat eller citrat af et alkalimetal, såsom kalium eller natrium, eller ammonium, inkluderende trinatriumphosphat, dinatriumhydrogenphosphat; trikaliumphosphat, dikaliumhydrogenphosphat, og calciumhydroxid, natriumglycinat, trometamol eller en aminosyre; og blandinger deraf.

21. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 20, hvor den hurtigt desintegrerende del eller dele har en hårdhed på mindre end ca. 15 kp/cm^2, og den langsomt desintegrerende del eller dele har en hårdhed på større end ca. 15 kp/ cm^2.

22. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 21, hvor den langsomt desintegrerende del eller dele omfatter en excipiens valgt fra, men ikke begrænset til, gruppen bestående af isomalt, saccharose, dextrose, dextrosemonohydrat, majssirup, lactitol, lycasin, mannitol, sorbitol, erythritol, xylitol, stivelser, gelatinerede stivelser, maltodextrin, lactose, lactosemonohydrat, dextrin, og blandinger og/eller derivater deraf.

23. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 -22, hvor den langsomt desintegrerende del eller dele omfatter mindst 50 vægtprocent, af en sukker valgt fra isomalt, saccharose, dextrose, majssirup, lactitol, og lycasin, og blandinger og/eller derivater deraf; hvor fortrinsvis den hurtigt desintegrerende del eller dele yderligere omfatter et brusemiddel-par omfattende et medlem valgt fra gruppen bestående af natriumbicarbonat, kaliumbicarbonat, calciumcarbonat, magnesiumcarbonat, og natriumcarbonat og

et medlem valgt fra gruppen bestående af citronsyre, æblesyre, fumarsyre, vinsyre, og alginsyre.

24. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18-23, hvor det farmaceutisk aktive middel er i form af partikler der yderligere er overtrukket med en smagsmaskeringspolymer og hvor den gennemsnitlige partikeldiameter af partiklerne er fra ca. 50 mikrometer til ca. 1000 mikrometer.

25. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 -24, hvor mindst én af de langsomt desintegrerende dele omfatter er flerhed af åbninger der eksponerer overfladearealet af den/disse del(e), og i det væsentlige dækker overfladearealet af mindst de hurtigt desintegrerende dele, hvor de langsomt desintegrerende del(e) yderligere omfatter en flerhed af indhak, som under kontakt med væsker i den orale kavitet, er tilpasset til at opløse og eksponere overfladearealet af de hurtigt desintegrerende del(e).

26. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 25, hvor et farmaceutisk aktivt middel inde i en hurtig desintegrerende del er valgt fra gruppen bestående af zink, chlorhexidin, L. reuteri, nystatin, amphotericin, miconazol, phenylephrin, dextromethorphan, pseudoephedrin, acetaminophen, ibuprofen, ketoprofen, loperamid, famotidin, calciumcarbonat, simethicon, pseudoephedrin, chlorpheniramin, methocarbomal, chlophedianol, ascorbinsyre, menthol, pektin, dyclonin, benzocain, og menthol, og farmaceutisk acceptable salte og derivater deraf.

27. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 26, hvor fronten af mindst en del har en konveks form og fronten af en tilstødende del har en konkav form.

28. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 27 der har geometriske lighedspunkter til en sfære, et åbent eller lukket aflangt objekt, en sandwich, en hamburger eller en torus.

29. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 28 der har lag mellem delene der omfatter et spiseligt klæbemiddel-lignende materiale; hvor fortrinsvis det spiselige klæbemiddel-lignende materiale omfatter en bestanddel valgt fra gruppen bestående af polyethylenglycol, polyethylenoxid, polycaprolacton, carnaubavoks, mikrokrystallinsk voks, oppanol, shellakvoks og bivoks.

30. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 29, hvor mindst én hurtigt desingrerende del omfatter mindst ét farmaceutisk middel valgt fra gruppen af phenylephrin, dextromethorphan, chlorpheniramin, chlophedianol, og pseudoephedrin, og hvor mindst én langsomt desintegrerende del omfatter mindst ét farmaceutisk middel valgt fra gruppen af menthol, nikotin, dyclonin, pektin, benzocain, thymol, methylsalicylat og eucalyptol.

31. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 – 30, hvor mindst én hurtigt desintegrerende del er i det væsentlige fri for nikotin, hvor i det væsentlige fri er defineret som indeholdende 0,05 mg pr. enhedsdosis eller derunder.

32. Flerdelt intraoral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 – 31, hvor mindst én hurtigt desintegrerende del er en sammenpresset del og hvor mindst én langsomt desintegrerende del har en matriks der er et bolsje-glas.

33. Flerdelt inter-oral doseringsform ifølge et hvilket som helst af de foregående krav, hvor den langsomt eller den hurtigt desintegrerende del(e) har indhak og/eller huller fyldt med de andre desintegrerende dele.

34. Flerdelt inter-oral doseringsform ifølge et hvilket som helst af kravene 1 - 16 eller 18 - 33 omfattende nikotin-og/eller metabolitter deraf, såsom cotinin, nikotin-N'-oxid, nornikotin, (S)-nikotin-N-β-glucuronid og blandinger, isomerer, salte og komplekser deraf i en hvilken som helst form til anvendelse i terapi hvor terapien er behandling af en sygdom valgt fra gruppen bestående af tobaks- eller

nikotinafhængighed, Alzheimer's sygdom, Crohn's sygdom, Parkinson's sygdom, Tourette's syndrom, ulcerøs colitis.

35. Flerdelt inter-oral doseringsform ifølge et hvilket som helst af de foregående krav, **kendetegnet ved at** det ene eller flere farmaceutisk aktive midler er valgt fra de anti-inflammatoriske midler diclofenac, ketorolac, indometacin, tornoxicam, piroxicam, tenoxicam, ketoprofen, celecoxib og roficoxib; de muskelafslappende midler orphenadrin og baclofen; lægemidlerne alendronsyre og risendronsyre der påvirker knoglemineralisering; de smertestillende midler propoxyphen, buprenorfin, ketobenidon, hydromorphon, tramadol, morfin, og tapentadol; antimigrænepræparaterne: dihydroergotamin, ergotamin, eletriptan, naratriptan, rizatriptan, sumatriptan og zolmitriptan; anti-Parkinson-lægemidlerne pramipexol, ropinirol og selegilin; de angstdæmpende midler alprazolam, diazepam, lorazepam og oxazepam; sovemidlerne flunitrazepam, midazolam, nitrazepam, triazolam, zaleplon, zopiclon, zolpiderm, clometiazol og propiomazin; psykostimulanten koffein; lægemidlerne bupropion, lobelin, naltrexon og metadon mod stofafhængighed; mavesårsmedicinen famotidin; det krampestillende middel hyoscyamin; kvalmemidlerne metoclopramid, ondansetron, scopolamin, hyoscin, perfenazin, procloperazin og haloperidol; de anti-diabetiske midler rosiglitazon; de kardiovaskulære midler etilefrin, glyceryltrinitrat, isosorbid-dinitrat og isosorbid-mononitrat; det blodtrykssænkende middel hydralazin; de vanddrivende midler furosemid og amilorid; de beta-receptor blokerende midler propranolol og timolol; det kalciumkanal blokerende middel amlodipin; ACE-inhibitorerne kaptopril, lisinopril og fosinopril; det serum-lipid-reducerende middel simvastatin; anti-psoriasismidlet acitretin; det antiastmatiske middel terbutalin; de hostehæmmende midler kodein og noskapin, og antihistaminerne clemastin, chlorpheniramin, cyproheptadin, loratadin og acrivastin; det anti-depressive og anti-seksuel dysfunktions lægemiddel dapoxetin; anti-seksuel dysfunktions-lægemidlerne sildenafil (Viagra), tadalafil, vardenafil, cabergolin og pramipexol, det antiepileptiske middel topiramat, og
det oralt og/eller gastrointestinalt og/eller generelt helbredsfremmende middel Lactobacillus reuteri.

36. Flerdelt inter-oral doseringsform ifølge krav 35, **kendetegnet ved at** den omfatter nikotin og Lactobacillus reuteri.

37. Flerdelt inter-oral doseringsform ifølge krav 35, **kendetegnet ved at** den omfatter terbutalin og loratadin.