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(54) **Adagolási forma nehezített/gátolt visszaélési lehetőséggel**

Dosage Form with Impeded Abuse

The present disclosure relates to a multiparticulate dosage form with impeded abuse potential containing, in addition to one or a plurality of active ingredients with abuse potential (A), optionally at least one physiologically compatible excipient (B), at least one synthetic or natural polymer (C), optionally at least one wax (D) and at least one disintegrant (E), wherein the individual particles of the dosage form have a fracture resistance of at least 500 N and an active ingredient release of at least 75% after 45 minutes, as well as methods for producing the disclosed dosage form.

In addition to outstanding efficacy in their relevant area of application, many pharmaceutically active ingredients also have an abuse potential, i.e. they can be used by an abuser in order to produce effects that do not correspond to their intended purpose.

For example, opiates, which show outstanding efficacy in controlling severe to very severe pain, are often used by abusers to achieve intoxication-like euphoric states. Active substances having a psychotropic effect in particular are abused in this manner.

For the purpose of such abuse, the corresponding dosage forms, such as tablets or capsules, are crushed by the abuser, i.e. in a mortar, the active ingredient of the powder obtained in this manner is extracted using a preferably aqueous liquid, and the resulting solution, optionally after filtering through cotton or cellulose, is parenterally administered, particularly intravenously. In this type of administration, the active ingredient is absorbed in a more accelerated form compared to abusive oral administration, producing the effect desired by the abuser, namely the kick. This kick or these intoxication-like euphoric states are also achieved when the powdered dosage form is administered nasally, i.e. sniffed.

In order to prevent these possibilities of abuse, US-A-4070494 proposes adding a swellable agent to the dosage form. This agent swells when water is added to extract the active ingredient, with the result that the filtrate separated from the gel contains only a minimal amount of the active ingredient.

A corresponding approach for preventing parenteral abuse is also proposed in WO 95/20947 as a multilayer tablet that contains the active ingredient with abuse potential and at least one gel-forming agent separated in different layers respectively.

A further approach for preventing parenteral abuse is disclosed in WO 03/015531 A2. In this document, a dosage form containing an analgesic opioid and a dye as an aversive agent is described. The dye, which is released on unlawful manipulation of the dosage form, is intended to deter the abuser from using this manipulated dosage form.

Another known possibility for impeding abuse is to add to the dosage form antagonists of the active ingredients, such as naloxone or naltrexone in the case of opioids, or compounds that lead to physiological rejection reactions, such as *Radix Ipecacuanha* = ipecac root.

Another known method of impeding abuse is to impede or prevent the pulverization of the dosage forms necessary for abuse by the means ordinarily available to a potential abuser. Corresponding solid dosage forms containing active substances with abuse potential, which ensure the desired therapeutic effect when used as directed, but in which the active substances cannot be converted to a form suitable for abuse by simple pulverization, are known from DE-A-10336400.5.

DE 102005005446 discloses a dosage form comprising a physiologically active substance with at least partially delayed release; optionally, one or a plurality of physiologically compatible auxiliaries; and a synthetic or natural polymer; wherein the dosage form has a fracture resistance of at least 400 N.

D 10336400 describes an abuse-proofed, thermoformed dosage form and method for its production, which, in addition to one or a plurality of active ingredients with abuse potential, and optionally physiologically compatible auxiliaries, contains at least one synthetic or natural polymer with a fracture resistance of at least 500 N.

EP 1138321 relates to oral dosage forms with delayed active ingredient release and high mechanical stability containing one or a plurality of active ingredients, a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone, water-soluble polymers or low or high molecular weight lipophilic additives, as well as further, common auxiliaries, and their use and production.

The document DE 102004032051 discloses a method for producing an abuse-proofed, solid dosage form, containing at least one active ingredient with abuse potential and a synthetic or natural polymer with a fracture resistance of ≥ 500 N, characterized in that a corresponding mixture is processed by melt extrusion using a planetary roller extruder.

These abuse-proofed dosage forms are characterized by controlled, preferably delayed, release of the active ingredient with abuse potential. For numerous therapeutic applications, such as pain management using active ingredients with abuse potential, rapid release of the active ingredient is necessary.

It was therefore the object of the present invention to provide a dosage form containing an active ingredient with abuse potential whose abuse is at least impeded and which ensures reproducible, rapid release of the active ingredient with abuse potential.

This object is achieved by providing the multiparticulate dosage form with impeded abuse according to the invention, comprising

- at least one active ingredient with abuse potential (A), which has a psychotropic effect, selected from the group of the opioids;

- at least one synthetic or natural polymer (C);

- optionally at least one natural, semisynthetic or synthetic wax (D);

- at least one disintegrant (E), which is at least partially mixed with the particles of the dosage form;

- an excipient (B2), which is not a constituent of the particles, selected from the group of the fillers;

- optionally one or a plurality of further physiologically compatible auxiliaries (B),

wherein the individual particles of the dosage form have a fracture resistance of at least 500 N and an active ingredient release of at least 75% after 45 minutes measured according to Pharm. Eur. in a paddle stirrer apparatus with sinker in 600 ml of an aqueous buffer solution with a pH of 1.2 at 37°C and 75 revolutions per minute.

By using polymers with a minimum fracture resistance of at least 500 N (measured as indicated in the application) in amounts such that the particles of the dosage form according to the invention also have such a minimum fracture resistance of at least 500 N, it becomes possible to prevent pulverization of the dosage form by ordinary means and thus considerably impede or prevent subsequent abuse.

Specifically, without sufficient crushing, parenteral, and in particular intravenous risk-free administration or abusive nasal administration is not possible, so that the resulting intoxication-like, euphoric states cannot be achieved with the desired intensity and rapidity.

Within the meaning of the invention, crushing is understood to refer to pulverizing the dosage form with ordinary means commonly available to an abuser, such as a mortar and pestle, a hammer, a mallet, or other commonly-used means for pulverizing by the effect of force.

The multiparticulate dosage forms according to the invention are therefore suitable for impeding the parenteral and/or nasal abuse of active ingredients, preferably pharmaceutically active ingredients, with abuse potential, and because of their composition according to the invention, ensure rapid, controlled active ingredient release. They are therefore equivalent to the so-called IR dosage forms (immediate release dosage forms), as the release profile of the active ingredient meets the

corresponding standard requirements. Most particularly preferably, the multiparticulate dosage forms according to the invention release the active ingredient within 1 to 30 minutes.

Pharmaceutically active substances with abuse potential are known to the person skilled in the art, as well as the amounts thereof to be used and methods for their production, and can be present as such in the form of their corresponding derivatives, particularly esters or ethers, or respectively in the form of corresponding physiologically compatible compounds, particularly corresponding salts or solvates thereof, in the dosage form according to the invention as racemates or stereoisomers. The multiparticulate dosage form according to the invention is also suitable for the administration of a plurality of pharmaceutically active ingredients in one dosage form. The dosage form preferably contains only one specified active ingredient with abuse potential.

The quick-release dosage form according to the invention is particularly well-suited for impeding or preventing the abuse of at least one pharmaceutically active ingredient with abuse potential, which has a psychotropic effect, selected from the group comprising opioids, and preferably from the group comprising tranquilizers, benzodiazepines, barbiturates, stimulants, and other narcotics.

The dosage form according to the invention is particularly suitable for impeding or preventing abuse of an opioid, tranquilizer, 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), (±)-[α]-methylphenethylamine (amphetamine), 2-(α-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-benzodiazepin-2(*3H*)-one (bromazepam), 2-bromo-4-(2-chlorphenyl)-9-methyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epopxy-7α[(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 (cathin/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine 4-oxide (chlordiazepoxid), 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-chlorphenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (–)-methyl-[3β-benzoyloxy-2β(1α*H*,5α*H*)-tropane carboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorphenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphene), dezocin, diampromide, diamorphone, diamorphine (heroin), 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6α-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol, 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-methylphenethylamino)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]oxazolo[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, hydroxymethylmorphinan, 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-dimethylamino-4,4-diphenyl-3-heptanone (levomethadone), (–)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphan, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2-a][1,4] benzodiazepin-1(4*H*)-on (loprazolam), 7-chloro-5-(2-chlorphenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-(2-chlorphenyl)-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-morphinene-3,6α-diol (morphine), myrophine, (±)-trans-3-(1,1-dimethylheptyl)-7,8,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo-[b,d]pyran-9(6α*H*)-one (nabilone), nalbuphene, 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, exudation from 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*) (*Papaver somniferum*), 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-piperidincarboxylat) (pethidin), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenylmorpholine (phenmetrazind), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propinyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydrylalcohol (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, pseudoephedrine, N-{1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl{3-[4-methoxycarbonyl-4-(N-phenylpropanamido)piperidino]propanoate) (remifentanile), 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-chlorphenyl)-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-dimethylaminomethyl-cyclohexyl)-phenol, (1S, 2S)-3(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2R,3R)-1-dimethylamino-3(3-nethoxy-phenyl)-2-methyl-pentan-3-ol, (1RS, 3RS, 6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, preferably as 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)-xpropionate, 3-(2-dimethylaminomethyl-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, with their corresponding derivatives in each case, particularly amides, esters, or ethers, and their physiologically compatible compounds in each case, in particular salts and solvates thereof, with hydrochlorides being particularly preferred.

The dosage form according to the invention is particularly suitable for impeding or preventing the abuse of an opioid active ingredient selected from the group comprising oxycodone, diamorphine, ethylmorphine, hydrocodone, oxymorphone, hydromorphone, morphine, tramadol and physiologically compatible derivatives or compounds thereof, preferably salts and solvates thereof, preferably hydrochlorides, physiologically compatible enantiomers, stereoisomers, diastereomers, and racemates and physiologically compatible derivatives thereof, preferably ethers, esters, or amides.

The dosage form according to the invention is further suitable in particular for impeding or preventing the 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-dimethylaminomethyl-cyclohexyl)-phenol, physiologically compatible

salts thereof, preferably hydrochlorides, phosphates, maleates, physiologically compatible enantiomers, stereoisomers, diastereomers, and racemates, and physiologically compatible derivatives thereof, preferably ethers, esters, or amides.

These compounds or methods for their production are described in EP-A-693475 and/or EP-A-780369.

In order to achieve the required fracture resistance of the particles of the dosage form according to the invention, at least one synthetic or natural polymer (C) having a fracture resistance, measured according to the method disclosed in the present application, of at least 500 N is used. At least one polymer selected from the group comprising polyalkylene oxides, preferably polymethylene oxides, polyethylene oxides, polypropylene oxides; polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, polyacrylates, copolymers thereof, and mixtures of at least one of the above-mentioned polymers is preferably used for this purpose. Preferred are high molecular weight, thermoplastic polyalkylene oxides. Particularly preferred are high molecular weight polyethylene oxides with a molecular weight of at least 0.5 million, preferably at least 1 million, particularly preferably 1 million to 15 million, and most particularly preferably 1 to 10 million, determined by rheological measurements. These polymers have a viscosity at 25°C of 4500 to 17600 cP, measured in a 5 wt.% aqueous solution using a Brookfield viscosimeter, model RVF (spindle no. 2/rotation speed 2 rpm), 400 to 4000 cP, measured in a 2 wt.% aqueous solution using said viscosimeter (spindle no. 1 or 3/rotation speed 10 rpm), or 1650 to 10000 cP, measured in a 1 wt.% aqueous solution using said viscosimeter (spindle no. 2/rotation speed 2 rpm).

The polymers are preferably used as powders. They may be soluble in water.

Additionally, moreover, in order to achieve the necessary fracture resistance of the particles of the dosage form according to the invention, at least one natural semi-synthetic or synthetic wax (D) having a fracture resistance, measured according to the method disclosed in the present application, of at least 500 N can be used. Preferred are waxes with a softening point of at least 50°C, and particularly preferably 60°C.

Particularly preferred are carnauba wax and beeswax, in particular carnauba wax. Carnauba wax is a natural wax obtained from the leaves of the carnauba palm which has a softening point of at least 80°C. In additional use of the wax component, this component is used with at least one polymer (C) in such amounts that the particles of the dosage form have a fracture resistance of at least 500 N.

Preferably, component (C) is used in an amount of 35 to 99.9 wt.%, particularly preferably at least 40 wt.%, and most particularly preferably 40 to 70 wt.%, based on the total weight of the dosage form.

As a disintegrant (E), physiologically compatible disintegrants can be used such as those used for producing pharmaceutical dosage forms. Preferably, at least one disintegrant selected from the group comprising crosslinked sodium carboxymethyl cellulose (croscarmellose), modified maize starch, sodium carboxymethyl starch, and crosslinked polyvinylpyrrolidone (crospovidone) is used as disintegrant (E). The dosage forms according to the invention preferably contain 0.5 to 25 wt.%, and particularly preferably 1 to 10 wt.%, based on the total weight of the dosage form, of at least one disintegrant (E).

Preferably, the disintegrant is used in powdered form, and is present in the dosage form according to the invention in the particles and/or on the particles and/or loosely distributed next to the particles. The disintegrant (E) is preferably at least partially present as a formulation component in the particles of the dosage form according to the invention and/or at least partially enveloping the particles, preferably in a coating of the particles. The disintegrant (E) is at least partially mixed with the particles of the dosage form. Most particularly preferably, the disintegrant is present both as a formulation component in the particles and as an envelope component surrounding the particles.

As further auxiliaries (B), the usual auxiliaries (B1) known for formulating solid dosage forms, preferably temperature-resistant auxiliaries, can be used. Preferably, these are plasticizers, fillers, antioxidants, and/or redox stabilizers.

Preferably used as particularly suitable antioxidants are ascorbic acid, α-tocopherol, butylhydroxyanisole, butylhydroxytoluene, salts of ascorbic acid, ascorbyl palmitate, monothioglycerol, phosphoric acid, vitamin C, vitamin E and derivatives thereof such as vitamin E succinate or vitamin E palmitate and/or sodium bisulfite, particularly preferably butylhydroxytoluene (BHT) or butylhydroxyanisole (BHA) and/or α-tocopherol.

The antioxidant is preferably used in amounts of 0.01 to 10 wt.%, and preferably 0.03 to 5 wt.%, based on the total weight of the dosage form.

Particularly preferred as suitable redox stabilizers, such as chelating agents, are citric acid, EDTA (ethylene diamine tetraacetic acid), maleic acid, and fumaric acid.

Polyalkylene glycols, preferably polyethylene glycols, fatty acids, fatty acid esters, waxes and/or microcrystalline waxes are preferably used in an amount of 5-20 wt.% as plasticizers.

As fillers in the particles of the dosage form according to the invention, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, calcium dihydrogen phosphate, and/or tricalcium phosphate can also preferably be used.

Fillers can be used as additive substances or excipients (B2) which are not constituents of the particles. The additive substances are preferably constituents of the particles and/or are preferably taste improvers or lubricants.

Examples of lubricants that can be used are silicon dioxide, stearic acid, talc, fatty acid esters, sugar esters, and/or magnesium stearate.

Aromatic additives, foaming additives, sugars, sugar alcohols, or sugar substitutes can also be used as taste improvers.

Microcrystalline cellulose, calcium dihydrogen phosphate, sugar alcohols such as mannitol, sugars such as lactose, cellulose powder, Kollidon, and/or polyvinylpyrrolidone can be used as fillers.

The multiparticulate dosage forms according to the invention are characterized in that because of their hardness, they cannot be pulverized using the crushing means available to the abuser, such as a mortar and pestle. This therefore impedes or prevents parenteral abuse, and in particular intravenous or nasal abuse. However, in order to prevent any possible abuse of the dosage forms according to the invention, the dosage forms according to the invention may also contain, in a preferred embodiment, further abuse-impeding or abuse-preventing agents as auxiliaries (B3).

The multiparticulate dosage form according to the invention, in addition to one or a plurality of active ingredients with abuse potential, comprises at least one hardness-forming polymer (C), at least one disintegrant (E), optionally at least one wax (D), optionally further auxiliaries (B1, B2), and may thus also comprise at least one of the following components (a)-(e) as auxiliaries (B3):

(a) at least one substance that irritates at least the nasal cavity,

(b) at least one antagonist for each of the active substances with abuse potential present in the dosage form,

(c) at least one emetic,

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

(e) and at least one bitter substance.

Components (a) through (e) are in each case suitable by themselves for additional safeguarding of the dosage form according to the invention against abuse. Thus, component (a) is preferably suitable for safeguarding against nasal and/or parenteral, preferably intravenous abuse, component (b) is preferable against nasal and/or

parenteral, particularly preferably intravenous abuse, component (c) is preferable against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (d) is preferable as a visual deterrent against oral or parenteral abuse, and component (e) is preferable against oral or nasal abuse. By including at least one of the above-mentioned components in use according to the invention, it is possible to more effectively impede the abuse of dosage forms according to the invention.

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

In a further embodiment, the dosage form according to the invention can comprise all of components (a)-(e).

If the dosage form according to the invention for safeguarding against abuse contains component (a), all substances are suitable according to the invention as substances irritating the nasal cavity and/or the pharynx that on corresponding administration via the nasal cavity and/or the pharynx cause a reaction in the body that is so unpleasant to the abuser that he either no longer wishes to or is unable to continue administration, e.g. a burning sensation, or that counteracts in a physiological manner the intake of the corresponding active ingredient, e.g. due to increased nasal secretion or sneezing. The substances that ordinarily irritate the nasal cavity and/or the pharynx can also cause an unpleasant sensation, and even unbearable pain, in parenteral, particularly intravenous administration as well, so that the abuser no longer wishes to or cannot continue administration.

Particularly well-suited substances that irritate the nasal cavity and/or the pharynx are substances that cause burning, itching, sneezing, increased secretion, or a combination of at least two of these irritating symptoms. Corresponding substances and the amounts thereof that are ordinarily to be used are known to the person skilled in the art or can be determined by means of simple preliminary tests.

The substance of component (a) that irritates the nasal cavity and/or the pharynx is preferably based on one or a plurality of constituents or one or a plurality of plant parts of at least one pungent drug.

Corresponding pungent drugs are known *per se* to the person skilled in the art and are described for example in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" [Pharmaceutical Biology – Drugs and their Ingredients] by Prof. Dr. Hildebert Wagner, 2nd revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pg. 82 ff.

A dosing unit of the multiparticulate dosage form according to the invention is understood to mean a separate or separable dose, such as a capsule filling of the dosage form according to the invention.

As component (a), one or a plurality of ingredients of at least one pungent drug can preferably be added to the dosage form according to the invention, selected from the group composed of Allii sativi bulbus, Asari rhizoma c. herba, Calami rhizoma, Capsici fructus (paprika), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma, Curcumae xanthorrhizae rhizoma, Galangae rhizoma, Myristicae semen, Piperis nigri fructus (pepper), Sinapis albae (Erucae) semen, Sinapis nigri semen, Zedoariae rhizoma, and Zingiberis rhizoma, particularly preferably from the group composed of Capsici fructus (paprika), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper).

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

Particularly preferably, at least one ingredient of the pungent drugs is selected from the group composed of myristicin, elemicin, isoeugenol, α-asaron, safrol, 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.

Preferably, the dosage form according to the invention can contain the plant parts of the corresponding pungent drugs in an amount of 0.01 to 30 wt.%, and particularly preferably 0.1 to 0.5 wt.%, in each case based on the total weight of a dosage unit or unit dosage.

If one or a plurality of ingredients of corresponding pungent drugs are used, the amount thereof is preferably 0.001 to 0.005 wt.% based on the total weight of the dosage unit or unit dosage.

Moreover, the dosage form according to the invention can also contain component (b) for impeding abuse of and safeguarding the dosage form, specifically one or a plurality of antagonists for the active ingredient or the active substances with abuse potential, wherein the amount of the antagonists is preferably spatially separated from the other components of the dosage form according to the invention and exerts no effect when the dosage form is used as directed.

Suitable antagonists for impeding abuse of the active substances are known *per se* to the person skilled in the art and can 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 respectively in the form of corresponding physiologically compatible compounds, in particular salts or solvates thereof.

If the active ingredient present in the dosage form is an opioid, as an antagonist, one should preferably use an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, or naluphine, in each case optionally in the form of a corresponding physiologically compatible compound, in particular in the form of a base, a salt, or a solvate.

Preferably, if component (b) is to be provided, the corresponding antagonists are used in an amount of ≥ 1 mg, particularly preferably in an amount of 3 to 100 mg, and most particularly preferably in an amount of 5 to 50 mg per dosage form, i.e. per dosage unit.

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

The dosage form according to the invention preferably comprises these antagonists in a common therapeutic dosage known to the person skilled in the art, and particularly preferably in an amount two to three times the usual dosage per dosage unit.

If the combination for impeding abuse and safeguarding the dosage form according to the invention against abuse comprises component (c), it may contain at least one emetic, preferably in an a spatially separated arrangement from the other components of the dosage form according to the invention, which should not have any effect in the body when used as directed.

Suitable emetics for impeding the abuse of an active ingredient are known *per se* to the person skilled in the art, and can 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 compatible compounds, in particular in the form of salts or solvates thereof.

In the dosage form according to the invention, an emetic can be considered based on one or a plurality of ingredients of Radix Ipecacuanha (ipecac root), preferably based on the ingredient emetine, such as those described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982.

Preferably, the dosage form according to the invention can comprise as component (c) the emetic emetine, preferably in an amount of ≥ 3 mg, particularly preferably ≥ 10 mg, and most particularly preferably ≥ 20 mg per dosage form, i.e. dosage unit.

Also preferably, apomorphine can advantageously be used as an emetic in the abuse-proofing according to the invention, preferably in an amount of ≥ 3 mg, particularly preferably ≥ 5 mg, and most particularly preferably ≥ 7 mg per dosage unit.

If the dosage form according to the invention contains component (d) as a further abuse-impeding excipient, by using such a dye, in particular in the attempt to extract the active ingredient for parenteral, preferably intravenous administration, intense colouring of a corresponding aqueous solution can be produced that can deter the potential abuser. Oral use, which is usually initiated by aqueous extraction of the active ingredient, can also be impeded by this colouration. Suitable dyes and the amounts thereof required for the necessary deterrent effect are given in WO 03/015531.

If the dosage form according to the invention contains component (e) as an additional abuse-proofing excipient, this addition of at least one bitter substance additionally impedes oral and/or nasal abuse due to the taste impairment of the dosage form.

Suitable bitter substances and the amounts thereof effective for use are specified in US 2003/0064099 A1.

Suitable bitter substances preferably include aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aromatic 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 for oral administration.

The multiparticulate dosage form according to the invention can be manufactured by various methods that will be discussed in further detail below; the invention also relates to dosage forms that are obtainable according to any of these methods.

The method for producing the dosage form according to the invention preferably comprises the following steps:

(a) mixing components (A), optionally (B), (C), optionally (D) and optionally at least a portion of (E);

(b) optionally preforming the mixture obtained from step (a), preferably by the effect of heat and or force on the mixture obtained from step (a), wherein the amount of heat supplied is preferably insufficient to heat component (C) up to its softening point;

(c) hardening the mixture by the effect of heat and force, wherein the heat can be supplied during and/or before the effect of force and the amount of heat supplied is therefore sufficient to heat component (C) at least up to its softening point;

(d) dividing the hardened mixture;

(e) optionally forming it into the dosage form;

(f) and optionally coating with a coating containing component (E) and/or mixing with component (E) and optionally additives (B2).

The heat can be supplied directly or using ultrasound. The effect of force and/or forming of the dosage form can for example be carried out using suitable extruders, in particular twin-screw extruders (twin-roller extruders) or planetary roller extruders.

The following process variants are particularly preferred:

Process variant 1:

In this embodiment, the dosage form according to the invention is preferably produced using an extruder, in that preferably components (A), optionally (B), (C), the optionally present component (D), and optionally at least a portion of component (E)

are mixed, and the resulting mixture, optionally after granulation to the dosage form, is formed by the effect of force under prior or simultaneous heating.

This heating and effect of force for producing the dosage form is carried out using an extruder.

Mixing of components (A), optionally (B), (C) and optionally (D) is carried out in a mixing device known to the person skilled in the art. For example, the mixing device can be a roller mixer, shaking mixer, shearing mixer, or forced mixer.

The force is applied until the dosage form has reached a fracture resistance of at least 500 N.

Granulation can be carried out by wet granulation or melt granulation in known granulators.

Particularly preferably, this variant of the invention for producing the dosage form according to the invention is carried out as follows:

(a) components (A), optionally (B), (C), the optionally present component (D), and optionally at least a portion of component (E) are mixed,

(b) the resulting mixture is heated in the extruder at least to the softening point of component (C) and extruded by the effect of force through the outlet opening of the extruder,

(c) the still-plastic extrudate is separated and optionally formed into the multiparticulate dosage form, and optionally mixed with and/or enveloped by component (E).

Preferably, the mixing of components according to process step a) can also take place in the extruder.

Preferably, before blending with the further components, component (C) and the optionally present component (D) are provided with an antioxidant according to the invention. This can be carried out by mixing the two components (C) and the antioxidant, preferably by dissolving or suspending the antioxidant in a slightly volatile solvent, uniformly mixing this solution or suspension with component (C) and the optionally present component (D), and removing the solvent by drying, preferably in an inert gas atmosphere.

The mixture from the extruder, which is heated in the extruder at least up to the softening point of component (C) and is preferably melt-flowable, is extruded through a nozzle with at least one bore.

In order to carry out the method according to the invention, the use of a suitable extruder is required, preferably a screw extruder (roller extruder), wherein extruders equipped with two screws (rollers) are particularly preferred. The screws preferably have eccentric nozzles, and the extruder is preferably equipped with a displacer cone.

Extrusion is preferably carried out such that expansion of the extrusion strands as a result of extrusion is preferably a maximum of 50%, i.e., in use of an extrusion nozzle with 1 mm bores, for example, the extruded strands would have a maximum diameter of 1.5 mm.

It is further preferred if the strand expansion is a maximum of 40%, more preferably a maximum of 35%, most preferably a maximum of 30%, and in particular a maximum of 25%. Surprisingly, it was found that when the extruded material is subjected to excessive mechanical stress in the extruder, this causes considerable strand expansion, which results in undesirable irregularities in the properties, particularly the mechanical properties of the extruded strand.

The extruder preferably comprises at least two temperature zones, wherein in the first zone, which is adjacent to a feed zone and optionally a mixing zone, the mixture is heated at least up to the softening point of component (C).

After heating at least up to the softening point of component (C), the molten mixture is transported by means of the screws and further homogenized, compressed, or compacted, so that it has a minimum pressure immediately before leaving the extruder nozzle of 5 bar, and preferably at least 10 bar, and is extruded through the nozzle as an extrusion strand or extrusion strands, depending on the number of bores the nozzle has. The nozzle preferably has a plurality of bores. The nozzle geometry or the geometry of the bores is freely selectable. The nozzle or the bores can thus have a round, oblong, or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 5 mm. The nozzle or the bores preferably has/have a round cross-section. The barrel of the extruder used according to the invention can be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is determined in that the mixture to be extruded has at least one average temperature (product temperature) corresponding to the softening temperature of component (C), and such that it does not exceed a temperature at which the physiologically active substance (A) to be processed can be damaged. The temperature of the mixture to be extruded should be adjusted to less than 180°C, and preferably less than 150°C, but at least to the softening temperature of component (C).

After extrusion of the molten mixture and optional cooling of the extruded strands, separation of the extrudates is preferably carried out. This separation can preferably be carried out by cutting up the extrudates using revolving or rotating knives, water jet cutters, wires, blades, or laser cutters. The separation is preferably followed by pelletizing.

The effect of force in the extruder on the at least plasticized mixture is adjusted by controlling the rotation speed of the transport device in the extruder and the geometry thereof and by dimensioning the outlet in such a way that, preferably before direct extrusion of the plasticized mixture, the pressure required for this builds up in the extruder. The required extrusion parameters for the respective composition that result in a dosage form with a fracture resistance of at least 500 can be determined by means of simple preliminary tests.

An example of a suitable extrusion device is a twin-screw extruder manufactured by Leistritz (Nuremberg) of the type ZSE 18 HP 40D, preferably with screws that are equipped with eccentric screw ends. A heatable nozzle plate with 8 bores having a diameter of 1.0 mm each can serve as a nozzle. For example, the extrusion parameters can be set as follows: screw rotation speed: 150 rpm; throughput: 2 kg/h; product temperature: 50 to 140°C, preferably 80 to 140°C, particularly preferably 100 to 140°C, and most particularly preferably 110 to 140°C, with corresponding barrel temperature.

Process variant 2:

In this process variant for producing the dosage form according to the invention, the energy supply takes place by means of ultrasound.

For this purpose, a homogeneous mixture of at least component (A), component (C), optionally component (D), and optionally a portion of component (E) is first produced. Further auxiliaries (B1), such as fillers, plasticizers, lubricants, or dyes, can also be blended with this mixture. Preferably, a low molecular weight polyethylene glycol is used as a plasticizer.

The mixing can be carried out using conventional mixers. Examples of suitable mixers include roller mixers, which are also known as tumbler, drum, or rotary mixers, container mixers, barrel mixers (drum hoop mixers or tumbling mixers), shaking mixers, shearing mixers, forced mixers, plough-share mixers, planetary kneader mixers, Z-kneaders, sigma-kneaders, fluid mixers, or intensive mixers.

The selection of suitable mixers depends among other factors on the flowability and cohesive forces of the mixing product.

The mixture is then subjected to forming. Forming of the mixture is preferably carried out during or after sonication.

In the case of sonication, it is particularly preferably to have a direct contact between the mixture and the sonotrode of the ultrasound device.

During sonication, a frequency of 1 kHz to 2 MHz, and preferably 15 to 40 kHz, should be maintained. Sonication should be continued until softening of the polymer (C) is achieved. This is preferably achieved within a few seconds, more preferably within 0.1 to 5 seconds, and particularly preferably within 0.5 to 3 seconds.

Before forming is carried out, the mixture can be granulated after the mixing step, after which the resulting granulates are formed into the dosage form, such as tablets, by sonication and the effect of force.

Granulation can be carried out in the machines and apparatuses known to the person skilled in the art.

If granulation is carried out in the form of wet granulation, water or aqueous solutions, such as ethanol/water or isopropanol/water, can be used as the granulation fluid.

The mixture or the granules produced therefrom can preferably also be subjected to melt extrusion for further forming, wherein the mixture is melted by sonication and the action of force and is then extruded through nozzles. The extrudates obtained in this manner are then separated to the desired length using known devices. The separated blanks obtained in this manner can also optionally be pelletized in order to obtain the multiparticulate dosage form according to the invention with a minimum fracture resistance of 500 N. The particles are preferably also provided with the optionally remaining amount of disintegrant and optionally additives (B2) before they are filled into a dosage unit, e.g. into capsules, or compressed into a tablet.

When using ultrasound, suitable parameters for plasticization are frequency of 20 kHz and amplitude of 50%. Furthermore, a force of 250 N should be applied. For example, the action of ultrasound and force by means of the sonotrode can last 0.5 seconds, wherein the action of ultrasound and force preferably take place simultaneously.

Process variant 3:

In this process variant for producing the multiparticulate dosage form according to the invention, components (A), (C), optionally (D), optionally at least a portion of the disintegrant (E), and optionally present auxiliaries (B1) such as antioxidants and plasticizers are processed into the dosage form according to the invention using a planetary roller extruder.

Planetary roller extruders are known, and are extensively described, among other sources, in the Handbuch der Kunststoff-Extrusionstechnik [Handbook of Plastics Extrusion Technology] 1 (1989), "Principles" in chapter 1.2 "Classification of Extruders," pp. 4 through 6. The corresponding description is hereby incorporated herein by reference and is considered to be part of the disclosure.

In the following, the use of a planetary roller extruder for producing the dosage form according to the invention is explained with reference to Figs. 1 and 2. These explanations are given solely by way of example and do not limit the general concept of the invention.

Fig. 1 shows a section through a planetary roller extruder, and

Fig. 2 shows the functioning of the planetary roller extruder.

Fig. 1 shows a planetary roller extruder that can preferably be used for producing the dosage forms according to the invention. This extruder essentially comprises a shaft 1 which, relative to the transport direction of the mixture of the above-mentioned components to be extruded, is first configured as a feed screw 5 and further as a central spindle 3 of the planetary roller extruder. Three to seven planetary spindles 4 are preferably arranged around the central spindle 3, which in turn are enclosed by a barrel in the form of a housing 6.

In the planetary roller extruder, with reference to Fig. 1, extrusion of the composition to be used for producing a dosage form according to the invention is preferably carried out as follows. As shown by the arrow 2, the components to be extruded are dosed by the dosing unit 7 in the area of the feed screw 5 and are transported by the rotation

thereof (drive not shown) in the direction of the central spindle 3. The person skilled in the art understands that it is possible to mix the starting substances (components) in the area of the feed screw. However, it is also possible to premix the components of the dosage form and to dose this mixture via the dosing unit 7 in the area of the feed screw 5. The mixture is transported in the feed area of the planetary roller extruder. By heating at least up to the softening point of component (C), the mixture is melted, and in the area of the central spindle, i.e. in the extrusion area, the molten mixture is transported by the interaction of the central spindle 3 and the planetary spindles 4, further homogenized, compressed, or compacted, and extruded through the nozzle bores 8 as extrusion strands. The nozzle geometry or the geometry of the bores is freely selectable. The bores can thus have a round, oblong, or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 5 mm. The bores preferably have a round cross-section. Both the barrel 6 of the planetary roller extruder used according to the invention and the central spindle can be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is determined in that the mixture to be extruded has at least one average temperature corresponding to the softening temperature of the component (C), and such that it does not exceed a temperature at which the substance (A) to be processed can be damaged. The temperature of the mixture to be extruded should be adjusted to less than 180°C, and preferably less than 150°C, but at least to the softening temperature of component (C). The reference numbers used refer exclusively to Figs. 1 and 2.

After extrusion of the molten mixture and optionally cooling the extruded strands, separation of the extrudates, which is not shown in Fig. 1, is carried out. This separation can preferably be carried out by cutting up the extrudates using revolving or rotating knives, water jet cutters, wires, blades, or laser cutters.

Optionally, after further cooling of the separated extrudates, which are preferably in the form of discs, shaping into the final form of the dosage form is carried out, preferably by pelletizing, wherein further heating is carried out if necessary.

The separated extrudates, optionally further shaped, are preferably provided with the (remaining) disintegrant (E) and optionally additives.

Processed in this manner, they can be compressed not only into tablets, but also in multiparticulate form, into pellets or spheroids, or can be filled into capsules, sachets, or stick packs in order to use the dosage form according to the invention as a dosage unit.

Fig. 2 shows a cross-section through a planetary roller extruder. Around the rotating central spindle 3, at least 3, and in the case shown 6 planetary spindles 4 are arranged, whose flanks 41 interact on the one hand with the flanks 31 of the central spindle 4 and on the other with the flanks 61 of the barrel 6 of the planetary roller extruder. Because of the rotation of the central spindle 3 and the rolling of the respective flanks on one another, each of the planetary spindles 4 rotates as shown by the arrow 42 around its own axis and, as shown by arrow 43, around the central spindle 4. This produces the desired compression or compacting of the component mixture used according to the invention for the dosage forms produced according to the invention. The reference numbers used refer exclusively to Figs. 1 and 2.

If necessary, the planetary roller extruder used can comprise not only an extrusion area, but at least one further area for optional degassing of the mixture to be extruded.

The method can be carried out discontinuously or continuously, and preferably continuously.

An example of a suitable extruder is a planetary roller extruder with four planetary spindles of model BCG 10 manufactured by LBB Bohle (Ennigerloh, Germany), with an extrusion nozzle having a diameter of 8 mm. A gravimetric dosage of 3.0 kg per hour is suitable. The extrusion can be carried out for example with a revolution speed of 28.6 rpm at a product temperature of approx. 88°C.

Process variant 4:

In this variant for producing the dosage form according to the invention, at least components (A), (C), optionally (D), optionally at least a portion of the disintegrant

(E), and optionally present auxiliaries (B1) such as antioxidants and/or plasticizers are processed into the multiparticulate dosage form while adding a solvent for component (C), i.e. for the polymer(s) (C).

For this purpose, components (A), optionally (B1), (C), the optionally present component (D), and optionally at least a portion of the disintegrant (E), are mixed, and after addition of the solvent, the formulation mixture is separated and further formed.

Mixing of the components can be carried out in a device known to the person skilled in the art. For example, the mixing device can be a roller mixer, shaking mixer, shearing mixer, or forced mixer.

The solvent for the polymers (C) is added at least in sufficient amounts so that the formulation mixture is uniformly wetted.

Suitable solvents for the polymers (C) are preferably aqueous solvents such as water, mixtures of water and aliphatic alcohols, preferably C1 to C6 alcohols, esters, ethers, hydrocarbons, particularly preferably distilled water, short-chain alcohols such as methanol, ethanol, isopropanol, and butanol, or aqueous alcohol solutions.

The solvent should preferably be added while stirring. The uniformly wetted mass is then dried, preferably after separation. The drying is preferably carried out under heating at temperatures at which discoloration of the mass can be ruled out. This temperature can be determined by means of simple preliminary tests.

It is also possible to carry out wetting of the formulation mixture such that before adding the solvent, the formulation mixture, preferably distributed into forms on partial masses, is dispersed while stirring in a liquid dispersant, and the solvent is then added. Component (C) is not soluble in the dispersant, which must be miscible with the solvent.

Preferred as suitable dispersants are hydrophilic solvents such as aliphatic alcohols, ketones, and esters. Short-chain alcohols are preferably used.

Alternatively, wetting of the formulation mixture can also be carried out in such a way that the solvent is worked into the formulation mixture as a foam. Such a foam of the solvent should be produced by means of high-speed mixers, preferably with the addition of common foam stabilizers. Examples of suitable stabilizers are hydrophilic polymers such as hydroxypropyl methyl cellulose.

Preferably, the foam is also worked into the formulation mixture while stirring, which preferably allows a granulated mass to be obtained.

The granulated mass is dried and then shaped into the multiparticulate dosage form, e.g. by pelletizing.

The drying and shaping can preferably take place as specified above. The method according to the invention can also be carried out such that so much solvent is added to the formulation mixture that a formable paste is produced.

Such a paste can be divided into partial masses before or after drying, which can be carried out as described above.

These partial masses can be configured in the form of strands that can be produced using a sieve or a strand former. The dried strands are preferably separated and finally shaped into the dosage form, e.g. by pelletizing.

It is also possible to process the paste into a sheetlike structure and punch the dosage form out of the dried structure.

The paste is advantageously processed by means of an extruder, wherein depending on the type of extrusion, the strands or sheetlike structures are formed, which are then separated by fragmenting or cutting or stamping. The separated partial masses can be finally shaped or punched out to obtain the dosage form, as specified above. Corresponding devices are known to the person skilled in the art.

In any event, the finally formed, multiparticulate dosage forms are optionally further provided with the (remaining) amount of component (E) and optionally with additives (B2) before they are filled or compressed as a unit dose. The solution method according to the invention can be carried out continuously or discontinuously.

It is also possible to add enough solvent to the formulation mixture so that at least the polymer component (C) is dissolved. Such a solution or dispersion/suspension is preferably processed into a sheetlike structure, wherein an extruder with a flat nozzle is preferably used or the solution is poured out onto a sheetlike, even substrate.

After drying, as mentioned above, the multiparticulate dosage forms can be obtained from the sheetlike structures by punching or calendering. It also possible, as mentioned above, to process the solution into strands and then separate them, preferably after drying, and shape them into the dosage form.

Alternatively, the solution can also be divided into partial amounts such that in each case, after drying, they correspond to the mass of a unit of the dosage form, wherein forms corresponding to the shape of a unit of the dosage form are preferably already used.

If the solution is divided up into desired partial amounts, the partial amounts can optionally again be combined into a dosage unit after drying, which e.g. can be filled into a capsule or compressed into a tablet.

Preferably, the formulation mixtures blended with solvent are processed at temperatures of 20°C to 40°C, wherein no higher temperatures are used, except in drying to remove the solvent and the optionally present dispersant. The drying temperature must be set below the decomposition temperature of the components. Optionally, drying can be repeated after shaping into the dosage form, with said drying corresponding to that described above.

Combinations of individual method steps of the above process variants are also possible in order to produce the dosage form according to the invention.

The multiparticulate dosage forms according to the invention are preferably surrounded by an envelope of a disintegrant (E) so as to ensure the IR release of the active ingredient. It is at least advantageous to mix the particles, preferably pellets, of the dosage form according to the invention with a disintegrant (E) and to further dilute the mixture, preferably with further fillers (B2) such as microcrystalline cellulose, magnesium stearate, calcium dihydrogen phosphate, lactose, fatty acid esters, mannitol, hydroxypropyl methyl cellulose, cellulose powder, talc, silicon dioxide, Kollidon, sugar esters, and/or polyvinylpyrrolidone.

Such mixtures can be filled as a dosage unit into capsules, sachets, or stick packs or processed into chewable tablets, dispersible tablets, or IR tablets. Most particularly preferably, the particles or pellets of the dosage form according to the invention have a coating comprising at least one disintegrant (E), applied by means of powder coating or film coating. Depending on the application, the above-mentioned dosage units can also comprise aromatic substances, foaming additives, sugar, sweeteners, and/or colourants.

If the dosage form according to the invention contains component (c) and/or (e), the dosage is to be selected such that no negative effect is produced on oral administration as directed. However, if the intended dosage is exceeded by an abuser, nausea, vomiting, or a bad taste will be produced. The respective amount of component (c) and/or (e) that is tolerated by the patient in oral administration as directed can be determined by the person skilled in the art by means of simple preliminary tests.

However, if the use of components (b) and/or (c) and/or (e) is provided, even though it is not possible in practice to pulverize the dosage form according to the invention for safeguarding said dosage form, these components should preferably be used in such a high dosage that they will cause an intense negative effect to the abuser in the event of improper administration of the dosage form. This is preferably carried out by means of spatial separation at least of the active ingredient or the active substances from components (b) and/or (c) and/or (e), wherein the active ingredient or the active substances is/are preferably present in at least one subunit (X) and components (b)

and/or (c) and/or (e) are present in at least one subunit (Y), and wherein components (b), (e) do not exert their effect on ingestion and/or in the body when the dosage form is administered as directed and the other formulation components, in particular component (C) and optionally (D) and (E), are identical.

If the dosage form according to the invention comprises at least 2 of components (b) and (c) or (e), the components can be present in each case in the same or in different subunits (Y). Preferably, if they are all present, all components (b), (c) and (e) should be in one and the same subunit (Y).

Subunits within the meaning of the present invention are solid formulations that in each case contain, in addition to the usual auxiliaries known to the person skilled in the art, the active ingredient(s), at least one polymer (C) and at least one disintegrant (E), the optionally present component (D) and optionally at least one of the optionally present components (a) and/or (e), or in each case at least one polymer (C) and optionally (D) and at least one disintegrant (E), and the antagonist(s) and/or the emetic(s) and/or component (d) and/or component (e), and optionally at least one of the optionally present components (a). It should be noted here that each of the above-mentioned subunits is formulated according to the methods specified above.

An essential advantage of separate formulation of the active substances from components (b) or (c) or (e) in subunits (X) and (Y) of the dosage form according to the invention lies in the fact that when the dosage form is administered as directed, the amounts of components (b) and/or (c) and/or (e) absorbed on ingestion or in the body are virtually nil, or they are released in such small amounts that they have no effect on the patient or the success of treatment, or on passing through the body of the patient, are released only at sites that do not have sufficient resorption for the components to exert their effect. Preferably, when the dosage form is administered as directed, components (b) and/or (c) and/or (e) are released in the body of the patient hardly at all or are not noticeable to the patient.

The person skilled in the art understands that these above-mentioned conditions can vary depending on the respectively used components (b), (c) and/or (e) and the

formulation of the subunits or the dosage form. The optimum formulation for the respective dosage form can be determined by simple preliminary tests. It is decisive that the respective subunits contain the polymer (C), the disintegrant (E), and optionally component (D) and are formulated in the manner specified above.

In the event that against expectations, the abuser should succeed in crushing such a dosage form according to the invention containing components (b), (c) and/or (e) in subunits (Y) for the purpose of abusive consumption of the active ingredient and obtain a powder that is extracted with a suitable extracting agent, in addition to the active ingredient, the abuser will also obtain the respective component (b), (c) and/or (e) in a form in which it cannot easily be separated from the active ingredient, so that on administration of the manipulated dosage form, particularly in oral and/or parenteral administration, its action manifests itself on consumption and/or in the body and additionally causes a negative effect in the abuser corresponding to component (b) and/or (c) and/or (e), or deters the abuser by means of colouring from extracting the active ingredient and thus prevents abuse of the dosage form.

The formulation of a dosage form according to the invention in which the active ingredient or the active substances is/are spatially separated from components (b), (c) and/or (e), preferably by formulation in different subunits, can take place in a widely varying manner, wherein the corresponding subunits of the dosage form according to the invention can be present in any desired spatial arrangement with respect to one another, provided that the above-mentioned conditions for the release of components (b) and/or (c) and/or (e) are met.

The person skilled in the art understands that the optionally present component(s) (a) can preferably be formulated in the dosage form according to the invention both in the respective subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that the type of formulation does not affect safeguarding of the dosage form against abuse and the active ingredient release on administration as directed, and that the polymer (C), the disintegrant (E), and optionally (D) can also be included in the formulation and formulation can be carried out according to the methods described above in order to obtain the necessary hardness.

In a preferred embodiment of the dosage form according to the invention, the two subunits (X) and (Y) are in multiparticulate form, wherein microtablets, granulates, spheroids, beads, or pellets are preferred and the same form, i.e. configuration, is selected for both subunit (X) and subunit (Y) so that no separation of subunits (X) and (Y), e.g. due to mechanical separation, is possible. The multiparticulate forms should have a size in the range of 0.1 to 5 mm, and preferably 0.2 to 3 mm.

The dosage form according to the invention is in multiparticulate form, preferably in the form of microtablets, granulates, spheroids, beads, or pellets, optionally as a dosage unit, filled into capsules or compressed into tablets for oral administration. Preferably, the multiparticulate forms have a size in the range of 0.1 to 5 mm, and particularly preferably in the range of 0.2 to 3 mm (determination method according to the published dissertation "Systematische Untersuchungen zur Eignung von Kappa-Carrageenan als Pelletierhilfsstoff in der Feuchtextrusion/Sphäronisation, [Systematic investigations on the suitability of kappa-carrageenan as a pelleting auxiliary in wet extrusion/spheronization] pp. 16, 21-23, by Markus Thommes in the "Deutschen Bibliothek" of the German National Bibliography, 1st Edition, Cuvillin Verlag, Göttingen, 2006).

The subunits (X) and (Y) in multiparticulate form can also preferably be filled into a capsule, sachet, or stick pack or compressed into a tablet, wherein the subunits (X) and (Y) also remain intact in the resulting dosing units.

The respective multiparticulate subunits (X) or (Y) of identical form should not be visually distinguishable from each other, so that they cannot be separated from each other by simple sorting by the abuser.

Preferably, the release of components (b), (c) and/or (e) from subunit (Y) of the dosage form according to the invention should be impeded by means of an envelope, so that the subunit can consist of common materials known to the person skilled in the art, provided that it contains at least one polymer (C), and optionally (D) in order to meet

the hardness requirement of the dosage form according to the invention and is provided with the disintegrant (E).

The materials listed below can preferably be used for an envelope.

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

Particularly suitable materials can be selected from the group comprising methyl cellulose, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (of low, medium, or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, 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, polyvinylisobutyl ether, polyvinyl acetate and polyvinyl chloride.

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

Further materials particularly suitable for the formulation of an envelope are starch-filled polycaprolactone (WO98/20073), aliphatic polyester amides (DE 19753534 A1, DE 19800698 A1, EP 0820698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates and polyhydroxyvalerates), casein (DE 4309528), polylactides, and copolylactides (EP 0980894 A1).

The above-mentioned materials can optionally be blended with further common auxiliaries known to the person skilled in the art preferably selected from the group comprising plasticizers, lubricants, and antioxidants such as glycerol monostearate, semisynthetic triglyceride derivatives, semisynthetic glycerides, hydrogenated castor oil, glycerol palmitostearate, glycerol behenate, polyvinylpyrrolidone, gelatin, magnesium stearate, stearic acid, sodium stearate, talc, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols, polyalkylene glycols, and derivatives thereof.

The dosage form according to the invention shows IR release of the active ingredient, as defined above. It is therefore preferably suitable for treatment in which a rapid-onset effect is to be achieved, such as acute pain management.

Method for determining fracture resistance

In order to determine whether a material can be used as component (C) or (D), the material is compressed into a tablet with a diameter of 10 mm and a height of 5 mm with a force of 150 N at a temperature corresponding at least to the softening point of the material and determined using a DSC diagram of the material. Fracture resistance is determined with tablets produced in this manner according to the method for determining fracture resistance of tablets published in the European Pharmacopoeia 1997, pp. 143, 144, Method No. 2.9.8., using the equipment listed below. The equipment used as a measuring apparatus was a Zwick material testing unit "Zwick Z 2.5", material testing machine Fmax 2.5 kN with a maximum traverse of 1150 mm, which is configured using a column and a spindle, a rear working clearance of 100 mm

and a test speed adjustable between 0.1 and 800 mm/min and the software testControl. A pressure stamp with screwable inserts, a cylinder (diameter 10 mm), and a force transducer, Fmax. 1 kN, diameter 8 mm, class 0.5 as of 10 N, class 1 as of 2 N according to ISO 7500-1, with a manufacturer's test certificate M according to DIN 55350-18 (Zwick-Bruttokraft Fmax 1.45 kN) were used for measurement (all equipment manufactured by Zwick GmbH & Co. KG, Ulm, Germany) with the order no. BTC-FR 2.5 TH. D09 for the testing machine, the order no. BTC-LC 0050N. P01 for the force transducer, and the order number 80 70000 S06 for the centring device.

Fig. 3 shows measurement of the fracture resistance of a tablet, in particular the adjustment device (6) of the tablet (4) used for this purpose before and during measurement. For this purpose, the tablet (4) is clamped between the upper pressure plate (1) and the lower pressure plate (3) of the device, which is not shown, for applying force using two 2-part clamping devices, both of which are firmly attached (not shown) to the upper or lower pressure plate after adjustment of the distance (5) necessary for taking up and centring the tablet to be measured. In order to adjust the distance (5), each of the 2-part clamping devices can be horizontally moved outward or inward on the respective pressure plates on which they are installed.

Tablets for which no fracturing is observed, but optionally for which plastic deformation takes place without fracturing of the tablet due to the effect of force, are also classified as fracture resistant under a certain effect of force.

In the following, the invention is explained by means of examples. These are given solely by way of example and do not limit the general concept of the invention.

Examples:

Tramadol hydrochloride was used as an active ingredient in a series of examples. Tramadol hydrochloride was used, even though it is not an active ingredient with the usual abuse potential and therefore does not fall under the Narcotics Act, in order to facilitate the experimental work. Moreover, tramadol is a representative of the opioid class having outstanding water solubility.

Example 1

1.1. Pellet production

Composition of the pellets:

		Percent [%]
Tramadol HCl	50 mg	40%
Polyethylene oxide, NF 7 000 000 (MG)	50 mg	40%
(Polyox WSR 303, Dow Chemicals)		
(Metolose 90 SH, 100000 cP) hydroxypropyl methyl cellulose (Shin-Etsu)	12.5 mg	10%
PEG 6000 (Polyethylene glycol)	12.5 mg	10%

The components were weighed and mixed in a free-fall mixer for 15 minutes. They were then extruded with a twin-screw extruder manufactured by Leistritz, model ZSE18HP40D with a micropelletizer. Eccentric screw ends and a displacer cone were used. The nozzle plate had eight bores with a diameter of 1.0 mm, and the length/diameter ratio was 2.5. The resulting pellets had a length of 1 mm ± 20%. The process parameters were as follows:

Cylinder temperature HZ1 set 40°C / actual:	39.6°C
Cylinder temperature HZ2 and HZ2	100°C
Cylinder temperature HZ4 to HZ8	120°C
Cylinder temperature HZ10	120°C
Cylinder temperature HZ11	140°C
Product temperature at discharge component	134.1 °C
Discharge rate	33.43 g/min

Screw revolution speed (1/min)	150/min

The fracture resistance of the pellets was determined by the method described above using the equipment shown in Fig. 3. No fracture occurred by the effect of force of 500 N. The pellets could not be crushed with a hammer, nor was this possible with a mortar and pestle.

1.2. Capsule production

Composition of the capsule filling

Pellets produced according to example 1.1. (≅ 50 mg tramadol)	125 mg	95%
Crospovidone	6.3 mg	5%
Total amount	131.3 mg	100%

The pellets produced according to 1.1. were mixed with crospovidone until a homogenous mixture was obtained. This mixture was filled into gelatin two-piece capsules of size 0.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}. 600 ml of pH 1.2 buffer was used as a release medium. The amount of tramadol released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	56%
30 min	80%
45 min	89%

Example 2

2.1. Pellets produced according to example 1.1. were used.

2.2. Composition of the capsule filling

Pellets produced according to 1.1. (≅ 50 mg tramadol)	125 mg	95%
Croscarmellose	6.3 mg	5%
Total amount	131.3 mg	100%

The pellets were mixed with croscarmellose and filled into gelatin two-piece capsules of size 0.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}, 600 ml of pH 1.2 buffer was used as a release medium. The amount of the active ingredient released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	44%
30 min	71%
45 min	82%

Example 3

3.1. Pellets produced according to example 1.1. were used.

3.2. Composition of the capsule filling

Pellets produced according to example 1.1. (≅ 50 mg tramadol)	125 mg	73.8%
Crospovidone	6.3 mg	3.7%
Microcrystalline cellulose (Avicel PH101)	37.5 mg	22.1%
Magnesium stearate	0.6 mg	0.4%
Total amount	169.4 mg	100%

The pellets were mixed with croscarmellose, microcrystalline cellulose, and magnesium stearate and filled into gelatin two-piece capsules of size 0.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}, 600 ml of pH 1.2 buffer was used as a release medium. The amount of the active ingredient released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	70%
30 min	88%
45 min	92%

Example 4

4.1. Pellets produced according to example 1.1. were used.

4.2. Composition of the capsule filling

Pellets produced according to example 1.1. (≅ 50 mg tramadol)	125 mg	66.7%
Croscarmellose	6.25 mg	3.3%
Microcrystalline cellulose (Avicel PH101)	50.0 mg	26.7%
Calcium dihydrogen phosphate	6.25 mg	3.3%
Total amount	187.5 mg	100%

The pellets were mixed with the auxiliaries and filled into gelatin two-piece capsules of size 0.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}. 600 ml of pH 1.2 buffer was used as a release medium. The amount of the active ingredient released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	51%
30 min	80%
45 min	88%

Example 5

5.1. The pellets produced according to example 1.1. were used.

5.2. Composition of the capsule filling

Pellets produced according to example 1.1. (≅ 50 mg tramadol)	125 mg	95.2%
Micronized crospovidone	6.25 mg	4.8 %
Total amount	131.25 mg	100%

Crospovidone (micronized) and pellets were mixed in a high-shear mixer (Diosna Laborgranulator 4) for 15 minutes. The coated pellets were filled into a gelatin capsule of size 0.

The fracture resistance of the pellets was determined by the method described above using the equipment discussed. No fracture occurred by the effect of force of 500 N. The pellets could not be crushed with a hammer. This was also impossible with a mortar and pestle.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}. 600 ml of pH 1.2 buffer was used as a release medium. The amount of the active ingredient released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	52%
30 min	77%
45 min	86%

Example 6

6.1 Pellet production

Composition of the pellets

	Per capsule filling	Percent [%]
Tramadol HCl	50 mg	45%
Polyethylene oxide 7,000,000 (MW) (Polyox WSR 303, Dow Chemicals)	44.4 mg	40%
Macrogol 6000 (Polyethylene glycol 6000 BASF)	11.1 mg	10%
Crospovidone	5.6 mg	5%

The components were weighed in and mixed in a free-fall mixer for 15 minutes. They were then extruded with a twin-screw extruder manufactured by Leistritz, model ZSE18HP40D with a micropelletizer. Eccentric screw ends and a displacer cone were used. The nozzle plate had eight bores with a diameter of 1.0 mm, with a length/diameter ratio was 2.5. The pellets had a length of 1 mm ± 20%. The extrusion parameters were as follows:

Cylinder temperature HZ1 set 40°C / actual:	39.6°C
Cylinder temperature HZ2 and HZ2	100°C
Cylinder temperature HZ4 to HZ8	120°C
Cylinder temperature HZ10	120°C
Cylinder temperature HZ11	140°C
Product temperature at discharge component	134.1°C
Discharge rate	33.43 g/min
Screw revolution speed (1/min)	150/min

The fracture resistance of the pellets was determined by the method described above using the equipment described. No fracture occurred by the effect of force of 500 N.

The pellets could not be crushed with a hammer; nor was this possible with a mortar and pestle.

6.2. Composition of the capsule filling

Pellets produced according to example 6.1. (≅ 50 mg tramadol)	111 mg	100%
Total amount	111 mg	100%

The pellets produced according to 6.1. were filled into gelatin two-piece capsules of size 0.

The *in vitro* release of tramadol from the capsule was determined in the paddle stirrer apparatus with sinker according to Pharm Eur. The temperature of the release medium was 37°C, and the rotation speed of the stirrer was 75 min^{-1}. 600 ml of pH 1.2 buffer was used as a release medium. The amount of the active ingredient released in the solution medium at each specified time was determined using a spectrophotometer (at 271 nm).

Time	Amount of active ingredient released
15 min	55%
30 min	77%
45 min	87%

Az EP 2 131 830 lajstromszámú európai szabadalom igénypontjainak magyar fordítása:

1. Multipartikuláris adagolási forma nehezített/gátolt visszaélési lehetőséggel, amely tartalmaz

- legalább egy, visszaélési potenciállal rendelkező hatóanyagot (A), amelynek pszichotrop hatása van, és az opioidok köréből van kiválasztva;
- legalább egy szintetikus vagy természetes polimert (C);
- adott esetben legalább egy természetes, félszintetikus vagy szintetikus viaszt (D);
- legalább egy (E) dezintegráló szert, amely legalább részben össze van keverve az adagolási forma részecskéivel;
- egy(B2) excipienst, amely nem alkotója a részecskének, és amely a töltőanyagok köréből van kiválasztva; és
- adott esetben egy vagy több további fiziológiásan kompatibilis segédanyagot (B),

ahol az adagolási forma egyes részecskéinek a törőszilárdsága legalább 500 N az Európai Gyógyszerkönyv (Pharm. Eur.) szerint mérve, és a hatóanyag-leadása legalább 75 % 45 perc eltelte után az Európai Gyógyszerkönyv szerint, lapátos keverővel ellátott készülékben, 600 ml 1,2-es pH-jú vizes puffer-oldatban 37 °C-on és 75 percenkénti fordulatszám mellett mérve.

2. Az 1. igénypont szerinti adagolási forma, azzal jellemezve, hogy mikrotabletták, mikropelletek, szemcsék, gömbök, gyöngyök vagy pelletek formájában van.

3. Az 1. vagy 2. igénypontok egyike szerinti adagolási forma, azzal jellemezve, hogy a (C) polimer legalább egy olyan polimer, amely a polialkilén-oxidok, polietilének, polipropilének, poli(vinil-klorid)ok, polikarbonátok, polisztirolok, poliakrilátok és ezek kopolimerjei köréből van kiválasztva.

4. Az előző igénypontok bármelyike szerinti adagolási forma, azzal jellemezve, hogy a (C) polimer legalább egy polialkilén-oxid, amely a polimetilén-oxid, polietilén-oxid, polipropilén-oxid, ezek kopolimerjei, ezek blokk-kopolimerjei és ezek keverékei közül van kiválasztva, előnyösen legalább egy polietilén-oxid.

5. A 3. vagy 4. igénypont szerinti adagolási forma, azzal jellemezve, hogy reológiai mérések alapján a polialkilén-oxid molekulatömege legalább $0,5 \times 10^6$.

6. Az 5. igénypont szerinti adagolási forma, azzal jellemezve, hogy reológiai mérések alapján a polialkilén-oxid molekulatömege legalább 1×10^6.

7. Az előző igénypontok bármelyike szerinti adagolási forma, azzal jellemezve, hogy tartalmaz legalább egy (E) dezintegráló szert 0,1 – 15 tömeg%, előnyösen 1 – 10 tömeg%, különösen előnyösen 3 – 7 tömeg% mennyiségben az adagolási forma teljes tömegére vonatkoztatva.

8. Az előző igénypontok bármelyike szerinti adagolási forma, azzal jellemezve, hogy az (E) dezintegráló szer legalább egy a térhálós nátrium-karboximetilcellulóz (kroszkarmellóz), módosított kukoricakeményítő, nátrium-karboximetil-keményítő, térhálós poli(vinil-pirrolidon) (kroszpovidon) köréből választott dezintegráló szer.

9. Az előző igénypontok bármelyike szerinti adagolási forma, azzal jellemezve, hogy a további (B) segédanyag (B1) formuláló segédanyag.

10. A 9. igénypont szerinti adagolási forma, azzal jellemezve, hogy a (B1) formuláló segédanyag legalább egy, előnyösen hővel szemben stabil vegyület, amely a lágyítók, antioxidánsok, redox-stabilizátorok és töltőanyagok köréből van kiválasztva.

11. Az előző igénypontok bármelyike szerinti adagolási forma, azzal jellemezve, hogy a (B2) excipiens töltőanyag, amely a mikrokristályos cellulóz, kalcium-dihidrogén-foszfát, cukrok, így például laktóz, cellulózpor és/vagy poili(vinil-pirrolidon) köréből van kiválasztva.

12. Eljárás az 1-11. igénypontok egyike szerinti adagolási forma előállítására, amely a következő eljárási lépéseket tartalmazza:

(i)

a) összekeverjük az (A), (C), adott esetben (B1), adott esetben (D) komponenst és adott esetben az (E) dezintegráló szer legalább egy részét;

b) adott esetben előformázzuk az a) lépésben kapott keveréket, előnyösen az a) lépésben kapott keverékre történő hő és/vagy erő alkalmazásával a C) komponens lágyítása nélkül;

c) kikeményítjük a keveréket hő és erő alkalmazásával, ahol a hőt az erő-hatás alatt és/vagy előtt alkalmazzuk, és olyan mértékben, amely elegendő ahhoz, hogy a (C) komponenst legalább lágyuláspontjáig melegítse;

d) a kikeményített keveréket rész-tömegekre osztjuk;

e) elkülönítjük a kikeményített résztömegeket és adott esetben formákat;

f) összekeverjük az (E) dezintegráló szer a)-ból megmaradt részével és további excipiensekkel (B2);

g) és adott esetben készre formáljuk vagy az adagolási forma adagolási egységébe töltjük;

vagy

(ii)

a) összekeverjük az (A), (C), adott esetben (B1), adott esetben (D) komponenseket és adott esetben az (E) dezintegráló szer legalább egy részét a (C) polimerhez legalább annyi oldószert adva, amennyitől a keverék nedvessé, ugyanakkor formálhatóvá válik,

b) a formálható tömeget szárítás előtt vagy után résztömegekre osztjuk,

c) elkülönítjük az adott esetben egy további szétosztás után kapott résztömegeket és adott esetben formákat,

d) összekeverjük az (E) dezintegráló szer a)-ban megmaradt részével és további (B2) excipiensekkel, és

e) adott esetben készre formáljuk és/vagy az adagolási forma dózisegységébe töltjük.

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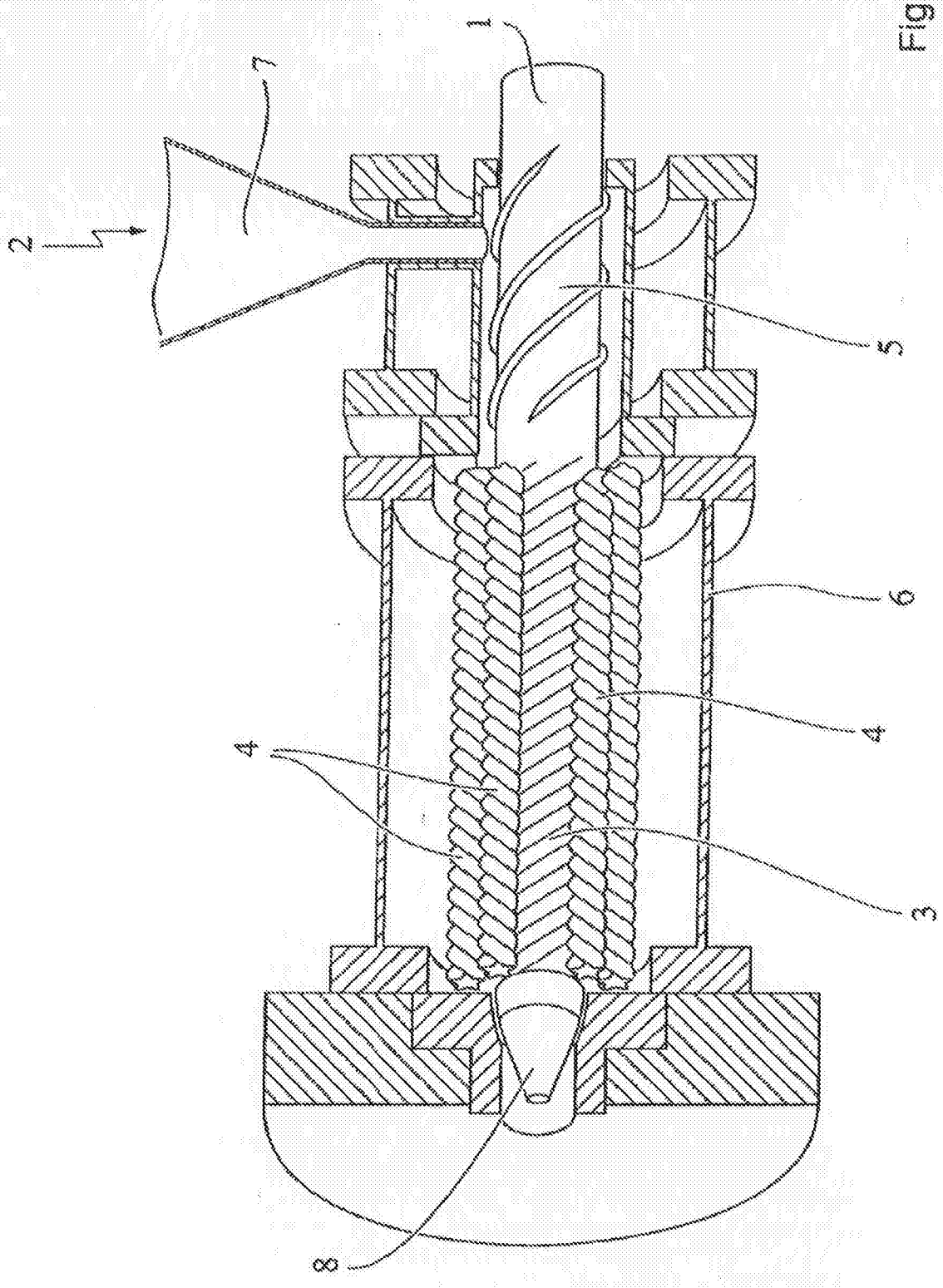
Dr. Miskolczi Mária
ügyvivő
[illegible]

Meghatalmazott:

Fig. 1



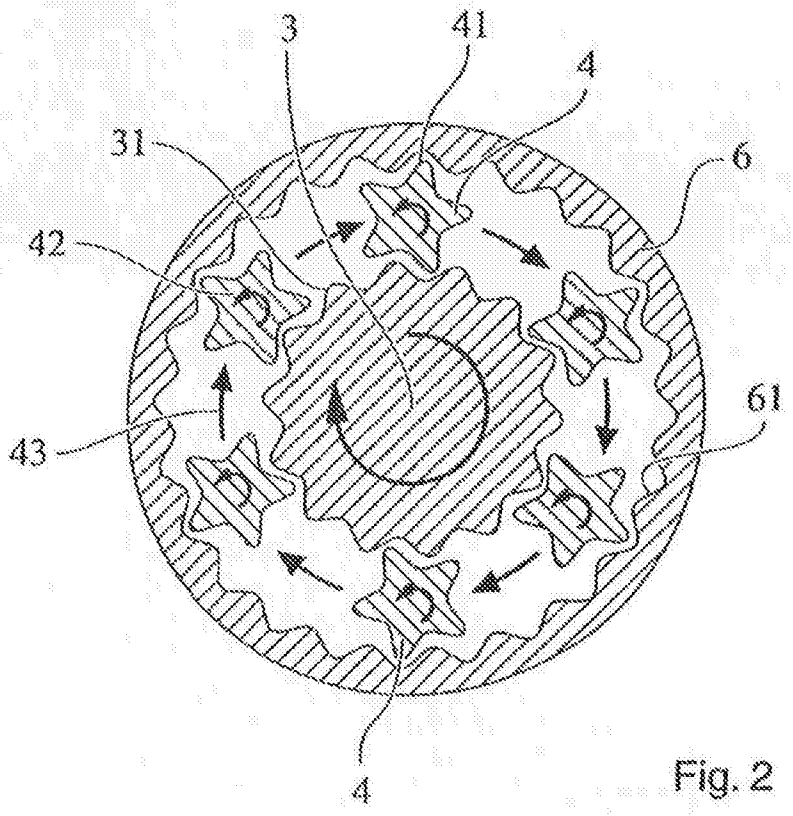


Fig. 2

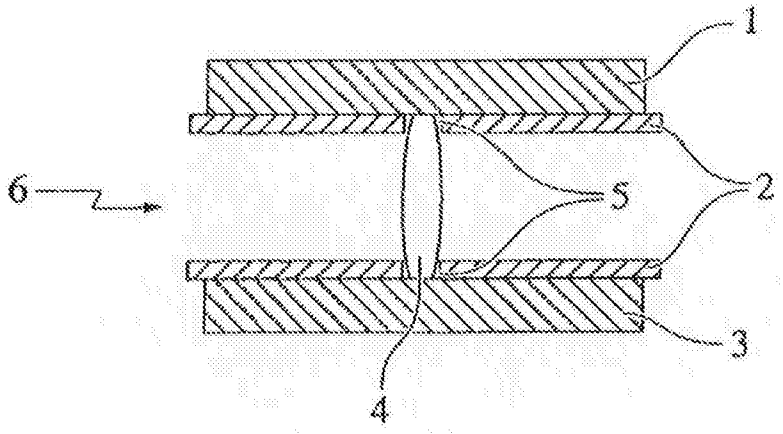


Fig. 3