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DESCRIPTION

Description

[0001] The present invention relates to a method for providing an extreme chemical resistant film whereby a tie layer and a contact layer are coextruded with a base layer which is a metal foil, as well as films and laminates obtained by the method and uses of the films and laminates to wrap aggressive chemical substances such as nicotine, fentanyl, lidocaine and rivastigmine.

Background of the invention

[0002] In the pharmaceutical industry substances, including highly aggressive substances such as nicotine, fentanyl, rivastigmine and lidocaine, are packed as tablets in inhalers, patches etc. resulting in special requirements for the packing, laminate, or film for sealing these substances in order to ensure that no adverse degradation takes place.

[0003] One common example is the problem relating to the packaging of nicotine, in particular as nicotine patches, because nicotine is highly aggressive towards its environment and highly volatile. These properties are problematic for the consumer safety and product durability if not addressed, because it is important that the amount of nicotine in, for example a tablet, gum or a patch is stable and complies with the product specification. Further, it is important to avoid adverse reactions between the packaging and the pharmaceutical substance. Additionally, from a business perspective a long stable shelf time is highly desirable. Thus, the chemical requirements of a packaging, film or laminate are typically:

- Resistance towards highly aggressive substances such as nicotine.
- Inert properties for ensuring that chemical compounds do not migrate from the exterior environment of for example a laminate, through the laminate getting into contact with a sealed substance;
- Possibly ensuring that the packaging is child proof to increase safety of potentially hazardous compounds.

[0004] A known polymer that fulfils the requirements of extreme chemical resistance and inert properties is a polyacrylonitrile (PAN) based film, which is sold for example as resins under the trademark Barex[®], which is manufactured *i.a.* by the company Ineos. Barex[®] is widely used and approved for drugs and food applications and is used because it is a good barrier towards oxygen, nitrogen and carbon dioxide compared to other common polymers, and because it has excellent chemical resistance towards different functional groups such as hydrocarbons,

ketones, esters, alcohols, bases and acids and/or pharmaceuticals such as nicotine. Furthermore, extruded Barex[®] resin is heat stable and therefore weldable at a temperature around 160 - 220°C, which makes it possible to use in flexible packagings. However, Barex[®] is sold at a high price due to the difficulties in the production and subsequent extrusion to film resulting in a high loss of material. Furthermore, the water and oxygen resistance of Barex[®] is not satisfactory for all purposes.

[0005] Another solution can be found in WO 00/44559 disclosing a material for packaging nicotine containing products (e.g. patches, tablets, lozenges, nasal spray), wherein the material comprises a polymer based on dimethyl-2,6-naphthalene dicarboxynate and/or 2,6-naphthalene dicarboxylic acid monomers. Further, it is disclosed that a polymeric film is combined with other barrier materials in a laminate to further improve the barrier characteristic of the laminate. The preferred material for a laminate is aluminium due to its good oxygen and water barrier properties.

[0006] In addition to the barrier properties, in particular for pharmaceuticals, it is important that the concentration of the substances is stable and reliable, which also poses requirements of the packaging and laminates in terms of inertness and permeability.

[0007] Hence, given the increased market and demands for packagings, there is an instant need for finding solutions for packaging, of in particular highly aggressive substances and pharmaceuticals, which fulfil all the requirements while still being economical.

Summary of the invention

[0008] With this background it is an object of the present invention to provide solutions that meet one or more of the needs described above, that is, *i.a.* provide impermeability and inertness to a packaging. Furthermore, it is an object to provide a laminate that is weldable at temperatures suitable for the manufacture of flexible wrappings, such as for use in preparing packagings for patches. It is a further object to provide methods and products that are cost efficient without compromising the quality of the products.

[0009] Accordingly, in a first aspect this is solved by a method for providing a film, said method comprising the steps of:

1. i) providing a base layer, which is water and/or oxygen resistant wherein the base layer is selected from a metal foil, preferably aluminium;
2. ii) coextruding a layer comprising a tie layer and a contact layer to provide a coextrusion layer;
3. iii) coating the coextrusion layer to the base layer;
4. iv) allowing the coextrusion layer coated to the base layer to adhere to provide an aggressive chemical resistant film, the aggressive chemical being nicotine, fentanyl,

lidocaine or rivastigmine, the film comprising the tie layer and the contact layer formed as a coextrusion layer coated to the base layer, wherein the tie layer comprises at least one layer and wherein the contact layer comprises a polymer having a RED value based on Hansens Solubility parameter (HSP) towards an aggressive chemical, namely nicotine, fentanyl, lidocaine or rivastigmine, of > 0.8 , more preferred a RED value in the range of 0.8 to 10, even more preferred 0.8 to 5, and most preferred between 1 to 2, and further wherein the polymer is a polyamide.

[0010] It has surprisingly been found that when coextruding the tie layer and the contact layer according to the invention, the respective layers can be thinner while maintaining the overall mechanical and chemical robustness of the final film and laminates and wrappings made with the film. The co-extrusion also results in a better adherence of the various layers resulting in a homogenous film in which the layers do not separate.

[0011] While it was previously believed that usable polymers should be hydrophobic (in order to repel water from the surroundings), the present inventors have found that by providing the film according to the invention where the coextrusion layer comprises a tie layer and a contact layer, and where the contact layer comprises a polymer having a relative energy difference (RED) value in the range 0.8 to 10 relative to the aggressive substance, it has surprisingly turned out that the desired effect of the laminate being inert to aggressive compounds, such as nicotine, rivastigmine and lidocaine, while still providing a barrier to external factors such as water/moist and oxygen, is obtained.

[0012] A polymer candidate for use as a contact layer in the present invention is selected by calculating the RED value, which is generally used to predict the solubility of a polymer in a particular solvent, or the compatibility of two polymers in a blend. In the present invention the RED values for various polymer/solvent systems have been calculated, wherein the polymer is the polymer forming the contact layer, and the solvent is an aggressive chemical substance such as nicotine, rivastigmine, fentanyl and lidocaine etc.

[0013] The RED value for the polymer and the aggressive chemical substance is calculated by using the theory of the Hansen solubility Parameters (HSP), which is described in C.M. Hansen: "Hansen Solubility Parameters, A User's Handbook", CRC Press, Boca Raton, 1999.

[0014] The HSP system between the polymer and the aggressive chemical substance is described by parameters set up in a 3 dimensional coordinate system:

- δ_D for dispersion cohesion energy
- δ_P for dipolar cohesion energy
- δ_H for hydrogen bonding cohesion energy

[0015] The HSP distance, R_a , between polymer and the aggressive chemical substance is given by:

$$R_a^2 = 4(\Delta \delta_D)^2 + \Delta \delta_P^2 + \Delta \delta_H^2$$

[0016] The \otimes indicates the difference in the given parameter for the aggressive substance and the polymer.

[0017] The relation between the HSP distance, R_a and RED is given as:

$$RED = R_a/R_o$$

[0018] Where R_o is the interaction radius, which determines the radius of the sphere in Hansen space, and the center are the three Hansen parameters. All values are calculated or determined with empiric data and it is known to the person skilled in the art how to calculate the values.

[0019] The obtained RED value indicates whether or not the polymer is likely to dissolve in the aggressive chemical substance or not:

RED < 1 the polymer and the aggressive chemical substance will dissolve

RED = 1 the polymer and the aggressive chemical substance will partially dissolve

RED > 1 the polymer and the aggressive chemical substance will not dissolve

[0020] The resulting RED value is used to give an indication of the likelihood of dissolution or not.

[0021] All values can be calculated using the Hansen Solubility Parameter in Practice by (HSPiP) Software, commercially available at <http://hansen-solubility.com>.

[0022] Contact layer polymers according to the invention surprisingly turned out to have a RED value in the range from 0.8 and higher, preferably, 0.8 to 10 and more preferred 0.8 to 5 and most preferred 1 to 2. It is highly unexpected that polymers which in theory range from being soluble to insoluble with an aggressive substance to be packed fulfill the requirements set for films according to the invention as is supported by the examples provided here with.

[0023] The base layer, which is water and/or oxygen resistant, is selected from the group consisting of a metal foil, preferably aluminum foil.

[0024] According to the invention water and/or oxygen resistance is preferably encompassing materials having an oxygen transfer rate (OTR) equal to or below 1 cm³/m²/24hr/bar according

to ASTM standard D3985 at 23°C and 0% RH and/or water (or moisture) vapor transfer rate (WVTR) equal to or below 1 g/m²/24hr according to ASTM standard F1249 at 38°C and 90%RH, preferably both the WVTR and the OTR are below 0.01 g/m²/24hr or 0.01 cm³/m²/24hr/bar respectively.

[0025] According to the invention, the base layer of the film is selected to provide a number of properties to the film and a laminate and packaging comprising the film. The base layer may give desired barrier and support properties to the final laminate. Furthermore, the base layer may in one embodiment be a gas and water impermeable base layer, more preferably a water and/or oxygen resistant base layer.

[0026] In embodiments the contact layer is hygroscopic.

[0027] Aluminum is price competitive, a superior barrier of all gases and moisture and furthermore similar to other metal-like materials aluminium has good dead-fold properties, i.e. it does not unfold once folded, it reflects radiant heat, and gives a decorative appeal to laminates and packages.

[0028] According to the invention the tie layer is selected to provide sufficient adhesion between the base layer and the coextrusion layer. The tie layer may give melt strength and support the coextrusion coating of both the tie layer and the contact layer. It is preferred that the melting profile of the tie layer polymers and the contact layer polymers are in the same range to provide optimal films that do not separate. Preferably both layers comprise polymers that melt at the operating temperature of the process of the invention and even more preferred the melting profiles (i.e. melting points) should differ with less than 30°C, preferably with 0-15°C, such as 5-15°C.

[0029] In one embodiment the tie layer is made of 1, 2, 3, 4 or 5 layers. In this way, the properties of the film and resulting laminates and packagings may be improved to accommodate the specific chemical and physical properties of the contact layer and/or the base layer.

[0030] In a further embodiment all the layers are coextruded with the contact layer for a simplified processing and for ensuring homogeneity of the layers.

[0031] In a further embodiment the tie layer is constituted of one layer where the layer is made of a copolymer made of a material selected from a copolymer of ethylene and acrylic acid, ethylene and methacrylic acid and a terpolymer comprising ethylene, acrylic ester and a third polymer, which third polymer is preferably a glycidyl methacrylate, and more preferably a maleic anhydride. Most preferably the tie layer has a melting profile similar to that of the contact layer.

[0032] According to the invention the contact layer must be chemically resistant to the

aggressive substance and excipient if present ultimately to be packed. Further it must show an extreme low absorption of the aggressive substances migrating through the film or laminate. The degree of absorption for a given substances is typically dictated by the manufacturer of the substance but often the accepted values lie in the range of 0 to 1 % (w/w). For some products up to 10 % (W/W) is acceptable typically for products with a low initial API content. The absorption is calculated as the weight of API in packaging relative to the initial weight of the API in the commercial product.

[0033] Hence, in the context of the present invention aggressive chemical resistant film means that no more than 1% of the original amount of API to be packaged (or sometimes no more than 10%) is migrated into the packaging material after 24 weeks. Typically, the degree of uptake is complete after 12 weeks or less.

[0034] The contact layer comprises a polyamide (PA).

[0035] In a further embodiment the tie layer and contact layer comprise the same polymer, such as a cyclic olefin copolymer (COC), a polyamide (PA), or, an ethylene vinyl alcohol (EVOH) the latter being particularly preferred.

[0036] The HSP and RED Values calculated using <http://hansen-solubility.com>, mentioned above resulted in the following values for the preferred polymers according to the invention using lidocaine/rivastigmine as solvent (API):

Table 1: HSP and RED values for preferred polymers according to the invention

Polymer	D	P	H	RED value (chi)
Lidocaine/Rivastigmine	18.1	8.2	6.1	-
PA 66	16	11	24	1.72
COC	18	3	2	1.32
EVOH	20.5	10.5	12.3	1.12

[0037] Tests have shown that the resistance of laminates in which the film is coated with polyamide (PA) shows results unexpectedly superior to those of laminates coated/laminated with Barex[®].

[0038] PA has typically been used in laminates due to the superior mechanical properties like tear strength or as a barrier. It is unexpected that PA may be used as a contact layer and/or co-extrusion layer (i.e tie and contact layer) for providing a chemical resistant film due to the hydrophilic nature of PA.

[0039] Because of the hydrophilic nature of PA, in a preferred embodiment, the film obtained according to the invention may be tightly packed in a moisture barrier, in particular if it has to be stored. The film or laminate according to the invention may be packed immediately after manufacture of the chemical resistant film or laminate and should be kept safely packed until

further use, for example in a packing line.

[0040] COC has not previously been recognized as being suitable for extrusion coating and for the production of heat sealable laminates. Without the wish to be bound by any theory this is believed to be due to the stress which the polymer is subjected to during an extrusion process. The stress causes irregular heating and melting within the COC, resulting in the final film or laminate to be unacceptable from a visual point of view for use in various packaging industries. Hence, it is very surprising that the inventors of the present invention have succeeded in providing a coextrusion layer comprising COC as a contact layer for sealing aggressive substances. The inventors have found that an improved processing of COC is obtained when COC is coextruded with a tie layer having a glass transition temperature higher than or equal to that of a COC polymer such as a terpolymer of ethylene, acrylic ester and maleic anhydride. In another embodiment of the invention the tie layer has a melting point that differs from COC with 30°C or less, preferably with 0-15°C, such as 5-15°C.

[0041] In a further embodiment, the melting point of the tie layer is at least the same as COC, preferably 5 to 30 °C higher, more preferably 15 to 30 °C higher than COC.

[0042] To obtain a satisfactory coextrusion layer it is important that the polymer constituting a contact layer and a copolymer constituting a tie layer are compatible with respect to the melting characteristic of the polymers and the copolymer. As an effect of having been able to process a chemical resistant laminate with a coextrusion layer laminated to the base layer, thin laminates may be obtained, and generally improved process ability during the manufacture of the laminates or wrappings are achieved.

[0043] Consequently, in one embodiment the tie layer or plurality of layers constituting the tie layer, has a loading in the range of 7 to 20 g/m² and/or the contact layer has a loading in the range of 4 to 20 g/m² and the loading of the laminate is not more than 40 g/m².

[0044] In terms of the invention loading means the amount of polymer left, in the layer when the film has dried.

[0045] In a particular embodiment the contact layer of the coextrusion layer is made from a blend of at least two polymers. Using blends can be a means for reducing the costs and for adapting the physical and chemical properties of the co-extrusion process, such as reducing or increasing the melting temperature to comply with the profile of the tie layer(s) and the polarity of the blend to improve the adhesion properties of the layers and hence the robustness of the final product.

[0046] In a preferred embodiment the contact layer consists of one polymer type. Experiments showed that using one type of polymer resulted in improved resistance of the film and laminate towards the chemical substance to be packed.

[0047] According to an embodiment, in any of the blends or homo layers at least one of or all

the polymer(s) forming the contact layer of the coextrusion layer is a cyclic olefin copolymer, a polyamide, or, an ethylene vinyl alcohol. Each of the polymers are commercial available for example under the tradenames EVAL[®] C109B sold by Kuraray, Selar PA 3426 R sold by Dupont[®], 6013M-07 sold by Topas[®].

[0048] In one embodiment the polyamide makes up at least 50% w/w of the blend, preferably at least 60% w/w, more preferably at least 80% w/w, most preferably at least 95% w/w.

[0049] The adhering of step iv) preferably occurs instantly for example by cooling the co-extrudate in cooling cylinders during the lamination process.

[0050] According to the invention a chemical resistant film has various applications. In an embodiment of the invention, the film is used to wrap a composition comprising a chemical selected from nicotine, fentanyl, lidocaine and rivastigmine.

[0051] In a particular embodiment of the invention, wherein the composition is provided as a patch, the amount of the aggressive chemical substance remaining at day 0 after storage for at least 7 days at 40°C is a maximum +/-10% in comparison to a Barex[®] patch as index 100.

[0052] In a further aspect of the invention an aggressive chemical resistant film is provided, said film comprising at least a base layer, which is water and/or oxygen resistant, wherein the base layer is selected from a metal foil, preferably aluminium and a coextrusion layer, wherein the coextrusion layer comprises a tie layer and a contact layer, and whereby the tie layer comprises at least one layer and wherein the contact layer comprises a polymer having a RED value of > 0.8, more preferred a RED value in the range of 0.8 to 10, even more preferred 0.8 to 5, and most preferred 1 to 2. Films according to the invention are resistant to aggressive chemical substances, namely nicotine, fentanyl, lidocaine or rivastigmine.

[0053] the term "aggressive chemical resistant film" means a film which when in contact with an aggressive substance does not allow more than 10 %, such as 5% w/w or 1.5% w/w based on the nominal content of the aggressive chemical to migrate to the packaging material.

[0054] The base layer, which is water and/or oxygen resistant, is selected from metal foil, preferably aluminum foil.

[0055] In a further embodiment the tie layer is constituted of one layer and wherein the layer is a copolymer made of a material selected from a copolymer of ethylene and acrylic acid, ethylene and methacrylic acid and a terpolymer comprising ethylene, acrylic ester and a third polymer, which third polymer is preferably a glycidyl methacrylate, and more preferably a maleic anhydride.

[0056] In a particular embodiment the contact layer is a polyamide.

[0057] In yet an embodiment the tie layer and the contact layer is the same material.

[0058] In a further embodiment the film is heat sealable. A heat sealable film or laminate is a laminate that is capable of sealing to itself during heat sealing without creating any deformation of films or laminates, which is highly undesired, especially, during the final wrapping of the product. The deformation is undesirable in relation to quality assurance, where any deformation must be noted and explained, which is highly labor intensive. Furthermore, the legislation in many countries is very strict. Hence, film and/or laminates with any deformation are not allowable for packing active ingredients.

[0059] In yet another aspect the invention relates to a laminate for packing nicotine, fentanyl, lidocaine or rivastigmine said laminate comprising at least

- a first outer layer made of a mechanically wear resistant material;
- an aggressive chemical resistant film as described above comprising the base layer, which is water and/or oxygen resistant and a coextrusion layer said coextrusion layer comprising a tie layer wherein the base layer side of the film is facing the first outer layer.

[0060] In one embodiment the first outer layer may be made from a material selected from but not limited to paper, polyethylene or polyamide based sheets, ortho-phthalaldehyde based sheets, or polyester based sheets, or combinations. It is preferred that the first outer layer is a combination of materials when polyester based sheets are used.

[0061] In an embodiment the first outer layer and the film are laminated to provide the packaging in one piece. Laminating the first outer layer to the film provides a strong laminate, which is easy to wrap, and, it is ensured that the individual parts of the laminate do not fall apart.

[0062] In another embodiment the laminate further comprises a second outer layer facing the exterior side of the first outer layer, preferably the second outer layer is a paper layer. The paper layer is typically printed with the name, color and/or logo of the product and manufacturer of the product. It is also contemplated that the first outer layer is printed.

[0063] It is also contemplated that an adhesive agent may be applied between the second and first outer layers. The adhesive layer may be the same or different from the tie layer. Additional suitable adhesives are adhesives approved for use in packaging products for human use and are well known to the skilled person. A suitable adhesive may be selected from but is not limited to polyurethane based adhesives, epoxy based adhesives, or acrylic based adhesives.

[0064] The laminate of the present invention must be inert and impermeable to the aggressive chemical substance which the laminate is wrapped around. Hence, in an embodiment of the invention a maximum of 10%, preferably a maximum of 5%, even more preferably a maximum

of 1.5%, most preferably a maximum 0.5% of the aggressive chemical is migrated into the laminate at day 0 after 12 weeks of storage at 40 °C.

[0065] The laminate encloses a compound selected from the group consisting of nicotine, rivastigmine, fentanyl and lidocaine. These compounds are known as aggressive chemicals/compounds and require specialized packaging.

[0066] Hence, the invention also contemplates an aggressive chemical substance, namely nicotine, fentanyl, lidocaine or rivastigmine, packed in a laminate or packaging as explained above and a method for providing the packaging the chemical substance, said method comprising the steps of:

1. a) providing a base layer selected from metal foil, preferably aluminium;
2. b) coextruding a layer comprising a tie layer and a contact layer to provide a coextrusion layer;
3. c) coating the coextrusion layer to the base layer;
4. d) allowing the coextrusion layer coated to the base layer to adhere to the base layer to provide a chemical resistant film comprising the tie layer and the contact layer formed as an coextrusion layer coated to the base layer;
5. e) providing a highly aggressive substance to the contact layer side of the film; and
6. f) sealing the chemical resistant film, preferably by heat sealing, in such a way to provide a hollow interior space for sealing the highly aggressive substance, said hollow space having an interior side and an exterior side, wherein the interior side of the film is the contact layer of the coextrusion layer and the exterior side of the film is the base layer.

[0067] The highly aggressive substance is selected from the group consisting of nicotine, lidocaine, rivastigmine, and fentanyl.

[0068] It is also contemplated that a first outer layer may be applied to the film; the first outer layer is made of a mechanically wear resistant material and typically serves to protect from children being able to break the sealed film, laminate or wrapping.

[0069] A packaging should preferably comply with International standards such as 16 CFR §1700.20 (for USA) and ISO 8317 (2003) corresponding to DIN EN ISO 8317 (2004) (for Europe).

[0070] A "packaging" is in the context of the invention intended to mean a film or laminate used to pack a substance. Packaging may be used interchangeably for film or laminate

[0071] It is also contemplated that a second outer layer may be applied to the film and/or laminate; the second outer layer is typically a paper layer. The paper layer is typically printed with the logo or colors etc. of the supplier of the product. The second outer layer is preferably applied when there is a first outer layer.

[0072] It is contemplated that the first and/or second outer layer is laminated to the film before steps e) and f) for example in one combined coextrusion and laminating step.

[0073] In yet another aspect, the invention provides the use of a polymer having a RED value of > 0.8, preferably having a RED value in the range of 0.8 to 10, more preferred 0.8 to 5, and most preferred 1 to 2 as a contact layer for providing chemical resistance to a film, wherein the film comprises a base layer which is water and/or oxygen resistant, wherein the base layer is selected from a metal foil, preferably aluminium, coated to a, optionally coextruded, layer comprising a tie layer and the contact layer, wherein the polymer is a polyamide.

[0074] Specific films according to the invention comprise but are not limited to base layer/tie-layer/contact-layer (the latter two coextruded EAA/terpolymer/PA, or EAA/PA).

[0075] A specific film according to the invention that is resistant to nicotine comprises but is not limited to base layer/tie-layer/contact layer (the latter two coextruded) Al/EAA/PA.

[0076] In a further embodiment of the invention, wherein the film is resistant to nicotine and the contact layer is PA and the base layer is aluminium, the tie-layer is preferably a copolymer of ethylene and acrylic acid.

[0077] A specific film according to the invention resistant to rivastigmine comprises but is not limited to base layer/tie-layer/contact layer (the latter two coextruded) Al/EAA/PA.

[0078] In a further embodiment of the invention, wherein the film is resistant to rivastigmine and the contact layer is PA and the base layer is aluminium, the tie-layer is preferably a copolymer of ethylene and acrylic acid.

[0079] A specific film according to the invention resistant to lidocaine comprises but is not limited to base layer/tie-layer/contact layer (the latter two coextruded) Al/EAA/PA.

[0080] In a further embodiment of the invention, wherein the film is resistant to lidocaine and the contact layer is PA and the base layer is aluminium, the tie-layer is preferably a copolymer of ethylene and acrylic acid.

[0081] A specific film according to the invention resistant to fentanyl comprises but is not limited to base layer/tie-layer/contact layer (the latter two coextruded) Al/EAA/PA.

[0082] In a further embodiment of the invention, wherein the film is resistant to fentanyl and the contact layer is PA and the base layer is aluminium, the tie-layer is preferably a copolymer of ethylene and acrylic acid.

[0083] It has surprisingly been shown that films provided from polymers having a red value between 0.8 and 10 relative to rivastigmine, lidocaine and/or nicotine and coextruded as

stipulated above have superior resistance to said chemical substances.

Figures

[0084]

Figure 1 is a cross section of an embodiment of a chemical resistant film according to the invention

Figure 2 is a cross section of another embodiment of a chemical resistant film according to the invention.

Figure 3 is a cross section of a laminate according to the invention.

Figure 4 shows the results of an absorption study of rivastigmine as API wrapped in laminates, one being according to the invention, as compared to a commercial available laminate with the commercial available polymer film Barex[®] after storing for 2, 4, 8 and 12 weeks at 40°C.

Figure 5 shows the amount of lidocaine remaining in a patch after 7 days at 40°C for embodiments not according to the invention and in comparison, with a commercial available Barex[®] laminate.

Detailed description

[0085] The invention will now be described in greater details. Each specific embodiment and variation of features applies equally to each aspect of the invention unless specifically stated otherwise.

[0086] The film, laminate and packaging according to the present invention is intended to be used in packaging highly aggressive substances, namely nicotine, rivastigmine, fentanyl or lidocaine.

[0087] The term "film" according to the invention contemplates a product comprising a base layer coated with a coextrusion layer comprising a tie layer and a contact layer or a base layer laminated with a tie layer and a contact layer.

[0088] The term "laminate" according to the invention contemplates the film to which a further layer is laminated, such as a first outer layer.

[0089] A "packaging" is in the context of the invention intended to mean a film or laminate used to pack a substance. Packaging may be used interchangeably for film or laminate.

[0090] The term "highly aggressive substance" should be understood as a substance which is both very reactive with metals, acids, bases or functional groups such as ketones, alcohols, hydro carbons and/or esters, and/or, volatile but also easily migrates through barriers. Similarly, the term "aggressive chemical resistant film" means a film which when in contact with an aggressive substance does not allow more than 1.5 % w/w of nominal content to migrate to the packaging material or that 90-110% w/w of the aggressive chemical substance remains in the product when compared to Barex[®] as index 100.

[0091] Therefore, the films, laminates or packagings applicable for packing highly aggressive substances should have both chemical-resistant properties but also limit the migration of the aggressive substance through the film, laminate or packaging. The aggressive substance according to the invention is also or alternatively susceptible to degradation when exposed to ambient conditions, such as oxygen and water, it is volatile and able to migrate or a combination. The aggressive substance is selected from nicotine, licodaine, fentanyl or rivastigmine.

[0092] The term "oxygen and water resistant" as used in the context of the present invention contemplates material for which the oxygen transfer rate (OTR) and/or water vapor transfer rate (WVTR) is no more than 1 preferably no more than 0.1 as also indicated above. The term WVTR may also be referred to as the moisture vapor transfer rate (MVTR). WVTR and MVTR are equivalent.

[0093] The term "mechanically wear resistant layer" as used for the first outer layer in the context of the present invention should be a material which is suitable for the manufacture of a flexible packaging. The mechanically wear resistant layer may be chosen from materials such as polyethylene or polyamide based sheets, ortho-phthalaldehyde based sheets, or polyester based sheets or combinations.

[0094] Further, the mechanically wear resistant material can be provided as a film that is biaxially oriented to give the film higher seal strength. The term "biaxial oriented" should be understood such that the provided polymer film has been stretched in both a longitudinal and a transverse direction during manufacturing.

[0095] The term "exterior side" should be understood in its broadest term. The term exterior environment is used for defining the direction opposite of the side that is facing the highly aggressive substance to be sealed by a laminate or packaging of the present invention. This means that the term exterior environment is independent on whether additional layers are coated, laminated or otherwise attached to the film. Thus, the word is used for specifying which direction a side of a layer is facing.

[0096] The various embodiments of the invention will now be illustrated with references to the figures and examples.

[0097] With reference to figure 1 a film of the invention will now be described in greater detail. The extreme chemical resistant film, 1, is obtained by providing a base layer, 2. A coextrusion layer, 5, comprising a tie layer, 3, and a contact layer, 4, is coated to one side of the base layer, 2, according to the method of the invention and is allowed to adhere. The base layer, 2, and the coextrusion layer, 5, define the film according to all the aspects of the invention. Consequently, the film is provided with a base layer side, 2, and a coextrusion layer side 5, wherein the base layer side, 2, is intended for facing the exterior environment and the coextrusion layer side, 5, is intended for facing the highly aggressive substance to be sealed.

[0098] The coextrusion layer may be coated to the aluminium layer by a co-extrusion system generally known in the art to provide the coextrusion layer coated on the first side of the aluminum layer. The coextrusion layer may be applied in an amount of 7-40 g/m³. After coating of the aluminium layer and subsequently cooling, the coextrusion layer is adhered to the side of the tie layer facing away from the aggressive chemical substance.

[0099] The coextrusion is preferably performed at a temperature of 240-330°C, more preferred 270 - 300°C and the speed of the application/coating is in the range of 150 to 600 m/min. The equipment suitable for extruding and laminating films and laminates according to the invention may be obtained from Bobst.

[0100] When using coextrusion, it is possible to obtain a multi layer which is thinner than multilayer layers provided by sequential film application techniques without compromising the extreme chemical resistance properties of the first laminate. Hence, the present invention does not only provide an extreme chemical resistance laminate, and packaging comprising the same but at the same time the manufacturing process is more cost effective since less polymer, forming the contact layer, has to be used.

[0101] Another embodiment of a film in which the tie layer comprises two layers is illustrated in figure 2. The extreme chemical resistant film, 1, is obtained by providing a base layer, 2. The coextrusion layer, 5, comprises a tie layer, 3, comprising a first layer, 3a, and a second layer, 3b, and a contact layer 4. The coextrusion layer is coated onto one side of the base layer, 2, according to the method of the invention and is allowed to dry.

[0102] In the embodiment illustrated, the tie layer, 3, comprises two layers. These layers may be made of EAA as the first layer, 3a, and polyethylene (PE) as the second layer, 3b, where the first layer of EAA faces the base layer and second layer of the PE faces the contact layer, 4.

[0103] The extreme chemical resistant film according to the invention is intended for use as a component of a packaging suitable for sealing a highly aggressive substance. The film may constitute the packing itself.

[0104] To further improve the mechanical wear resistance of the film a first outer layer may be laminated to the base layer side of the film or simply be wrapped around the film to provide a

laminate. Hence, in figure 3 is illustrated a cross section of an embodiment of a laminate according to the invention, 12, comprising a first outer layer, 21, a base layer, 22, and a coextrusion layer, 25. The first outer layer, 21 and the base layer side, 22, may be laminated together before, during or after the coextrusion layer 25 is applied/coated to the base layer.

[0105] The first outer layer, 21, is a mechanically wear resistant layer which adds safety properties to the wrapping ensuring that the wrapping is not inadvertently opened. Hence, the outer layer can also be seen as a child proof layer meaning that the layer is made of a material and is sealable in such a way that it is difficult for children to open. Additionally, the outer layer may be provided with a second outer layer, 20.

[0106] The second outer layer, 20, is typically a paper layer, wherein the paper layer is facing the exterior environment; the exterior facing side of the second layer may be printed as desired. The second outer layer, such as the paper layer is added to improve the stiffness of the packaging in addition to providing a printing platform.

[0107] Furthermore, it is within the inventive concept of the present invention that an adhesive agent is applied between the first outer layer and the base layer and/or between the first outer layer and the second outer layer. The obtained packaging may then be assembled in such a way that the various layers do not part during handling, printing and/or packaging of the substance to be packed.

[0108] After production, the film, laminate or packaging may be stored as rolls ready for use in further lamination or packaging of the aggressive substance to be packed.

[0109] In use, the packaging is sealed around the substance to be packed so that the contact layer of the coextrusion layer faces the interior side and the substance, and, the base layer, first outer layer or second outer layer, as applicable, face the exterior side, so as to create a hollow interior for containing the, substance, such as the aggressive substance.

[0110] The sealing of the packaging is achieved in such way that the contact layer of the coextrusion layer is facing the aggressive substance so that the remaining part of the package is protected by the contact layer of the coextrusion layer. In this way, the aggressive substance is encompassed by the inner side of packaging and will therefore only have direct contact with the contact layer of the coextrusion layer.

[0111] In general, the order in which the different layers of the packaging according to the invention are applied to the base layer is flexible. Hence, the first outer layer may be applied before the coextrusion layer and the other way around. The order depends on which production line is suitable in a specific situation.

[0112] In general, the lamination procedure for laminating the mechanically wear resistant or paper layer to each other or to the base layer is routine procedure for the person skilled in the art.

[0113] According to all aspects of the invention the base layer is selected from a metal foil, preferably aluminum foil, such as commercial Alu foil from e.g. Hydro.

[0114] According to all aspects of the invention the tie layer may be made of a material selected from but not limited to a copolymer made of a material selected from a copolymer of ethylene and acrylic acid, ethylene and methacrylic acid and a terpolymer comprising ethylene, acrylic ester and a third polymer, which third polymer is preferably a glycidyl methacrylate, and more preferably a maleic anhydride, such as the commercial product Lotader[®] 3410 sold by Arkema or Nucrel[®] 0609HSA sold by Dupont[®]

[0115] According to all aspects of the invention the contact layer may be made of a material selected from a polyamide, or mixtures of a polyamide, cyclic olefin copolymer or an ethylene vinyl alcohol such as the commercial products EVAL[®] C109B sold by Kuraray, Selar PA 3426 R sold by Dupont[®] or COC 6013M-07, COC 8007F-600, or 9506F500 sold by Topas[®] or EVOH obtainable from Nippon Gohsei under the tradename Soarnel.

[0116] According to all aspects of the invention the first outer layer may be made of a material selected from paper, polyethylene or polyamide based sheets, ortho-phthalaldehyde based sheets, or polyester based sheets, or combinations, such as the commercial product F-PAP sold by Flexpet.

[0117] The invention will now be illustrated in more details with reference to the following non limiting examples.

RED Calculation

[0118] Determination of the HSP values and interaction radius for nicotine, rivastigmine, fentanyl and lidocaine requires that the solubility of the drug is evaluated against at least 16 solvents having a range of polar and hydrogen bonding properties. The methodology of determining HSP values, interaction radius and RED values are described in C.M. Hansen: "Hansen Solubility Parameters, A User's Handbook", CRC Press, 2007, Second Edition and exemplified in EP 2 895 531.

[0119] Typical solvents used to determine the HSP may be but is not limited to the solvents present in table 2.

Table 2: Typical solvents used to determine the HSP of a polymer or substance of interest.

Typical solvents used in Determining of HSP of rivagstigmine, lidocaine, fentanyl and nicotine	
Chemical name	Trade Designation or Alternate Name
Acetonitrile	Acetonitrile

Typical solvents used in Determining of HSP of rivagstigmime, lidocaine, fentanyl and nicotine	
Chemical name	Trade Designation or Alternate Name
Ethylene glycol n-Butyl Ether	Butyl CELLOSOLVE™ Glycol Ether
Dibutyl Ether	Dibutyl Ether
Dimethyl Formamide	Dimethyl Formamide
Dimethyl Sulfoxide	Dimethyl Sulfoxide
Methanol	Methyl alcohol
2-Butanone	Methyl Ethyl Ketone
4-Methyl-2-pentanone	Methyl Isobutyl Ketone
n-Butyl Acetate	n-Butyl Acetate
n-Heptane	n-Heptane
1-Propanol	n-Propyl Alcohol
o-Dichlorobenzene	1,2-Dichlorobenzene
Tetrahydrofuran	Tetrahydrofuran
Toluene	Methylbenzene
Propylene Carbonate	Propylene Carbonate
Water	Water

[0120] For assessing the solubility of Rivastigmine, Lidocaine, fentanyl and nicotine in the solvents an experimental measurement is performed. The solubility is assessed based on the visual observation of 0.5 g of the chemical substance in a vial with 5 cm³ solvent at room temperature. The vial is capped with a polyethylene-lined lid and labeled with the solvent loaded. The vials are placed in a vial shaker at low speed at room temperature. After 24 hours, the samples are removed from the vial shaker, and allowed to sit for 30 min before they are visually rated. The rating is performed by giving each solvent a score being 0 for insoluble and 1 for soluble. The numerical ratings are then entered into the HSPiP software program to obtain the HSP (Hansen solubility parameters). R (radius) values for the compound of relevance, e.g. nicotine, rivastigmine, fentanyl and/or lidocaine is inserted, and a report is generated. The report lists the final parameters and R values calculated for nicotine, rivastigmine, fentanyl and/or lidocaine. The report also lists the solvents used in the evaluation, their HSP values (taken from a database), the rating of the visual observations, and their RED values with a specific polymer of interest.

Example 1- performance of a laminate according to the invention compared to a commercially used laminate

[0121] A study was conducted to evaluate the performance of four laminates, one (laminates 1) being according to the present invention, as compared to a commercially available laminate product comprising Barex[®] as the contact layer.

[0122] The wrappings according to the invention were compared to the performance of a Barex[®] laminate currently used in the field.

[0123] The test is a resistance test, wherein the migration of rivastigmine to the laminates is evaluated.

Table 3: The composition of the 6 wrappings was as follows, laminate 1 is a laminate according to the invention

	Adhesive/Polymer layer Coextrusion layer	Base layer	First outer layer	Second Outer layer
Commercially used Barex [®] laminate (prior art)	Adhesive/Barex [®] film	Al	PET	Paper
Laminates 1	Tie layer: Bipolymer of ethylene and acrylic acid (Nucrel 0609 HAS) Contact layer: PA (Selar PA 3426R)	Al	PET	
Laminates 2	Tie layer: Terpolymer of ethylene, acrylic ester and maleic anhydride (Lotader 3410) Contact layer: EVOH 60% (EVAL C109B) and PE 40%	Al	PET	
Laminates 3	Tie and contact layer: EvOH film (EVAL C109B)	Al	PET	
Laminates 4	Tie layer: Terpolymer of ethylene, acrylic ester and maleic anhydride (Lotader 3410) Contact layer: EVOH 100% (EVAL C109B)	Al	PE	PET
Laminates 5	Tie layer: Terpolymer of ethylene, acrylic ester and maleic anhydride (Lotader 3410) Contact layer: COC	Al	PE	PET

	Adhesive/Polymer layer Coextrusion layer	Base layer	First outer layer	Second Outer layer
*Between the paper/PET, PET/Al, and Al/EVOH film layers an adhesive was applied.				

[0124] Laminate 1 was obtained according to the method of the invention. For laminates 1, 2, 4 and 5 a coextrusion layer was coated to the base layer and in laminate 3 the combined tie and contact layer was laminated to the base layer. For the co-extrusion layers, the loading of the tie layers was between 4-18 g/m² and the loading of the contact layer was 8-12 g/m².

[0125] The resulting laminates were wrapped around a patch containing rivastigmine as API and the migration of the API to the packaging material/wrapping was measured after 2, 4, 8 and 12 weeks at 40 °C. The API in the wrapping was measured by extracting the packaging and analysing the amount of API therein using Mass spectrometry.

[0126] The Rivastigmine patches tested were commercially available patches originally containing 9.5 mg API/patch.

[0127] The results are shown in figure 4 illustrating the resulting migration of rivastigmine (weight API extracted from the laminate) to the laminate in percentage of the content of the original patches of 9.5 mg.

[0128] The columns are denoted 1, 2, 3 and 4 respectively to the order they are shown from left to right in figure 4. Hence column 1 (furthest to the left) for each contact layer polymer used shows the results for the 6 laminates after two weeks. Column 2 shows the results for the 6 laminates after four weeks. Column 3 shows the results for the 6 laminates after 8 weeks, and column 4 shows the results for the 6 laminates after 12 weeks.

[0129] The Barex[®] laminate is a reference known for applicability in the art and comparison were made for evaluating the properties of the laminates according to present invention.

[0130] From the figure it is clear that the results for laminates obtained by coextrusion of either of EVOH, PA, or COC as well as laminating EVOH provides for an improved chemical resistant laminate compared to the commercially used Barex[®] laminate, meaning that less migration occurs.

[0131] Also, a contact layer, illustrated as laminate 2, of a blend of EVOH and PE was prepared and tested. Though the properties of this blend with rivastigmine as API resulted in a higher migration of the API than Barex[®], the rate is still below the limit demanded in the industry and hence, it illustrates that blends as provided in laminate 2 are usable alternatives to Barex[®] as well. Surprisingly though the tie/contact layer made of 100% EVOH was markedly

superior to the blend.

[0132] Also, a contact layer, illustrated as laminate 3, a film of EVOH laminated to aluminum was prepared and tested. Surprisingly, it was shown that the use of EVOH in the form of a film laminated to aluminum provided a chemical resistant laminate.

Example 2 - stability test of a chemical substance wrapped in laminates

[0133] Similar to the test described in example 1, laminates were prepared as outlined in table 4 below. A lidocaine patch containing 40 mg lidocaine was wrapped in the pouch, packaged and stored at 40°C for seven days.

Table 4: Packagings for lidocaine stability test.

	Barex Commercially used Barex [®] laminate (prior art)	COC coex same as laminate 5 of example 1	Coex EVOH same as laminate 4 of example 1
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[0134] Stability of the API is important to ensure that the dose indicated on the packaging is correct. A value of 90% - 110% of the original dose after one week when stored at 40°C using Barex[®] as index 100 is considered acceptable. Figure 5 illustrates the results of the test where the y-axis indicates the weight decrease of the two laminates using Barex as index 100.

[0135] As can be seen from figure 5, both laminates have a lower value than the index 100 Barex[®] comparative product, however with a value within the acceptable limits. The lower %value of the laminates indicates that more lidocaine has disappeared from the patch.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- [WO0044559A \[0005\]](#)
- [EP2895531A \[0118\]](#)

Non-patent literature cited in the description

- **C.M. HANSEN**Hansen Solubility Parameters, A User's HandbookCRC Press19990000 [\[0013\]](#)
- **C.M. HANSEN**Hansen Solubility Parameters, A User's HandbookCRC Press20070000 [\[0118\]](#)

P A T E N T K R A V

1. Fremgangsmåde til at tilvejebringe en folie, hvor fremgangsmåden omfatter trin-
nene:

5 i) at tilvejebringe et basislag hvilket er vand- og/eller iltmodstandsdygtigt, hvor ba-
sislaget er valgt fra en metalfolie, fortrinsvis aluminium

ii) at coextrudere et lag omfattende et bindelag og et kontaktlag for at tilvejebringe
et coextruderingslag;

iii) at coate coextruderingslaget til basislaget

10 iv) at tillade coextruderingslaget, som er coatet til basislaget, at klæbe for at tilveje-
bringe en aggressivt-kemikaliemodstandsdygtig folie, hvor det aggressive kemikalie er
nikotin, fentanyl, lidocain eller rivastigmin, hvor folien omfatter bindelaget og kontaktlaget
dannet som et coextruderingslag, der er coatet på basislaget, hvori bindelaget omfatter
mindst ét lag, og,

15 hvori kontaktlaget omfatter en polymer, som har en RED værdi baseret på Hansens
opløselighedsparametre (HSP) mod et aggressivt kemikalie, navnlig nikotin, fentanyl, lido-
cain eller rivastigmin, på $> 0,8$, mere fortrinsvist en RED værdi i intervallet af 0,8 til 10,
endnu mere fortrinsvist 0,8 til 5, og mest fortrinsvist 1 til 2; og yderligere hvori polymeren
er et polyamid.

2. Fremgangsmåde ifølge krav 1, hvori bindelaget er lavet af 1, 2, 3, 4 eller 5 lag.

20 3. Fremgangsmåde ifølge krav 2, hvor alle lagene af bindelaget coextruderes med
kontaktlaget.

4. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvori bindela-
get udgøres af ét lag, og hvori laget er en copolymer, som er lavet er et materiale valgt fra
en copolymer af ethylen og akrylsyre, ethylen og methakrylsyre og en terpolymer, der
25 omfatter ethylen, akrylester og en tredje polymer, hvilken tredje polymer fortrinsvist er en
glycidylmethakrylat, og mere fortrinsvist en maleinsyreanhydrid.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 3, hvori bindelaget
omfatter mindst to lag, og hvori det første lag omfatter en copolymer ifølge krav 5 og det
mindst andet eller flere lag omfatter et materiale valgt fra EEA, PE, EMA, EAA eller en
30 kombination.

6. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvori bindela-
get eller de flere lag, som udgør bindelaget, har en belastning i intervallet af 7 til 20 g/m²,
og/eller kontaktlaget har en belastning i intervallet af 4 til 20 g/m², og belastningen af
folien ikke er mere end 40 g/m².

35 7. Aggressivt-kemikaliemodstandsdygtig folie, hvor det aggressive kemikalie er niko-
tin, fentanyl, lidocain eller rivastigmin, hvor folien omfatter mindst et basislag, som er
vand- og/eller iltmodstandsdygtigt, hvor basislaget er valgt fra en metalfolie, fortrinsvis
aluminium og et coextruderingslag, hvori coextruderingslaget omfatter et bindelag og et

kontaktlag, og hvori bindelaget omfatter mindst ét lag, og hvori kontaktlaget omfatter en polymer, som har en RED værdi baseret på Hansens opløselighedsparametre (HSP) mod et aggressivt kemikalie, navnlig nikotin, fentanyl, lidocain eller rivastigmin, på $> 0,8$, mere fortrinsvist en RED værdi i intervallet af 0,8 til 10, endnu mere fortrinsvist 0,8 til 5, og mest fortrinsvist 1 til 2, hvori polymeren er en polyamid.

8. Folie ifølge krav 7, hvori bindelaget udgøres af ét lag og hvori laget er lavet af en copolymer, hvor copolymeren omfatter et materiale valgt fra en copolymer lavet af ethylen og akrylsyre, ethylen og methakrylsyre og en tredje polymer, hvilken tredje polymer fortrinsvist er lavet af et materiale valgt fra glycidylmethakrylat, og mere fortrinsvist en maleinsyreanhydrid.

9. Folie ifølge kravene 7 eller 8, hvori bindelaget eller de flere lag, som udgør bindelaget, har en belastning i intervallet af 7 til 20 g/m², og/eller kontaktlaget har en belastning i intervallet af 4 til 20 g/m², og belastningen af folien ikke er mere end 40g/m².

10. Laminat til emballering af nikotin, fentanyl, lidocain eller rivastigmin, hvor laminatet omfatter mindst

- et første yderlag, som er lavet af et mekaniskslitagemodstandsdygtigt materiale;
- en aggressivt-kemikaliemodstandsdygtig folie ifølge et hvilket som helst af kravene 7 til 9, hvor basislagssiden af folien vender mod det første yderlag.

11. Laminat ifølge krav 10, hvori laminatet yderligere omfatter et andet yderlag, som vender mod ydersiden af yderlaget, fortrinsvist er det andet yderlag et papirlag.

12. Laminat ifølge et hvilket som helst af kravene 10 til 11, hvori laminatet omgiver en sammensætning valgt fra gruppen, som består af nikotin, rivastigmin, fentanyl, og lidocain.

13. Laminat ifølge krav 10, 11 og 12, hvori laminatet er varmforsægleligt.

14. Laminat ifølge krav 10 til 13, hvori et maksimum på 10%, fortrinsvist et maksimum på 5%, endnu mere fortrinsvist et maksimum på 2% af den aktive ingrediens er vandret ind i laminatet ved dag 0 efter 12 ugers lagring ved 40 °C.

15. Aggressivt kemiskstof, navnlig nikotin, fentanyl, lidocain eller rivastigmin emballeret i et varmforsægleligt laminat, hvor det varmforsæglelige laminat omfatter

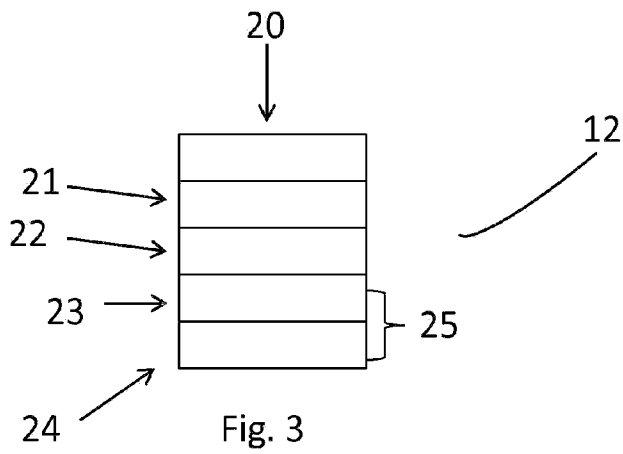
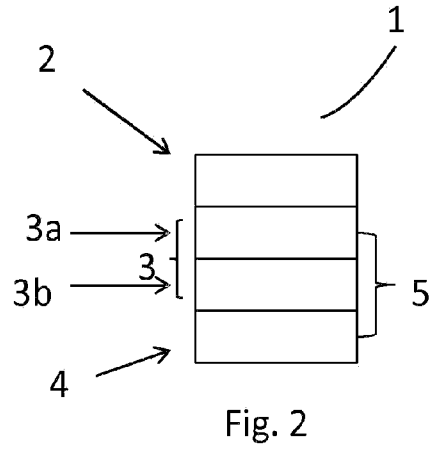
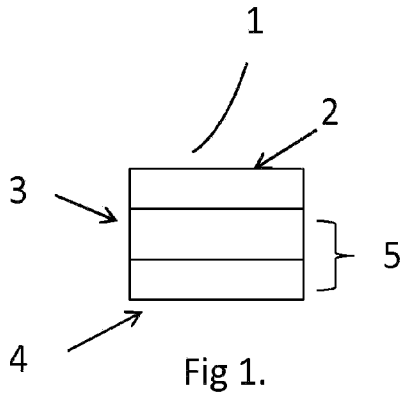
- et første yderlag, som er lavet af et mekaniskslitagemodstandsdygtigt materiale;
- en aggressivt-kemikaliemodstandsdygtig folie, hvori basislagssiden af folien vender mod yderlaget;

hvor den aggressive kemikaliemodstandsdygtige folie omfatter mindst et basislag, hvilket er vand- og/eller iltmodstandsdygtig, og et coextrusionslag, hvori coextruderingslaget omfatter et bindelag og et kontaktlag, og hvori bindelaget omfatter mindst ét lag, og hvori kontaktlaget omfatter en polymer, som har en RED værdi baseret på Hansens opløselighedsparametre (HSP) mod et aggressivt kemikalie, navnlig nikotin, fentanyl, lidocain eller rivastigmin, på $> 0,8$, mere fortrinsvist en RED værdi i intervallet af 0,8 til 10, endnu mere fortrinsvist 0,8 til 5, og mest fortrinsvist 1 til 2, hvori polymeren er en polyamid.

16. Anvendelse af en polymer, som har en RED værdi baseret på Hansens opløselighedsparametre (HSP) mod et aggressivt kemikalie, navnlig nikotin, fentanyl, lidocain eller rivastigmin, på $> 0,8$, mere fortrinsvist en RED værdi i intervallet af 0,8 til 10, endnu mere fortrinsvist 0,8 til 5, og mest fortrinsvist 1 til 2, som et kontaktlag til at tilvejebringe kemiskmodstandsdygtighed til en folie mod det aggressive kemikalie, navnlig nikotin, fentanyl, lidocain eller rivastigmin hvori folien omfatter et basislag hvilket er vand- og/eller iltmodstandsdygtigt, hvor folien er coatet på et, valgfrit coextruderet, lag, der omfatter et bindelag og kontaktlaget, hvori polymeren er en polyamid.

DRAWINGS

Drawing



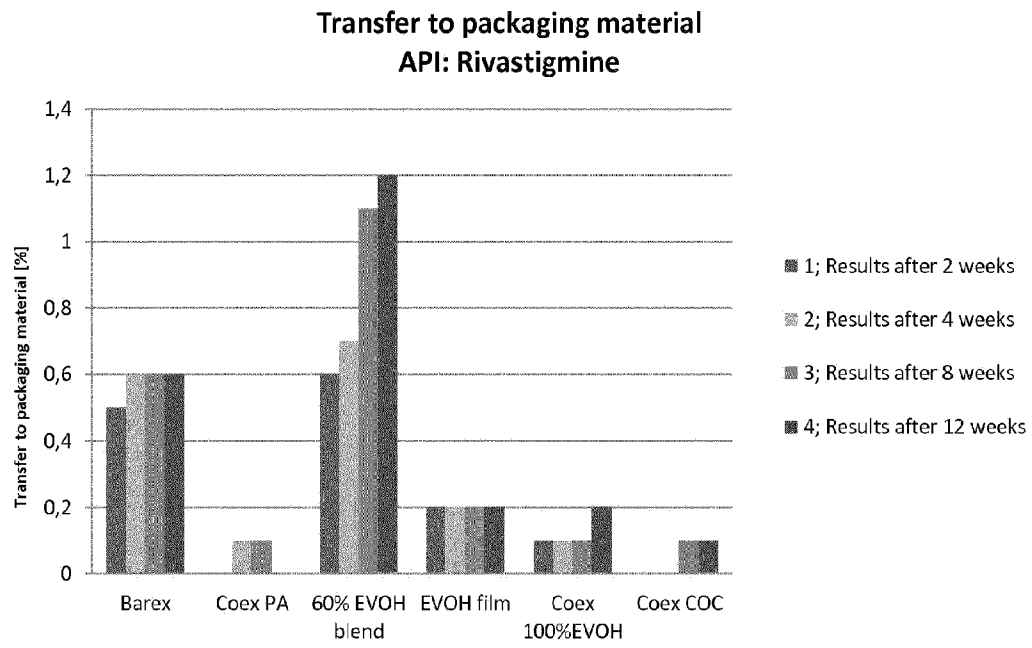


Fig. 4

Index on remaining API % in patch
API: Lidocaine

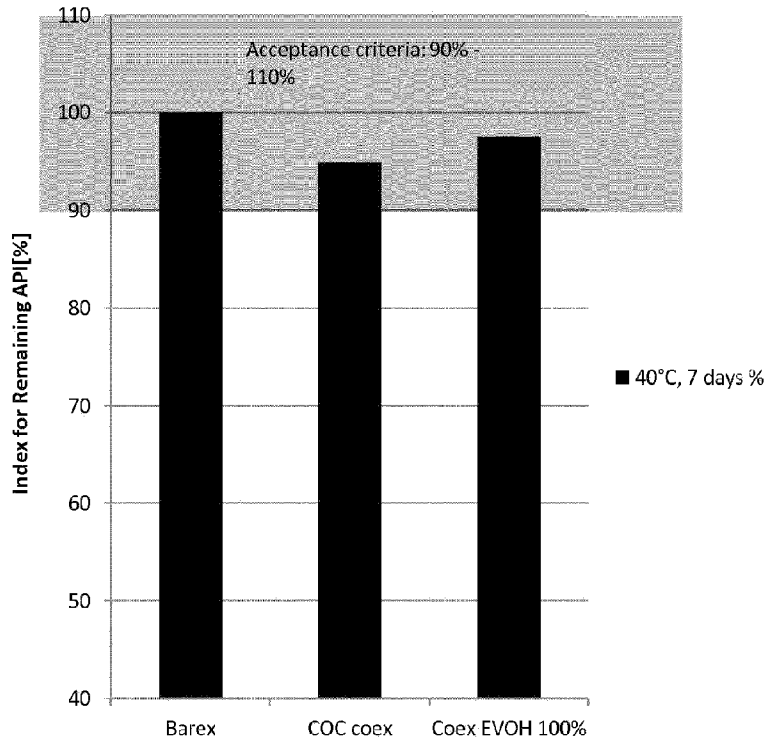


Fig. 5