PRODUCT FOR ORAL DELIVERY

FIELD OF INVENTION

The invention relates to a product for oral delivery of nicotine containing a core comprising a powder of free nicotine salt and pH adjusting agent, and a water insoluble coat, wherein said coat is permeable for saliva and therein dissolved parts of the powder, wherein said product upon contact with purified water gives a pH of at least 6. The invention also relates to a method to manufacture such a product.

BACKGROUND ART

Smoking articles, (*e. g.* cigarettes and cigars) are made from tobacco. The administration of nicotine by smoking provides satisfaction. Smoking is however associated with health hazards which are not necessarily related with the administration of nicotine itself. Important risk factors are substances which are formed or released during the combustion of tobacco, such as carcinogenic nitrosamines as well as other harmful components such as carbon monoxide and tar products.

As smoking of tobacco has health hazards it is desirable to formulate alternative means of administering nicotine in a pleasurable manner to facilitate reduction of or cessation from smoking. Nicotine is a strongly addictive substance and it is generally accepted that the difficulty to quit smoking results from the fact that smokers are dependent upon nicotine. It is therefore desirable to be able to provide nicotine with a low amount of other potential hazardous components. Prior art has suggested, as an alternative to smoking, a number of different nicotine administration forms such as gum, patch, nasal spray, lozenge and oral pouch.

When smoking a cigarette, nicotine is almost immediately absorbed into the smoker's blood and quickly reaches the brain. The quick uptake gives the smoker rapid satisfaction. Therefore, in the treatment with nicotine-containing products a rapid uptake of nicotine is desirable. It is therefore desirable to provide a nicotine

product which rapidly delivers nicotine to the user and thereby provides the user with the desired effect.

It is also desirable to provide a nicotine product which gives an almost complete delivery of the available nicotine to the user to avoid unnecessary waste.

Nicotine base is readily oxidized and formulations containing nicotine base may have problem with the volatility of nicotine. A number of different approaches have been developed to deal with the stability and volatility problems of nicotine base, such as starch microspheres, beta-cyclodextrin complexes and cellulose combinations. However, the nicotine release rate has normally not been the major concern for these formulations and in most cases the approach has resulted in a rather moderate release rate of nicotine. Further, the need for a nicotine complex or combination require a rather intricate manufacturing method. It is therefore desirable to provide a nicotine formulation with a satisfactory chemical stability and low volatility of the nicotine component without compromising the demands for a rapid nicotine delivery and a simple manufacturing method.

"Snus" or snuff is a tobacco mixture from which the consumer forms a portion and places it under the upper lip. Alternatively, the tobacco mixture is already preportioned into pouches which are placed under the upper lip. The use of "snus" normally results in nicotine blood levels with a rather high steady state nicotine blood concentration, but they do not provide the peak levels obtained from smoking. The reason for this is that nicotine is released too slowly from the "snus" product.

Further, "snus" normally deliver only a fraction of the available nicotine to the user. After 30 minutes use, for a number of "snus" products, the delivery of nicotine is often less than 50 %, for some products less than 25 % of the available amount of nicotine.

A nicotine product similar to tobacco "snus" pouches, but with a purer source of nicotine than tobacco, and a faster and more complete release of nicotine could be an important aid in smoke reduction or cessation.

To summarize, it is desirable to provide an improved product for reduction of or cessation from smoking. A product similar to tobacco "snus" pouches, but

without the disadvantages associated with tobacco "snus" pouches, could be an attractive option. The product should give a rapid and almost complete delivery of nicotine, be free from other harmful components, deal with the stability and volatility problems of nicotine base and finally be cheap and simple to manufacture.

SUMMARY OF THE INVENTION

The invention relates to a product for oral delivery of nicotine containing a core comprising a powder of at least one free nicotine salt, at least one pH adjusting agent and optionally other excipients, such as flavors, fillers, and granulating agents, and a water insoluble coat, wherein said coat is permeable for saliva and therein dissolved parts of the powder, wherein said product upon contact with purified water give a pH of at least 6. The invention also relates to a method to manufacture such a product.

Nicotine is generally in either free base or in salt form. Nicotine base is readily absorbed through mucosal membranes. Unfortunately, nicotine base is highly unstable and is difficult to contain using conventional packaging materials. Nicotine salts, on the other hand, are generally stable. Nicotine salts, however, are not readily absorbed through mucosal membranes. While the shelf life and packaging problems could be overcome by incorporating a nicotine salt into the product, such a product would have had an undesirably low nicotine absorption rate through the mucosal membranes. This problem has been solved by incorporating a pH adjusting agent which converts the nicotine salt into nicotine base *in situ*.

Many nicotine salts are known to be physically and chemically stable. By using a suitable pharmaceutically acceptable nicotine salt, instead of nicotine base, the problems with the oxidation and the volatility of nicotine base can be reduced or avoided. By using a nicotine salt it is not necessary to form a complex or a combination between the nicotine and particles or molecules in the powder to protect the nicotine from oxidation and high volatility. The nicotine salt can be free, i.e. it only needs to be mixed or granulated together with the other components in the powder. Further, the nicotine salt shall be reasonably water soluble in order to obtain a rapid dissolution of the nicotine salt in an aqueous liquid, such as the

saliva, in the oral cavity. For a person skilled in the art suitable nicotine salts possessing these properties can easily be selected.

The powder also contains one or more pH adjusting agents. These ensure that when the powder is dissolved in saliva, a local pH on the neutral or alkaline side is obtained. Such a high local pH is important to ensure that the dissolved nicotine is unprotonated and hence can be effectively absorbed through the oral mucosa.

In some embodiments it might be that the nicotine salts and pH adjusting agents need to be separated from each other A high pH can have a negative effect on the stability of the otherwise stable nicotine salt. In these cases the pH adjusting agent may be encapsulated or embedded with a polymer before mixing it with the other components thus physically separating it from the nicotine salt during storage.

The powder described above is contained in a water insoluble coat which prevents the powder particles to leave the coat. The coat can for example be a pouch such as in tobacco “snus” pouches, but other alternative coats can also be envisaged. The coat is permeable to aqueous liquids such as saliva. This means that in operation, saliva present in the oral cavity can penetrate through the coat, dissolve the nicotine salt and the pH adjusting agent in the core, and thereafter transport the dissolved substances out through the coat into the oral cavity. A reaction between the pH adjusting agent and the nicotine salt, results in the formation of unprotonated nicotine. The ratio between unprotonated and protonated nicotine depends on the local pH. Once in the oral cavity, the nicotine can be absorbed through the mucosal membranes.

In a second aspect the invention relates to a method to produce such a product comprising the steps of providing the components used in the powder and mixing the components. If needed, the pH adjusting agent may be encapsulated or embedded with a polymer. A drying step may be necessary if any of the excipients is a liquid. Depending on the desired properties, the powder mixture may or may not be granulated. The powder is thereafter positioned inside the coat which is sealed.

It is for the first time possible to obtain a product comprising a powder mixture with a free nicotine salt that gives a rapid and almost complete delivery of nicotine which becomes available for the consumer, is free from other harmful components, deals with the stability and volatility problems of nicotine base and finally is cheap and simple to manufacture. With the product the consumer will get a faster satisfaction compared to several other products available on the market today, such as nicotine gums.

BRIEF DESCRIPTION OF THE DRAWINGS

In the two figures below, the nicotine release from products according to the disclosed invention as well as reference products are presented.

Figure 1 shows the released nicotine after up to 64 minutes use time (in percent of the amount of nicotine in unused product). The test is an *ex vivo* study where the users change to position of the product under the upper lip with the tongue each fourth minute.

Figure 2 shows the released nicotine after up to 64 minutes use time (in percent of the amount of nicotine in unused product). The test is an *in vitro* study where the product has been placed on a filter paper wetted with either 4.0 g or 20.0 g purified water.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term “free” nicotine salt is intended to mean that the nicotine salt in the product during storage, before use by the consumer, does not form any complex or combination with any other material in the product. By providing the nicotine as a suitable salt, the nicotine source is not volatile or prone of oxidation and thereby stable during storage eliminating the need for a complex or combination.

The term “filler” is intended to mean a material that increase the volume of the powder. In one embodiment the filler is present to increase the volume of pouches to be used under the lip. If a pouch is too small it may stick to the lip and

be difficult or impossible to remove after use. A filler does not form a complex or combination with the nicotine salt in the powder during storage and hence leaves the nicotine salt free.

The term “pH adjusting agent” is intended to mean one or more substances added with the purpose to adjust and control the pH of an aqueous liquid, such as saliva, when the product containing the pH adjusting agent is dissolved or dispersed in said aqueous liquid.

The term “local pH” is intended to mean the pH in an aqueous liquid in close proximity to the product, such as the pH in saliva in close proximity to the product in use. The local pH may influence the properties of the product such as the degree of protonisation of the dissolved nicotine.

The term “physically and chemically stable” nicotine salt is intended to mean a nicotine salt which is physically and chemically stable over its intended storage time. For example, for a pharmaceutical product an acceptable storage time is often two or three years from the date of manufacture while for a tobacco “snus” product an acceptable storage time is often a couple of months from the date of manufacture.

The term “water soluble” nicotine salt is intended to mean a nicotine salt which has an aqueous solubility which adequate for its intended use. A high water solubility often also implies a high rate of dissolution in an aqueous liquid.

The term “purified water” is intended to mean water that is processed to remove impurities by a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.

The term "pharmaceutically acceptable" is intended to mean a non-toxic material that does not decrease the effectiveness of the biological activity of the active ingredients, i.e. the nicotine. Such pharmaceutically acceptable excipients are well-known in the art (see for example Remington's Pharmaceutical Sciences, 18th edition, A. R Gennaro, Ed., Mack Publishing Company (1990) and handbook of Pharmaceutical Excipients, 3rd edition, A. Kibbe, Ed., Pharmaceutical Press (2000).

The term ”encapsulated or embedded pH adjusting agent” is intended to mean a pH adjusting agent which has been encapsulated or embedded in order to

physically separate it from the nicotine salt and thereby give a product which is chemically stable over its intended storage time.

Product

The invention relates to a product for oral delivery of nicotine containing a core comprising a powder of one or more free nicotine salts, one or more pH adjusting agents and optionally other excipients such as flavors, fillers, and granulating agents, and a water insoluble coat, wherein said coat is permeable for saliva and therein dissolved parts of the powder, wherein said product upon contact with purified water give a pH of at least 6.

If the product shall be able to deliver nicotine rapidly and almost completely to the oral cavity under normal user conditions the following demands must be fulfilled.

Firstly, the powder must of course be formulated to release nicotine when subjected to an aqueous liquid. A formulation where the nicotine is tightly bound in for example a complex or a formulation comprising a nicotine salt with a very low aqueous solubility may have an unsatisfactory release of nicotine also in the presence of large amounts of aqueous liquid. It is obvious that formulations with such intrinsic low release rate of nicotine have unsatisfactory nicotine release rates in the oral cavity under normal user conditions.

Secondly, the formulation must have a satisfactory nicotine release also when the amount of aqueous liquid, such as saliva in the oral cavity, is limited. Different formulations may have different demands on the amounts of aqueous liquid needed for a rapid and almost complete delivery of nicotine. Certain formulations, which may release nicotine rapidly in the presence of large amounts of an aqueous liquid, may not satisfactorily deliver nicotine in the oral cavity under normal user conditions as the amount of saliva available is too limited.

Third, the coat must have a design which allows an easy flow of saliva into and out of the core.

Nicotine base is readily oxidized and formulations with nicotine base may have problem with the volatility of nicotine. On the other hand, many nicotine salts

are known to be chemically stable. By using a suitable pharmaceutically acceptable nicotine salt, instead of nicotine base, the problems with the oxidation and the volatility of nicotine can be avoided. By using a physically and chemically stable nicotine salt it is not necessary to bind it to other particles or molecules in the product in order to improve the storage stability *i.e.* the nicotine salt can be free.

The nicotine salt shall be reasonably water soluble in order to obtain a rapid and complete dissolution in the limited amount of saliva entering into the core when the product is used. The saliva is entering the core through the coat, dissolves the nicotine salt, and the dissolved nicotine molecules are transported out of the core, through the coat, with the saliva.

For a person skilled in the art suitable nicotine salts possessing these properties can easily be selected. Examples of suitable nicotine salts are nicotine hydrochloride, nicotine dihydrochloride, nicotine monotartrate, nicotine bitartrate, nicotine bitartrate dihydrate, nicotine sulphate, nicotine zinc chloride monohydrate and nicotine salicylate. In particular, nicotine bitartrate dihydrate is suitable for use in the powder of the invention.

The amount of nicotine salt in one portion may be from 0.1 mg to 10 mg of nicotine (calculated as nicotine base) such as 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0 or 9.0 mg of nicotine.

The pH adjusting agents shall be a pharmaceutically acceptable and provide a pH of 6 or above when the powder in the product is dissolved or dispersed in purified water. Examples of such pH adjusting agents are acetates, glycinates, gluconates, borates, glycerophosphates, ammonium, citrates such as citrates of alkaline metals, carbonates including monocarbonate, bicarbonate and sesquicarbonate, phosphates including monohydrogenphosphate, dihydrogenphosphate and trihydrogenphosphate, and mixtures thereof. One example of a suitable pH adjusting system is sodium bicarbonate and sodium carbonate and mixtures thereof.

In some embodiments it might be that the nicotine salts and pH adjusting agents need to be separated from each other during storage. A high pH can have a negative effect on the stability of the otherwise stable nicotine salt. In these cases

the pH adjusting agent may be encapsulated or embedded with a polymer before mixing it with the other components. Such a encapsulating or embedding will protect the nicotine salt from the alkaline components in the pH adjusting agent. The nicotine salt and the pH adjusting agent will mix only, during use, when the saliva is dissolving and releasing the components into the oral cavity.

Absorption of nicotine from the oral cavity, *i.e.* transmucosal uptake, to the systemic circulation is dependent on the local pH of the saliva inside and close to the product in use. Nicotine will predominantly be absorbed through the mucosa in the nonprotonated form. Therefore, it is preferable with a local pH which results in a high fraction of the nonprotonated nicotine. The pKa of nicotine is about 7.8 which means, for example, that at a pH of about 8.8 approximately 90 % of the nicotine is in the nonprotonated form. By pH adjusting, the local pH of the saliva can be increased and therefore the absorption of nicotine is increased compared to if no pH adjustment was performed. Theoretically, the higher the local pH the higher the fraction of nonprotonated nicotine. However, a too high pH will be irritating for the oral mucosa and therefore a practical upper limit of the pH may be for example about pH 10.

The pH adjusting agents adjust the pH to above 6 when the powder is dissolved or dispersed in purified water. For example, it may be desirable to obtain a pH of about 8.5 such as 7.5 to 9.5.

Thereby the nicotine salt in the powder is in a physical and chemical stable form until the product is used by a consumer and comes into contact with saliva. Saliva present in the oral cavity penetrate through the coat, dissolve the nicotine salt and the pH adjusting agent in the core, and thereafter transport the dissolved substances out through the coat into the oral cavity. A reaction between the pH adjusting agent and the nicotine salt results in the formation of unprotonated nicotine which can penetrate the oral mucosa and become absorbed.

The powder may comprise additional components which do not influence the powder as such but gives the powder improved properties when it comes to the experience of the powder and the effects of the powder on the consumer. The type of components and the amount of the different components in the powder may vary

depending on the desired properties of the final product. Excipients can for example be added to the powder in order to obtain an attractive taste or a good power flow Typically, the mixture may comprise one or more additives such as fillers, sweeteners, flavoring agents, as well as granulating agents. Compared to tobacco based products, the powder mixture is free from nitrosamines as well as other potential hazardous components which normally can be found in tobacco.

Examples of fillers include polysaccharides, polyols, sugars, natural fibres, microcrystalline cellulose, cellulose and cellulose derivatives. The filler may also have a secondary function, such as for example as sweetener. Examples of sweeteners include mono- di- tri- and polysaccharides, polyols, natural and synthetic sweeteners such as sucrose, glucose, dextrose, maltose, fructose, saccharin, aspartame, acesulfame, sucralose, saccharin and cyclamates. Examples of flavoring agents include bergamot, eucalyptus, orange, mandarin, citrus, lemon, peppermint, mint, menthol, liquorice, wintergreen and mixtures thereof.

The powder may, or may not, be granulated. A granulation may increase the particle size of the powder which can for example decrease the dustiness or improve the powder flow.

Other examples of excipients are well-known in the art and can be found in Handbook of Pharmaceutical Excipients edited by Rowe, R. C. et al., 4.sup.th edition, Pharmaceutical Press, London 2003, which is hereby incorporated by reference.

The nicotine in the powder is adapted to be administrated via the oral transmucosal route and delivered across or through the oral mucosal membrane. This may be done by administrating the powder in a coat to be placed for example under the upper lip. Accordingly, the invention relates to a coat surrounding the core comprising the powder as defined above. An ideal coat for nicotine delivery shall have the following characteristics: it shall be chemically and physically stable, it shall be insoluble in water, it shall be easy to manufacture, fill with powder and seal and it shall permit dissolved nicotine to freely pass through said coat. In a preferred environment the disclosed invention relates to products where said coat is a pouch containing a nicotine formulation having the above mentioned properties. A

pouch can be made from a woven or nonwoven material, wherein the core material is maintained in the coat by a welded sealing.

The coat material may be selected from the group consisting of biocompatible and physiologically acceptable polymeric materials. Examples of such materials are cellulose acetate and derivatives thereof, carboxymethylcellulose, polycellulose esther, other cellulose derivatives including ethylcellulose, propylcellulose, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyvinyl acetate, polymers of methacrylates and acrylates, natural rubber, polycarbonate, polyethylene terephtalate, polyesther, polyamid and nylon. The coat may be a pouch.

The product may comprise from 50 to 1000 mg of said powder, such as 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900 or 950 mg.

Method

The invention also relates to a method of manufacturing the product according to the invention.

The manufacture of the powder in the core comprise the steps of providing powders of at least one free nicotine salt and at least one pH adjusting agent and mixing, The mixing may be performed in a conventional blender. One or more sieving steps may be advantageous to improve the blending homogeneity.

If needed, the pH adjusting agent may be encapsulated or embedded with a polymer before mixing with the other components. This can be performed by adding a polymer solution to the pH adjusting agent and thereafter evaporate the solvent to form a powder consisting of the pH adjusting agent encapsulated or embedded with a polymer.

If additional components such as the excipients mentioned above are to be added additional manufacturing steps may be needed, such as if any of the components are added as a liquid. Typically, several flavors are liquids or liquid solutions and then there may be a need of a drying step. Further, depending on the desired properties the powder may be granulated, or not. If the powder mixture

shall be granulated, for example to improve the powder flow properties, a granulating step is added.

Finally, the powder is positioned inside the coat which is sealed.

By such a simple and controlled way of manufacturing the product it is possible in a cheap and simple way to obtain an effective product with excellent storage stability.

EXAMPLES

The following examples are illustrative of the present invention and should not be considered as limiting the scope of the invention. A person skilled in the art, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and the scope of the invention.

In the following examples excipients are added to the basic composition of the disclosed invention; fillers (for example Avicel PH200 and maltitol) are added to increase the powder volume and to improve the powder flow properties, flavoring agents and sweeteners are added to provide a more appealing taste to the product, and the powder is granulated to improve the powder flow properties. In examples 7 and 8, the pH adjusting agent has been encapsulated with a polymer to physically separate it from the nicotine salt.

EXAMPLE 1.

10.0 g Kollidon PVP 25 is dissolved in 18.0 g ethanol. 13.0 g Lemon Flavor (Firmenich), 2.5 g glycerol and 0.5 g menthol are added to form a homogeneous granulation solution.

The following solid components are mixed and sieved to form a powder mixture: 12.3 g nicotine bitartrate dihydrate, 185.3 g mannitol, 0.4 g Acesulfame K, 16.0 g sodium bicarbonate and 10.0 g sodium carbonate.

The granulation solution is slowly added to the powder mixture under stirring. The wet granulate is sieved and placed on a tray. The powder is dried at 60°C over night and is thereafter sieved.

The powder is manually filled into pouches (target weight 250 mg powder per pouch). The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 2.

70.0 g Kollidon PVP 25 is dissolved in 105.0 g ethanol. 17.5 g Lemon Flavor (Firmenich), 7.0 g Fresh Peppermint Flavor (Firmenich), 3.5 g Mandarin Flavor (Firmenich) and 1.4 g menthol are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 192.5 g Avicel PH200, 447,3 g mannitol, 1.8 g Acesulfame K, 56.0 g sodium bicarbonate and 35.0 g sodium carbonate.

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 3.

The following components are mixed to form a homogeneous granulation solution: 17.5 g Lemon Flavor (Firmenich), 7.0 g Fresh Peppermint Flavor (Firmenich), 3.5 g Mandarin Flavor (Firmenich), 1.4 g menthol, 35.0 g Kollidon PVP 25 and 31.5 g ethanol. This is granulation liquid 1.

The following components are mixed to form another homogeneous granulation solution: 35.0 g Kollidon PVP 25 and 73.5 g purified water. This is granulation liquid 2.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 639.8 g Dibasic Calcium Phosphate Dihydrate, 1.8 g Acesulfame K, 56.0 g sodium bicarbonate and 35.0 g sodium carbonate.

The Granulation liquid 1 is slowly added to the powder mixture under stirring in a planetary mixer. Thereafter, Granulation liquid 2 is slowly added under stirring in a planetary mixer. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 4.

70.0 g Kollidon PVP 25 is dissolved in 105.0 g ethanol. 21.0 g Lemon Flavor (Firmenich), 8.4 g Fresh Peppermint Flavor (Firmenich), 4.2 g Mandarin Flavor (Firmenich) and 1.8 g menthol are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 385.0 g Avicel PH200, 248.5 g maltitol, 2.3 g Acesulfame K, 56.0 g sodium bicarbonate and 35.0 g sodium carbonate.

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. Additional 20 g of ethanol is added after the addition of the granulation liquid. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller &

Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 5.

70,0 g Kollidon PVP 25 is dissolved in 105.0 g ethanol. 21.0 g Lemon Flavor (Firmenich), 8.4 g Fresh Peppermint Flavor (Firmenich) and 4.2 g Mandarin Flavor (Firmenich) are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 385.0 g Avicel PH200, 236.3 g maltitol, 2.3 g Acesulfame K, 56.0 g sodium bicarbonate, 35.0 g sodium carbonate and 14.0 g Menthol Durarome.

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. Additional 10 g of ethanol is added after the addition of the granulation liquid. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 6.

70.0 g Kollidon PVP 25 is dissolved in 105.0 g ethanol. 21.0 g Lemon Flavor (Firmenich), 8.4 g Fresh Peppermint Flavor (Firmenich) and 4.2 g Mandarin Flavor (Firmenich) are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 21.5 g nicotine bitartrate dihydrate, 385.0 g Avicel PH200, 257.6 g maltitol, 2.3 g Acesulfame K, 73.5 g sodium bicarbonate, 17.5 g sodium carbonate and 14.0 g Menthol Durarome

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. Additional 10 g of ethanol is added after the addition

of the granulation liquid. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 7.

Encapsulated pH adjusting agent is manufactured in the following way: 480 g sodium bicarbonate and 300 g sodium carbonate are mixed. 60.0 g Eudragit L100 is dissolved in 342 g ethanol. The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

70,0 g Kollidon PVP 25 is dissolved in 105.0 g ethanol. 21.0 g Lemon Flavor (Firmenich), 8.4 g Fresh Peppermint Flavor (Firmenich) and 4.2 g Mandarin Flavor (Firmenich) are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 385.0 g Avicel PH200, 229.3 g maltitol, 2.3 g Acesulfame K, 98,0 g encapsulated pH adjusting agent and 14.0 g Menthol Durarome.

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

EXAMPLE 8.

70.0 g Kollidon PVP 25 is dissolved in 80.0 g ethanol. 21.0 g Lemon Flavor (Firmenich), 8.4 g Fresh Peppermint Flavor (Firmenich) and 4.2 g Mandarin Flavor (Firmenich) are added to form a homogeneous granulation solution.

The following solid components are mixed in a planetary mixer and further blended by sieving to form a powder mixture: 43.0 g nicotine bitartrate dihydrate, 385.0 g Avicel PH200, 229.3 g maltitol, 2.3 g Acesulfame K and 14.0 g Menthol Durarome

The granulation solution is slowly added to the powder mixture under stirring in a planetary mixer. The wet granulate is sieved and placed on a tray. The powder is dried at ambient conditions over night and is thereafter sieved.

The obtained granulate is mixed with encapsulated pH adjusting agent (described in Example 7). For one part of granulated powder, 0.126 parts of encapsulated pH adjusting agent is added.

The mixed powder is filled into pouches (target weight 250 mg powder per pouch) using an in-house pouch filling machine. The pouch material is manufactured by Schoeller & Hoesch, Germany and has the article number NW nf 5/17/C. It consists of cellulose fibre, viscose and synthetic fibre.

The compositions of the nicotine pouches manufactured according to Examples 1 to 8 above are presented in Table 1.

TABLE 1. Compositions of the formulations presented in Examples 1 to 8 based upon the disclosed invention (mg per pouch)

Components/Batch	**TO-022**	**TO-025**	**TO-035**	**TO-042**	**TO-047**	**TO-058**	**TO-070**	**TO-071**
Example	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Nicotine bitartrate dehydrate	12.3 (*)	12.3	12.3	12.3	12.3	6.15 (*)	12.3	12.3
Dibasic Calcium Phosphate Dihydrate	-	-	183	-	-	-	-	-
Mannitol	185	128	-	-	-	-	-	-
Maltitol	-	-	-	71.0	67.5	73.6	65.5	65.5

Avicel PH 200	-	55.0	-	110	110	110	110	110
Sodium bicarbonate	16.0	16.0	16.0	16.0	16.0	16.0	-	-
Sodium carbonate	10.0	10.0	10.0	10.0	10.0	10.0	-	-
Encapsulated pH adjusting agent (***)	-	-	-	-	-	-	28.0	28.0
Acesulfame K	0.40	0.50	0.50	0.65	0.65	0.65	0.65	0.65
Glycerol	2.50	-	-	-	-	-	-	-
Lemon flavour	13.0	5.00	5.00	6.00	6.00	6.00	6.00	6.00
Fresh peppermint flavour	-	2.00	2.00	2.40	2.40	2.40	2.40	2.40
Mandarin flavour	-	1.00	1.00	1.20	1.20	1.20	1.20	1.20
Menthol	0.50	0.40	0.40	0.50	-	-	-	-
Menthol Durarome	-	-	-	-	4.00	4.00	4.00	4.00
Kollidon PVP25	10.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0

(*) Corresponds to nicotine base 4.0 mg per pouch

(**) Corresponds to nicotine base 2.0 mg per pouch

(***) 16.0 mg Sodium bicarbonate, 10.0 mg Sodium carbonate and 2.00 mg Eudragit L100

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EXAMPLE 9.

The pH is determined for products according to the disclosed invention. A pouch according to the disclosed invention is added to 15.0 g purified water. The
10 sample is stirred or shaken and after at least 30 minutes the pH is measured using a conventional pH meter. The investigated products are described in the Examples above and in Table 1.

TABLE 2. pH for samples manufactured according to the disclosed invention

Batches	pH
TO-025	8.46, 8.52, 8.47, 8.46
TO-035	8.50, 8.44, 8.21, 8,29
TO-042	8.63, 8.62
TO-058	8.44, 8.53
TO-070	8.34
TO-071	8.14

It is seen that the pH for the investigated samples is above pH 6.

EXAMPLE 10.

The release of nicotine from products according to the disclosed invention is presented. As a reference, the release of nicotine from products not according to the disclosed invention, determined with the same methods, is also presented.

Investigated samples

The products according to the disclosed invention are described in Examples 1 to 8 and in Table 1.

The two reference products are also manufactured from a nicotine containing powder filled into a pouch. The nicotine source is however not a nicotine salt as in the disclosed invention, but nicotine complexes.

The first reference product is a commercially available product, "Zonnic mint 4 mg" purchased in Sweden. Three batches of Zonnic have been investigated. The formulation is based upon a nicotine-cellulose combination and contains 4 mg nicotine per pouch. WO 2007/104573 and WO 2010/031552 relate to said nicotine –cellulose combination for the preparation of a nicotine pouch composition. In the patent applications it is stated that a nicotine –cellulose

combination is specially suitable for use in snuff compositions, as such a snuff composition on one hand releases nicotine relatively fast and thereby enables a fast onset of nicotine effect, and on the other hand enables the nicotine content to be completely or almost completely released after application to the oral cavity. It is therefore of interest to compare the nicotine release from products according to the disclosed invention with the nicotine release for a product according to the invention described in WO 2007/104573 and WO 2010/031552.

The second reference product is based on a nicotine polacrilex complex (Amberlite IRP 64). This complex is commercially available and is used in nicotine products for smoking reduction and cessation. It was purchased from Cambrex, and contains 15 % nicotine. In Table 3, the compositions for two reference formulations based upon the nicotine polacrilex complex are presented (TO-014 and TO-015). Both batches were manufactured in house in a similar way as described in the earlier examples with the important exception that a nicotine complex and not a nicotine salt was used.

TABLE 3. Compositions of two reference formulations based upon the nicotine polacrilex complex (mg per pouch)

Components/Batch	**TO-014**	**TO-015**
Nicotine polacrilex	42.0 (*)	42.0
Ascorbyl palmitate	4.00	4.00
Mannitol	152	122
Avicel PH 200	-	30.0
Sodium bicarbonate	15.0	15.0
Sodium carbonate	9.00	9.00
Acesulfame K	0.30	0.30
Glycerol	2.50	2.50
Lemon flavour	12.0	12.0
Menthol	0.50	0.50
Kollidon PVP25	15.0	15.0

(*) Corresponds to 6.3 mg nicotine base per pouch

Experimental methods

A nicotine pouch is normally placed under the upper lip where only a limited amount of saliva is available to release the nicotine. Therefore when trying to mimic the nicotine release rate *in vitro* it is an advantage to use experimental conditions where only a limited amount of aqueous liquid is present. Otherwise, when different nicotine products are compared *in vitro,* the order of the obtained release rates of nicotine may not reflect the order of the release rates of nicotine under normal user conditions.

Two experimental methods have been utilized to determine the nicotine delivery for products based upon the disclosed invention and for reference products; an *in vitro* method and an *ex vivo* method. For both methods, a limited amount of aqueous liquid was to available release the nicotine from the pouch.

Ex vivo. *Ex vivo* is an experimental technique where the experiment is performed *in vivo* and the residual amount of the active component in the product is analyzed *in vitro.* In the current case, the pouch is kept under the upper lip for a certain time. It is thereafter taken out and the residual nicotine in the pouch is analyzed. This is performed for different use times (using a new pouch each time).

During use, different handling of the pouch by the user may result in different nicotine release rates. Therefore, the handling of the pouch during use should be standardized. Two different approaches have been applied. In the first approach the pouch is placed "in the front" under the upper lip and kept in that position during use. In the second approach the product is placed under the upper lip slightly on the left or on the right side. The product is then moved to the opposite side of the upper lip each fourth minute. In the second approach more saliva is available to the pouch.

After use the pouch is immediately placed in a tube containing 15.0 g purified water and it is shaken until all the residual nicotine in the pouch is dissolved into the water phase (minimum time 30 min).

In vitro. To a 140 mm Petri dish, a certain amount (4.0 g or 20.0 g) of purified water is added. A 110 mm filter paper (Munktell grade 00R) is placed in the middle of the dish. It is ensured that the filter paper is completely wetted by the purified water and that all air bubbles are removed. The pouch is placed flat in the middle of the filter paper for a certain time. The pouch absorbs some water which dissolves the nicotine which is released from the pouch into the external water phase. After use the pouch is immediately placed in a tube containing 15.0 g purified water and it is shaken until residual nicotine in the pouch is dissolved in the water phase (minimum time 30 min).

Analytical method. The residual content of nicotine in each individual nicotine pouch is determined in the same way for the *ex vivo* and the *in vitro* samples: The nicotine containing water phase in the test tube is diluted to a suitable concentration. The UV absorbance of the solution is determined at 260 nm. The nicotine concentration is calculated using a calibration curve and the residual amount of nicotine in the pouch is calculated. The UV method is non-specific for nicotine. Therefore, other substances in the pouch that also have absorption at 260 nm may introduce a minor error in the nicotine determination.

The nicotine content is also determined in the same way for a number of unused nicotine pouches from the same batch. From the following equation the fraction of released nicotine at the time t is calculated:

$$X_{released(t)} = (N_{unused} - N_{used(t)})/N_{unused}$$

$X_{released(t)}$ is the fraction of released nicotine for the used pouch at the time t

N_{unused} is the average amount of nicotine in unused pouches from the batch

$N_{used(t)}$ is the residual amount of nicotine in the used pouch at the time t

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Results

In Table 4 below $X_{released(6)}$ and $X_{released(16)}$ (the fraction of released nicotine for a used pouch after 6 minutes and 16 minutes use time) are presented. For example, when analyzed and calculated according to the methods described above, the Zonnic reference batch 09E56 has released 21 percent of the nicotine content after

16 minutes in the *ex vivo* test where the pouch is moved every fourth minute by the user.

TABLE 4. The released nicotine after 6 and 16 minutes use time for the experimental conditions described above (in percent of the average amount of nicotine in unused pouches for the batch)

Batch	Comments (*)	Ex vivo (**)				In vitro			
		Fixed position		Moved every 4th minute		4.0 g water		20.0 g water	
		6 min	16 min	6 min	16 min	6 min	16 min	6 min	16 min
Zonnic	Reference								
09E56		-	-	11	21	11	23	16	28
10H23		-	-	-	-	14	24	21	34
10H24		-	-	-	-	14	26	23	31
TO-014	Reference	-	-	-	-	-	-	28	32
TO-015	Reference	-	-	-	-	-	-	17	24
TO-022	Invention	-	-	-	-	-	-	82	93
TO-025	Invention	-	-	15	41	19	32	60	86
TO-035	Invention	-	-	-	-	29	52	69	83
TO-042	Invention	8	21	22	33	33	44	59	78
TO-047	Invention	-	-	-	-	-	-	55	79
TO-058	Invention	-	-	-	-	-	-	51	71
TO-070	Invention	-	-	-	-	-	-	40	74
TO-071	Invention	-	-	-	-	-	-	48	64

(*) Reference means reference samples. Invention means sample according to the disclosed invention

(**) Average values for two users (same users in all experiments)

(-) not measured

For all experimental conditions, the nicotine release for nicotine products according to the disclosed invention is more rapid than for reference products, both the reference product based upon the nicotine –cellulose combination and the reference product based upon the nicotine polacrilex complex.

Under the experimental conditions used in the *in vitro* test with 20.0 g purified water the most rapid nicotine release is obtained. After 16 minutes use time the nicotine release is rather complete for the products according to the disclosed invention, in all cases, except one, it is above 70 %. On the other hand for the reference products, the nicotine release is closer to 30 – 35 %. This shows that for an almost complete delivery of nicotine from the pouch a lower amount of liquid or a shorter time is needed for the products according to the disclosed invention compared to the reference products.

For some of the products the nicotine release was measured also at other use times, up to 64 minutes. It s anticipated that a normal use time for a pouch is about 30 to 60 minutes. It is of interest that the nicotine delivery is as complete as possible after a normal use time. In Figure 1 the nicotine delivery for use times up to 64 minutes are presented for TO-025, TO-042 and Zonnic batch 09E56. The experimental conditions are an *ex vivo* study with two participants and the results are presented as average values of the two participants. It is the same two participants for all samples. The participants were instructed to change the position of the pouch every fourth minute from the left side to the right side of the upper lip. It is seen that the nicotine release for the samples according to the disclosed invention is, in general, higher than for the Zonnic samples. In particular, for the use times 32 minutes and 64 minutes the nicotine delivery is more complete for the formulations according to the disclosed invention than for Zonnic.

In Figure 2 the nicotine delivery for use times up to 64 minutes are presented for TO-025 and Zonnic batch 09E56. The experimental conditions are an *in vitro* study both with 4.0 g water and 20.0 g water. The same pattern as in the *ex vivo* study emerge. The nicotine release is more rapid and more complete for the product according to the disclosed invention than for the Zonnic product.