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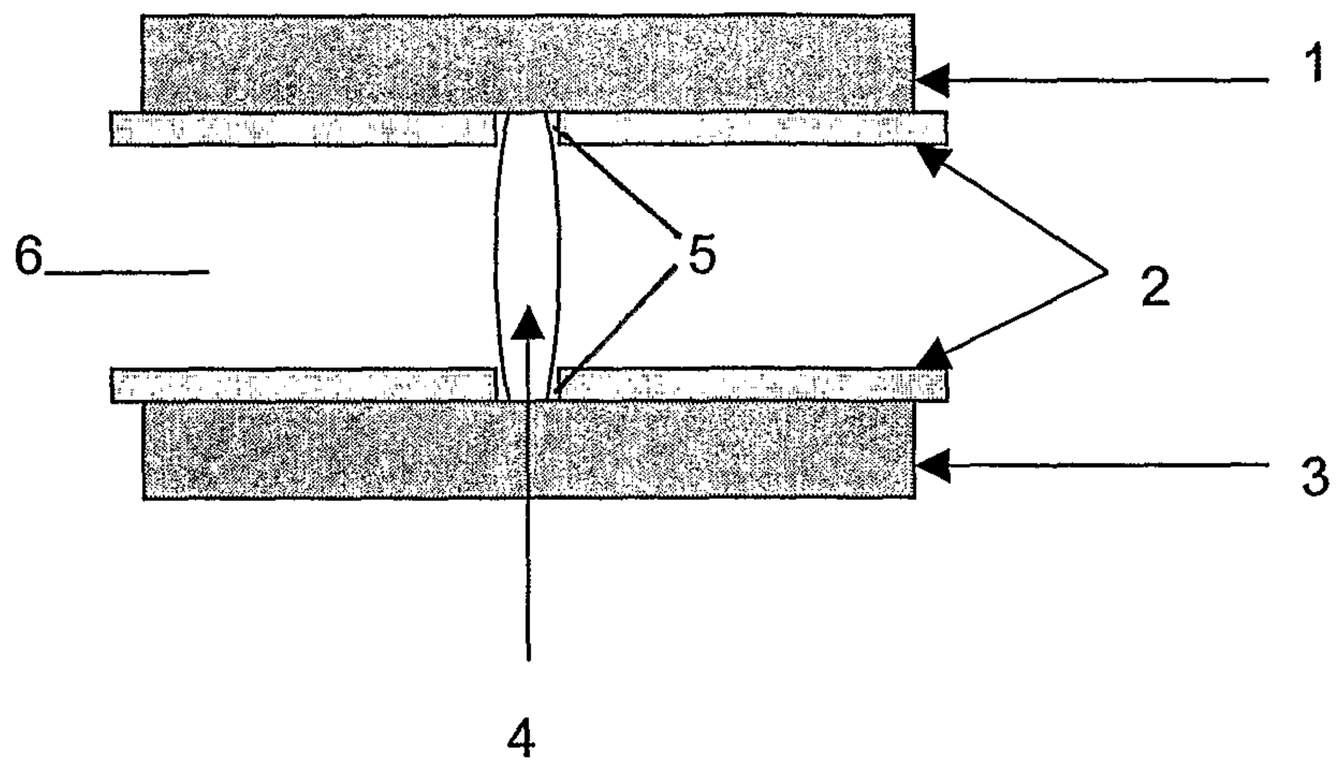
(54) Titre : FORME GALENIQUE EMPECHANT UN USAGE DETOURNE
(54) Title: FORM OF ADMINISTRATION SECURED AGAINST MISUSE



(57) Abrégé/Abstract:
The invention relates to a form of administration which is secured against misuse and which is thermoformed without extrusion, comprising at least one synthetic or natural polymer having a resistance to breaking of at least 500 N in addition to one or several active ingredients with a misuse potential and, optionally physiologically compatible auxiliary substances. The invention also relates to a method for the production thereof.

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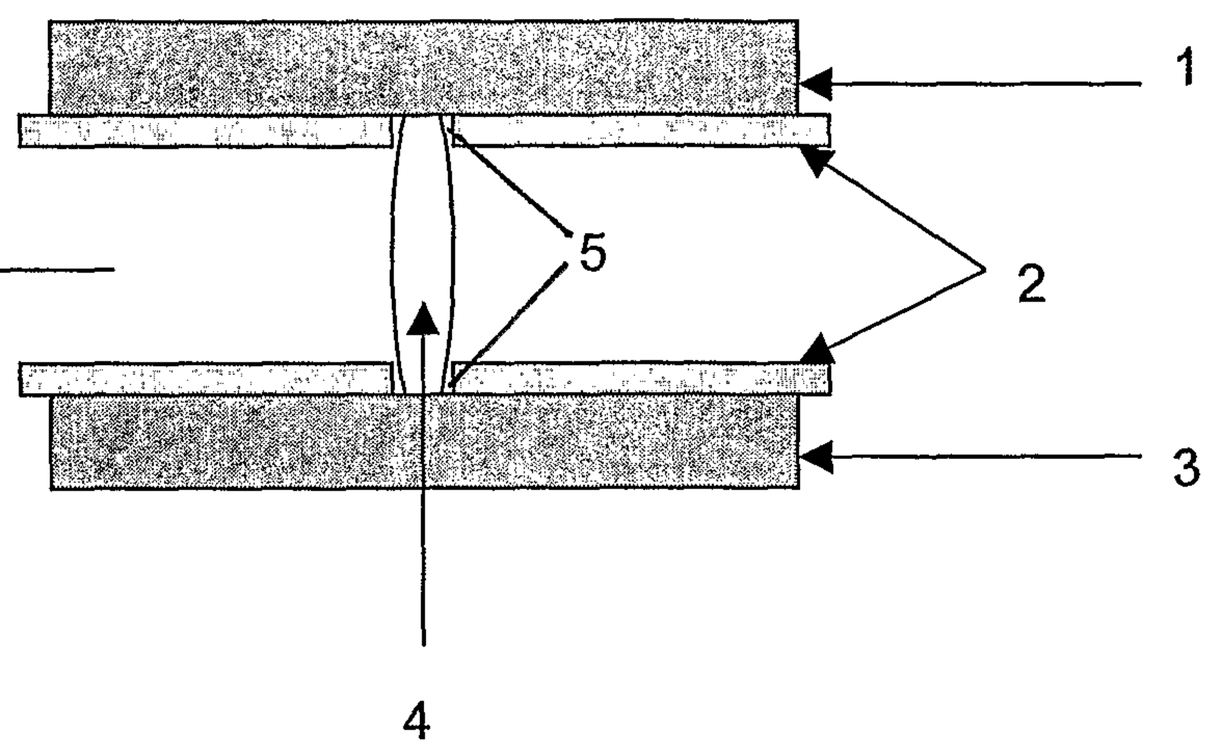
Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** FORM OF ADMINISTRATION SECURED AGAINST MISUSE

(54) **Bezeichnung:** GEGEN MISSBRAUCH GESICHERTE DARREICHUNGSFORM



(57) Abstract: The invention relates to a form of administration which is secured against misuse and which is thermoformed without extrusion, comprising at least one synthetic or natural polymer having a resistance to breaking of at least 500 N in addition to one or several active ingredients with a misuse potential and, optionally physiologically compatible auxiliary substances. The invention also relates to a method for the production thereof.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft eine gegen Missbrauch gesicherte, ohne Extrusion thermogeformte Darreichungsform enthaltend neben einem oder mehreren Wirkstoffen mit Missbrauchspotential sowie ggf. physiologisch verträglichen Hilfstoffen mindestens ein synthetisches oder natürliches Polymer mit einer Bruchfestigkeit von mindestens 500 N und deren Verfahren zur Herstellung.

WO 2005/016314 A1

Abuse-proofed dosage form

The present invention relates to an abuse-proofed dosage form thermoformed without extrusion containing, in addition to one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) and the optionally present component (D) in each case exhibits a breaking strength of at least 500 N, and to a process for the production of the dosage form according to the invention.

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have abuse potential, *i.e.* they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if

the powdered dosage form is administered nasally, *i.e.* is sniffed. Since controlled-release dosage forms containing active ingredients with abuse potential do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such dosage forms are also comminuted and extracted in order to be abused.

US-A-4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with abuse potential and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage form, for example naloxone or naltexone in the case of opioids, or compounds which cause a physiological defence response, such as for example ipecacuanha (ipecac) root.

However, since in most cases of abuse it is still necessary to pulverise the dosage form comprising an active ingredient suitable for abuse, it was the object of the present invention to complicate or prevent the pulverisation preceding abuse of the dosage form using the means conventionally available to a potential abuser and accordingly to provide a dosage form for active ingredients with abuse potential which ensures the desired therapeutic effect when correctly administered, but from which the active ingredients cannot be converted into a form suitable for abuse simply by pulverisation.

Said object has been achieved by the provision of the abuse-proofed dosage form thermoformed without extrusion according to the invention which contains, in addition to one or more active ingredients with abuse potential (A), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) and the optionally present component (D) in each case exhibits a breaking strength of at least 500 N.

The use of polymers having the stated minimum breaking strength (measured as stated in the application), preferably in quantities such that the dosage form also exhibits such a minimum breaking strength of at least 500 N, means that pulverisation of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too

long for the abuser or there is no "kick" when taken orally, as release is not instantaneous.

According to the invention, comminution is taken to mean pulverisation of the dosage form with conventional means which are available to an abuser, such as for example a mortar and pestle, a hammer, a mallet or other usual means for pulverisation by application of force.

The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of active ingredients, preferably of pharmaceutical active ingredients with abuse potential.

Pharmaceutical active ingredients with abuse potential are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stereoisomers. The dosage form according to the invention is also suitable for the administration of two or more pharmaceutical active ingredients. The dosage form preferably contains only one specific active ingredient.

The dosage form according to the invention is in particular suitable for preventing abuse of a pharmaceutical active ingredient selected from the group comprising opioids, tranquillisers, preferably benzodiazepines, barbiturates, stimulants and other narcotics.

The dosage form according to the invention is very particularly suitable for preventing abuse of an opioid, tranquilliser or another narcotic selected from the group comprising N-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-a-methyl-phenethylamine (amphetamine), 2-(a-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1*H*-1,4-benzodiazepine-2(3*H*)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5a-epoxy-7a[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl) dimethylcarbamate (camazepam), (1S,2S)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine 4-oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1*H*-thieno[2,3-e][1,4]diazepin-2(3*H*)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo-

[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (-)-methyl-[3β-benzoyloxy-2β(1a*H*,5a*H*)-tropancarboxylate] (cocaine), 4,5a-epoxy-3-methoxy-17-methyl-7-morphinan-6a-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphen), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5a-epoxy-3-methoxy-17-methyl-6a-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methyl-phenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex), *N*-(1-phenethyl-4-piperidyl)propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (flurazepam), 7-chloro-5-phenyl-1-

(2,2,2-trifluoroethyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolyl[3,2-d][1,4]benzodiazepin-6(5*H*)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinane, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6*H*)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethyl-amino-4,4-diphenol-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2-a][1,4]-benzodiazepin-1(4*H*)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-a]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (medazepam), *N*-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-o-tolyl-4(3*H*)-quinazolinone (methaqualone), methyl [2-phenyl-2-(2-piperidyl)acetate] (methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-

a][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)-acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinan-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[-*b*,*d*]pyran-9(6α*H*)-one (nabilone), nalbuphine, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nimetazepam), 7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nitrazepam), 7-chloro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation for the plants belonging to the species Papaver somniferum (opium), 7-chloro-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (oxazepam), (*cis-trans*)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6-(5*H*)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and parts of plants belonging to the species Papaver somniferum (including the subspecies setigerum), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl (1-methyl-4-phenyl-4-piperidine carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-

bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)piperidino]propanoate} (remifentanil), 5-*sec*-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), N-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}-propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (tetrazepam), ethyl (2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylamino-methylcyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexan-1,3-diol, preferably as a racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylamino-methyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester,

(RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester and corresponding stereoisomeric compounds, the corresponding derivatives thereof in each case, in particular amides, esters or ethers, and the physiologically acceptable compounds thereof in each case, in particular the salts and solvates thereof, particularly preferably hydrochlorides.

The dosage form according to the invention is in particular suitable for preventing abuse of an opioid active ingredient selected from the group comprising oxycodone, hydromorphone, morphine, tramadol and the physiologically acceptable derivatives or compounds thereof, preferably the salts and solvates thereof, preferably the hydrochlorides thereof.

The dosage form according to the invention is furthermore in particular suitable for preventing abuse of an opioid active ingredient selected from the group comprising (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol, (1R,2R)-3-(2-

dimethylaminoethyl-cyclohexyl)-phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

These compounds and processes for the production thereof are described in EP-A-693475 or EP-A-780369. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one synthetic or natural polymer (C) is used which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N. At least one polymer selected from the group comprising polyalkylene oxides, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. High molecular weight thermoplastic polyalkylene oxides are preferred. High molecular weight polyethylene oxides with a molecular weight of at least 0.5 million, preferably of at least 1 million up to 15 million, determined by rheological measurements, are particularly preferred. These polymers have a viscosity at 25°C of 4500 to 17600 cP, measured on a 5 wt.% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt.% aqueous solution using the stated viscosimeter (spindle no. 1 or 3 / rotational

speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt.% aqueous solution using the stated viscosimeter (spindle no. 2 / rotational speed 2 rpm).

The polymers are preferably used in powder form. They may be soluble in water.

In order to achieve the necessary breaking strength of the dosage form according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N. Waxes with a softening point of at least 60°C are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at least 80°C. When the wax component is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form has a breaking strength of at least 500 N.

Component (C) is preferably used in an amount of 35 to 99.9 wt.%, particularly preferably of at least 50 wt.%, very particularly preferably of at least 60 wt.%, relative to the total weight of the dosage form.

Auxiliary substances (B) which may be used are those known auxiliary substances which are conventional for the formulation of solid dosage forms. These are preferably plasticisers, such as polyethylene glycol, auxiliary substances which influence active ingredient release, preferably hydrophobic or hydrophilic, preferably

hydrophilic polymers, very particularly preferably hydroxypropylcellulose, and/or antioxidants. Suitable antioxidants are ascorbic acid, butylhydroxyanisole, butylhydroxytoluene, salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite, particularly preferably butylhydroxytoluene (BHT) or butylhydroxyanisole (BHA) and α-tocopherol.

The antioxidant is preferably used in quantities of 0.01 to 10 wt.%, preferably of 0.03 to 5 wt.%, relative to the total weight of the dosage form.

The dosage forms according to the invention are distinguished in that, due their hardness, they cannot be pulverised, for example by grinding in a mortar and pestle. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse. However, in order to prevent any possible abuse of the dosage form according to the invention, the dosage forms according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B).

The abuse-proofed dosage form according to the invention, which comprises, apart from one or more active ingredients with abuse potential, at least one hardening polymer (C) and optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(e) as auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for each of the active ingredients with abuse potential,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components

makes it possible still more effectively to prevent abuse of dosage forms according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

If the dosage form according to the invention comprises component (a) to counter abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these

stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary

root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, α-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

The dosage form according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt.%, particularly preferably of 0.1 to 0.5 wt.%, in each case relative to the total weight of the dosage unit.
If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to

0.005 wt.%, relative to the total weight of the dosage unit.

Another option for preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention, visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37°C, remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may

indeed be broken up into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious harm to the health of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25°C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used which are selected from the group comprising microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins, preferably from citrus fruits or apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel

04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150 ®), tara bean flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 20 wt.%, particularly preferably of 0.1 to 15 wt.% of the stated viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of ≥5 mg per dosage unit, *i.e.* per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

Component (C) may also optionally serves as an additional viscosity-increasing agent which, with the assistance of a

minimum necessary quantity of an aqueous liquid, forms a gel.

It is also possible to formulate the viscosity-increasing agent and the other constituents in the dosage form according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with abuse potential, wherein the antagonists are preferably spatially separated from the remaining constituents of the invention dosage according to the form and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opioid, the antagonist used is preferably an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding

antagonists, where component (c) is provided, are preferably used in a quantity of ≥1 mg, particularly preferably in a quantity of 3 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, *i.e.* per administration unit.

If the dosage form according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to four times the conventional dose per administration unit.

If the combination to discourage and prevent abuse of the dosage form according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding

derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine may preferably be considered in the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of ≥3 mg, particularly preferably of ≥10 mg and very particularly preferably in a quantity of ≥20 mg per dosage form, *i.e.* administration unit.

Apomorphine may likewise preferably be used as an emetic in the abuse-proofing according to the invention, preferably in a quantity of preferably ≥3 mg, particularly preferably of ≥5 mg and very particularly preferably of ≥7 mg per administration unit.

If the dosage form according to the invention contains component (e) as a further abuse-preventing auxiliary substance, the use of a such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous

administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate (Bitrex®). Denatonium benzoate is particularly preferred.

The solid dosage form according to the invention is suitable to be taken orally, vaginally or rectally, preferably orally. The dosage form is preferably not in film form.

The dosage form according to the invention may assume multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules,

spheroids, beads or pellets, optionally packaged in capsules or pressed into tablets, preferably for oral administration. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

The solid, abuse-proofed dosage form according to the invention is preferably produced without using an extruder by mixing components (A), (B), (C) and optionally (D) and optionally at least one of the optionally present further abuse-preventing components (a)-(f) or, if necessary, by separate mixing with the addition of component (C) and optionally component (D), and, optionally after granulation, shaping the resultant mixture or mixtures by application of force to yield the dosage form with preceding or simultaneous exposure to heat.

Heating and application of force for the production of the dosage form proceed without using an extruder.

Mixing of components (A), (B), (C) and optionally (D) and of the optionally present further components (a)-(f) and optionally of components (C) and the optionally present component (D) proceeds optionally in each case in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant mixture is preferably shaped directly by application of force to yield the dosage form according to the invention with preceding or simultaneous exposure to

heat. The mixture may, for example, be formed into tablets by direct tabletting. In direct tabletting with simultaneous exposure to heat, the tabletting tool, *i.e.* bottom punch, top punch and die are briefly heated at least to the softening temperature of the polymer component (C) and pressed together. In direct tabletting with preceding exposure to heat, the material to be pressed is heated immediately prior to tabletting at least to the softening temperature of component (C) and then pressed with the tabletting tool.

The resultant mixture of components (A), (B), (C) and optionally (D) and the optionally present components (a) to (f) or the mixture of at least one of these components (a) to (f) with component (C) may also first be granulated and then be shaped by application of force with preceding or simultaneous exposure to heat to yield the dosage form according to the invention.

When force is applied, it is applied until the dosage form has achieved a breaking hardness of at least 500 N.

Granulation may be performed in known granulators by wet granulation or melt granulation.

Each of the above-mentioned process steps, in particular the heating steps and simultaneous or subsequent application of force for production of the dosage form according to the invention proceeds without using an extruder.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a

capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, said components are able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or

active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C) and optionally (D), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), at least one polymer (C) and the optionally present component (D) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and optionally (D) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking

and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and optionally component (D) and has been formulated in the above-stated manner.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on

the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) and optionally (D) is included in the formulation and formulation is carried out in accordance with the above-stated process in order to achieve the necessary hardness.

In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, *i.e.* shape, is selected for

both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be pressed into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, controlled release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

The multiparticulate subunits may also be formulated as an oral dosage form as a slurry or suspension in pharmaceutically safe suspending media.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention,

wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form. In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, *i.e.* conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face of which and optionally one of the two main faces is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) and optionally (D) to fulfil the hardness condition of the dosage form according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from

subunit (Y) is virtually ruled out. The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose.

Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density

polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid with high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group comprising glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids,

substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form according to the invention exhibits controlled release of the active ingredient. It is preferably suitable for twice daily administration to patients.

The dosage form according to the invention may comprise one or more active ingredients at least partially in controlled release form, wherein controlled release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a controlled release matrix or by the application of one or more controlled release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect. Addition of materials effecting controlled release must moreover not impair the necessary hardness.

Controlled release from the dosage form according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is necessary according to the invention may furthermore also optionally serve as additional matrix materials.

If the dosage form according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the dosage form according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the controlled release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

Method for determining breaking strength

In order to verify whether a polymer may be used as component (C) or (D), the polymer is pressed to form a

tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the polymer. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143-144, method no. 2.9.8.. The apparatus used for the measurement is a "Zwick Z 2.5" materials tester, Fmax = 2.5 kN with a maximum draw of 1150 mm, which should be set up with 1 column and 1 spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diam. 10 mm), a force transducer, Fmax. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-18 (Zwick gross force Fmax = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with order no. BTC-FR 2.5 TH. D09 for the tester, order no. BTC-LC 0050N. P01 for the force transducer, order no. BO 70000 S06 for the centring device.

Figure 1 shows the measurement of the breaking strength of a tablet, in particular the tablet (4) adjustment device (6) used for this purpose before and during the measurement. To this end, the tablet (4) is held between the upper pressure plate (1) and the lower pressure plate (3) of the force application apparatus (not shown) with the assistance of two 2-part clamping devices, which are in each case firmly fastened (not shown) with the upper and lower pressure plate once the spacing (5) necessary for

accommodating and centring the tablet to be measured has been established. The spacing (5) may be established by moving the 2-part clamping devices horizontally outwards or inwards in each case on the pressure plate on which they are mounted.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

In the case of the dosage forms according to the invention, breaking strength is determined in accordance with the stated method, dosage forms other than tablets also being tested.

The following Examples illustrate the invention purely by way of example and without restricting the general concept of the invention.

Examples:

Tramadol hydrochloride was used as the active ingredient in a series of Examples. Tramadol hydrochloride was used, despite tramadol not being an active ingredient which conventionally has abuse potential, because it is not governed by German narcotics legislation, so simplifying the experimental work. Tramadol is moreover a member of the opioid class with excellent water solubility.

Example 1

Components	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	200 mg	200 g
Total weight	300 mg	300 g

Tramadol hydrochloride and polyethylene oxide powder were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80°C in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablet could not be comminuted using a hammer, nor with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. At the beginning of the investigation, each tablet was placed in a 600 ml portion of artificial gastric juice, pH 1.2. After 30 minutes, the pH value was increased to 2.3 by addition of alkali solution, after a further 90 minutes to pH 6.5 and after a further 60 minutes to pH 7.2. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Released quantity
30 min	15%
240 min	52%
480 min	80%
720 min	99%

Example 2

300 mg portions of the powder mixture from Example 1 were heated to 80°C and in placed in the die of the tabletting tool. Pressing was then performed. The tablet exhibits the same properties such as the tablet in Example 1.

Example 3

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	100 mg	200 g
Total weight	150 mg	300 g

Tramadol hydrochloride and the above-stated components were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 7 mm was heated to 80°C in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	15%
240 min	62%
480 min	88%
720 min	99%

Example 4

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	180 mg	180 g
Xanthan, NF	20 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80°C in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	14%
240 min	54%
480 min	81%
720 min	99%

The tablets could be cut up with a knife into pieces of an edge length of as small as approx. 2 mm. No further comminution proceeding as far as pulverisation was possible. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 5

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	90 mg	180 g
Xanthan, NF	10 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with a top punch, bottom punch and die for oblong tablets 10 mm in length and 5 mm in width was heated to 90°C in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	22%
120 min	50%
240 min	80%
360 min	90%
480 min	99%

The tablets could be cut up with a knife into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 6

A tablet with the following composition was produced as described in Example 1:

Components	Per tablet	Per batch
Oxycodone hydrochloride	20.0 mg	0.240 g
Xanthan, NF	20.0 mg	0.240 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	110.0 mg	1.320 g
Total weight	150.0 mg	1.800 g

Release of the active ingredient was determined as follows:

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed 75 rpm. The phosphate buffer, pH 6.8, described in USP served as the release medium. The quantity of active ingredient present in the solvent at the particular time of testing was determined by spectrophotometry.

Time	Mean
0 min	0%
30 min	17%
240 min	61%
480 min	90%
720 min	101.1%

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

The tablets could be cut up with a knife into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 7:

Components	Per tablet	Per batch
Tramadol HCl	100.0 mg	2.0 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	4.42 g
Hydroxypropylmethylcellulose (Metholose 90 SH 100 000 cP from ShinEtsu)	20.0 mg	0.4 g
Butylhydroxytoluene (BHT)	0.2 mg	0.004 g
Total weight	341.2 mg	6.824 g

The stated quantity of BHT was dissolved in ethanol (96%), such that a 7.7% (mass/mass) ethanolic solution was obtained. This was mixed with the polyethylene oxide and then dried for 12 h at 40°C.
All the further components were added to this dried mixture and mixed for 15 min in a free-fall mixer.

The tablets were produced using the same method as stated in Example 1. Round punches (diameter 10 mm) with a radius of curvature of 8 mm were used.

The breaking strength of the tablets was determined in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets could not be comminuted either with a hammer or with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the dosage form was determined in accordance with the details in Example 1 in order to determine release.

Time	Released quantity of active ingredient
30 min	17%
240 min	59%
480 min	86%
720 min	98%

Example 8:

Components	Per tablet	Per batch
Tramadol HCl	100.0 mg	2.0 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	4.42 g
Hydroxypropylmethylcellulose (Metholose 90 SH 100 000 cP from ShinEtsu)	20.0 mg	0.4 g
Total weight	341.0 mg	6.82 g

The individual components were mixed for 15 min in a free-fall mixer. The tablets were produced in accordance with Example 1 using a hot tabletting tool. Round punches (diameter 10 mm) with a radius of curvature of 8 mm were used.

The breaking strength of the tablets was determined in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets could not be comminuted either with a hammer or with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the preparation was determined as stated in Example 1.

Time	Released quantity of active ingredient
30 min	16%
240 min	57%
480 min	84%
720 min	96%

Claims:

1. An abuse-proofed dosage form thermoformed without extrusion, characterised in that, in addition to one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), it contains at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) and the optionally present component (D) exhibit a breaking strength of at least 500 N.

2. A dosage form according to claim 1, characterised in that it is in the form of a tablet.

3. A dosage form according to claim 1, characterised in that it is in multiparticulate form, preferably in the form of microtablets, micropellets, granules, spheroids, beads or pellets, optionally pressed into tablets or packaged in capsules.

4. A dosage form according to any one of claims 1 to 3, characterised in that it contains as polymer (C) at least one polymer selected from the group comprising polyethylene oxide, polymethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers and the mixtures thereof, preferably polyethylene oxide.

5. A dosage form according to any one of claims 1 to 4, characterised in that the polyethylene oxide (C) has a molecular weight of at least 0.5 million.

6. A dosage according to claim 5, characterised in that the molecular weight of the polyethylene oxide (C) is at least 1 million.

7. A dosage form according to claim 6, characterised in that the molecular weight of the polyethylene oxide (C) is 1-15 million.

8. A dosage form according to any one of claims 1 to 7, characterised in that it contains as the wax (D) at least one natural, semi-synthetic or synthetic wax with a softening point of at least 60°C.

9. A dosage form according to claim 8, characterised in that the wax (D) is carnauba wax or beeswax.

10. A dosage form according to any one of claims 1 to 9, characterised in that the component(s) (C) and optionally (D) is/are present in quantities such that the dosage form has a breaking strength of at least 500 N.

11. A dosage form according to any one of claims 1 to 10, characterised in that the active ingredient (A) is at least one active ingredient selected from the group comprising opioids, tranquillisers, stimulants, barbiturates and further narcotics.

12. A dosage form according to any one of claims 1-11, characterised in that it additionally comprises at least one of the following components a)-f):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for the active ingredient or active ingredients with abuse potential

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

13. A dosage form according to claim 12, characterised in that the component (a) irritant substance causes burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli.

14. A dosage form according to claim 11 or claim 12, characterised in that the component (a) irritant substance is based on one or more constituents of at least one hot substance drug.

15. A dosage form according to claim 14, characterised in that the hot substance drug is at least one drug

selected from the group comprising Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably at least one drug selected from the group comprising Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper).

16. A dosage form according to claim 14 or claim 15, characterised in that the constituent of the hot substance drug is an o-methoxy(methyl)phenol compound, an acid amide compound, a mustard oil or a sulfide compound or is derived from such a compound.

17. A dosage form according to any one of claims 14 to 16, characterised in that the constituent of the hot substance drug is at least one constituent selected from the group comprising myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or

methylsulfonyl mustard oil, and a compound derived from these constituents.

18. A dosage form according to any one of claims 12 to 17, characterised in that component (b) is at least one viscosity-increasing agent selected from the group comprising microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins from citrus fruit or apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150 ®), tara bean flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), apple pectin, sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®).

19. A dosage form according to any one of claims 12 to 18, characterised in that component (c) is at least one opioid antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine, naluphine and a corresponding physiologically acceptable compound, in particular a base, a salt or solvate.

20. A dosage form according to any one of claims 12 to 18, characterised in that the component (c) used is at least one neuroleptic as a stimulant antagonist, preferably selected from the group comprising haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

21. A dosage form according to any one of claims 12 to 20, characterised in that the component (d) emetic is based on one or more constituents of ipecacuanha (ipecac) root, preferably on the constituent emetine, and/or is apomorphine.

22. A dosage form according to any one of claims 12 to 21, characterised in that component (e) is at least one physiologically acceptable dye.

23. A dosage form according to any one of claims 12 to 22, characterised in that component (f) is at least one bitter substance selected from the group comprising aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol and mixtures thereof, fruit aroma substances, preferably from lemons, oranges, limes, grapefruit and mixtures thereof comprising at least 2 components, denatonium benzoate and mixtures thereof comprising at least 2 components.

24. A dosage form according to any one of claims 12 to 23, characterised in that the active ingredient or active ingredients (A) is/are spatially separated from

component (c) and/or (d) and/or (f), preferably without direct contact, wherein the active ingredient or active ingredients (A) is/are preferably present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and, when the dosage form is correctly administered, components (c) and/or (d) and/or (f) from subunit (Y) do not exert their effect in the body and/or on taking.

25. A dosage form according to any one of claims 1 to 24, characterised in that it contains at least one active ingredient at least partially in controlled release form.

26. A dosage form according to claim 25, characterised in that each of the active ingredients with abuse potential (A) is present in a controlled release matrix.

27. A dosage form according to claim 26, characterised in that component (C) and/or the optionally present component (D) also serve as a controlled release matrix material.

28. A process for the production of a dosage form according to any one of claims 1 to 27, characterised in that, without using an extruder,

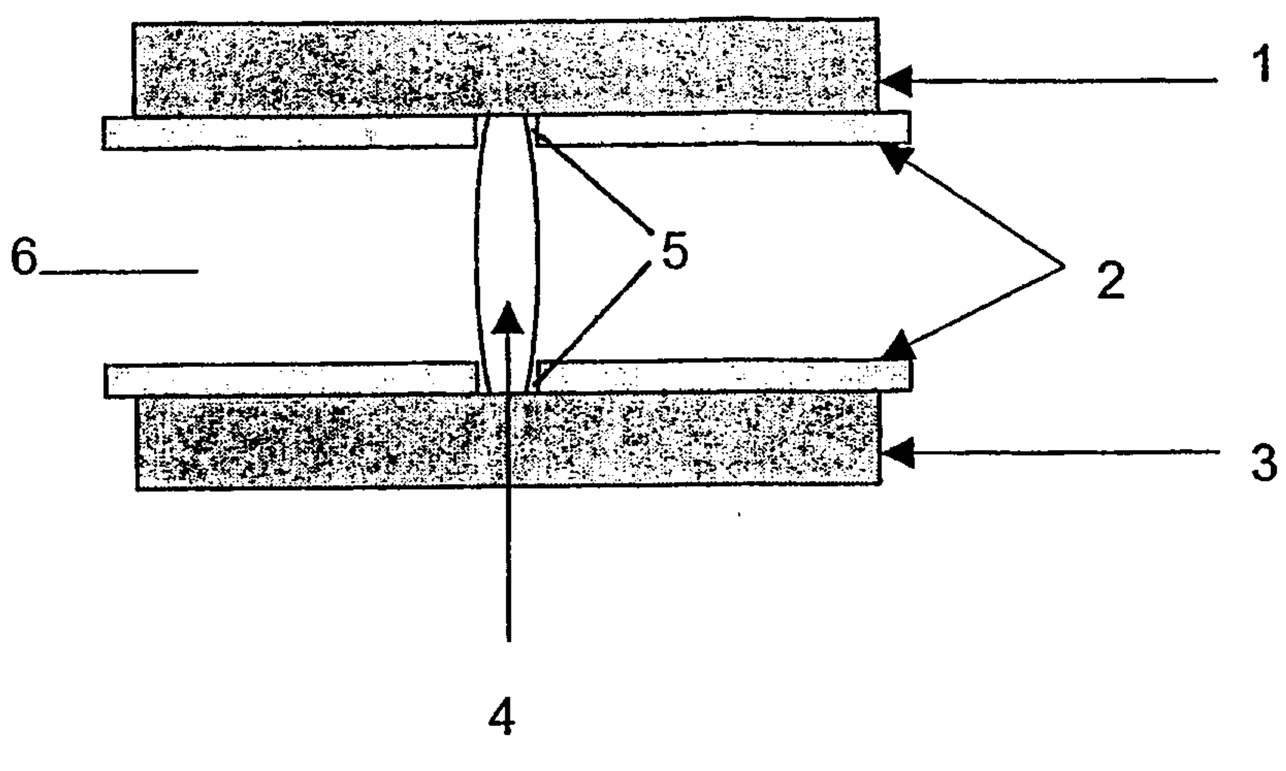
components (A), (B), (C) and the optionally present component (D) are mixed and the optionally present components (a) to (f) are co-mixed or, if necessary,

are separated mixed with addition of component (C) and optionally (D)

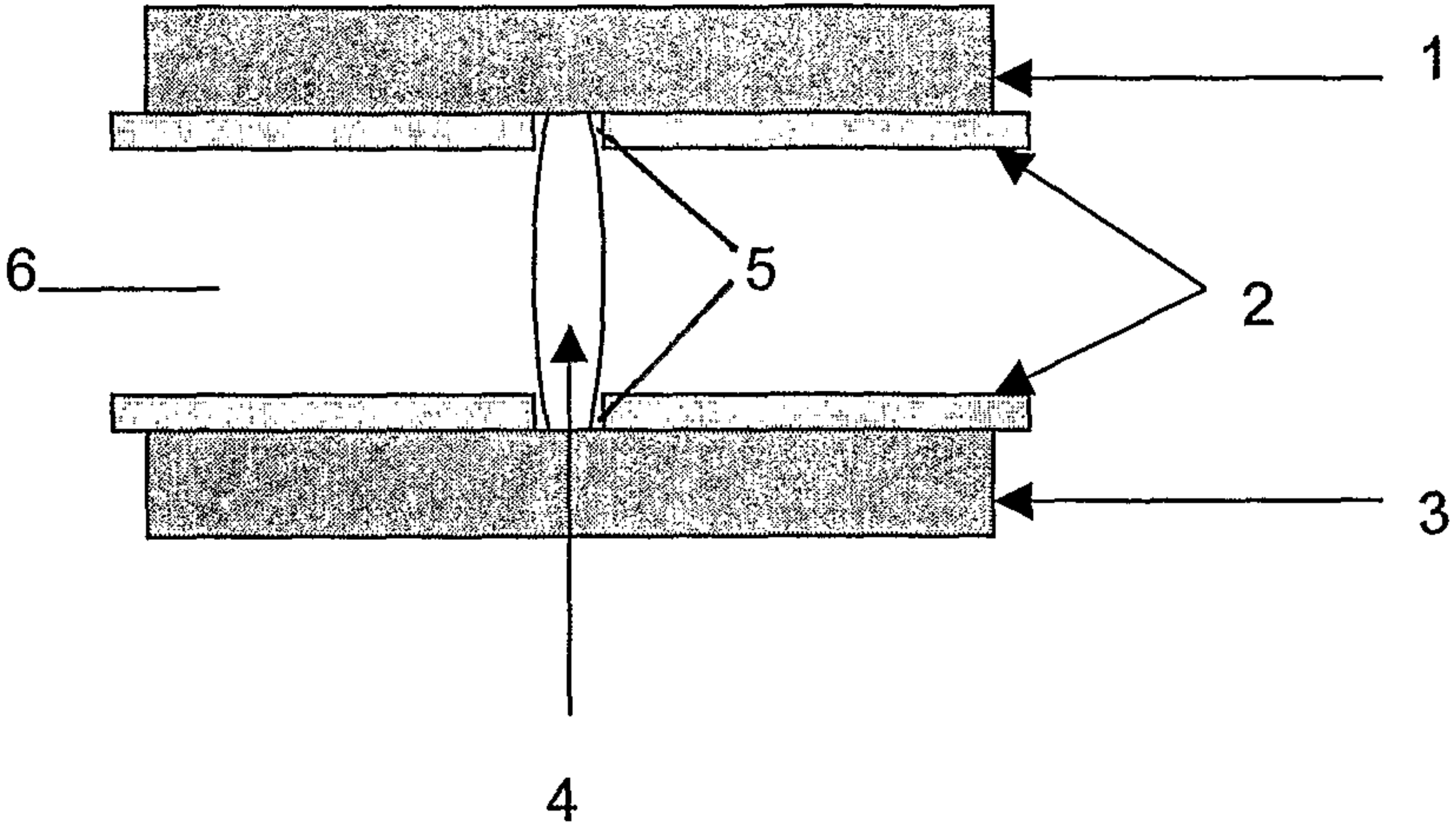
and the resultant mixture or mixtures, optionally after granulation, is/are shaped by application of force to yield the dosage form with preceding or simultaneous exposure to heat.

29. A process according to claim 28, characterised in that granulation is performed by melt granulation or wet granulation.

30. A dosage form according to any one of claims 1 to 27 obtainable by a process according to claim 28 or claim 29.



Figur 1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