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(54) **TAMPER-RESISTANT DOSAGE FORM WITH IMMEDIATE RELEASE AND RESISTANCE AGAINST SOLVENT EXTRACTION**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

2,524,855 A 10/1950 Schnider et al.
 2,806,033 A 9/1957 Lewenstein et al.

2,987,445 A 6/1961 Levesque
 3,332,950 A 7/1967 Blumberg et al.
 3,370,035 A 2/1968 Ogura et al.
 3,652,589 A 3/1972 Flick et al.
 3,806,603 A 4/1974 Gaunt et al.
 3,865,108 A 2/1975 Hartop
 3,941,865 A 3/1976 Miller et al.
 3,966,747 A 6/1976 Monkovic et al.
 3,980,766 A 9/1976 Shaw et al.
 4,002,173 A 1/1977 Manning et al.
 4,014,965 A 3/1977 Stube et al.
 4,070,494 A 1/1978 Hoffmeister et al.
 4,070,497 A 1/1978 Wismer et al.
 4,175,119 A 11/1979 Porter
 4,200,704 A 4/1980 Stanley et al.
 4,207,893 A 6/1980 Michaels
 4,262,017 A 4/1981 Kuipers et al.
 4,343,789 A 8/1982 Kawata et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AR 046994 A1 12/2004
 AR 045353 A1 10/2005

(Continued)

OTHER PUBLICATIONS

Tennant (Simultaneous Use of Stimulants and Opioids, 2011. [online] retrieved on Jul. 7, 2016 from: <http://www.practicalpainmanagement.com/treatments/pharmacological/opioids/simultaneous-use-stimulants-opioids>; 7 pages.*

Starch 1500 technical data from Colorcon 2016 6 pages.*

Fathima et al. (JAPS 2011;01(06):66-71).*

Alekseeva et al, Chemical-Pharmaceutical Journal, vol. 41, No. 9, 2007, 49-52. (Full translation attached.)

2.9 Methoden der pharmazeutischen Technologie, European Pharmacopeia, 143-144, 1997. (Full English translation attached).

Albertini, B. "New spray congealing atomizer for the microencapsulation of highly concentrated solid and liquid substances" European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 348-357.

Alekseeva et al, Chemical-Pharmaceutical Journal, vol. 41, No. 9, 2007, 49-52. (English abstract included.).

(Continued)

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(57) **ABSTRACT**

A tamper-resistant pharmaceutical dosage form comprising a multitude of particles which comprise a pharmacologically active compound, a polyalkylene oxide, and a disintegrant; wherein the pharmacologically active compound is dispersed in a matrix comprising the polyalkylene oxide and the disintegrant; wherein the content of the disintegrant is more than 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; wherein the content of the polyalkylene oxide is at least 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; and wherein the dosage form provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

21 Claims, 4 Drawing Sheets

(56)

References Cited

U.S. PATENT DOCUMENTS

4,353,887 A	10/1982	Hess et al.	5,811,126 A	9/1998	Krishnamurthy
4,404,183 A	9/1983	Kawata et al.	5,849,240 A	12/1998	Miller et al.
4,427,681 A	1/1984	Munshi et al.	5,866,164 A	2/1999	Kuczynski et al.
4,427,778 A	1/1984	Zabriskie	5,900,425 A	5/1999	Kanikanti et al.
4,457,933 A	7/1984	Gordon et al.	5,908,850 A	6/1999	Zeitlin et al.
4,462,941 A	7/1984	Lee et al.	5,916,584 A	6/1999	O'Donoghue et al.
4,473,640 A	9/1984	Combie et al.	5,928,739 A	7/1999	Pophusen et al.
4,483,847 A	11/1984	Augart	5,939,099 A	8/1999	Grabowski et al.
4,485,211 A	11/1984	Okamoto	5,945,125 A	8/1999	Kim
4,529,583 A	7/1985	Porter	5,948,787 A	9/1999	Merrill et al.
4,599,342 A	7/1986	LaHann	5,962,488 A	10/1999	Lang
4,603,143 A	7/1986	Schmidt	5,965,161 A	10/1999	Oshlack et al.
4,612,008 A	9/1986	Wong et al.	5,968,925 A	10/1999	Knidlberger
4,629,621 A	12/1986	Snipes	6,001,391 A	12/1999	Zeidler et al.
4,667,013 A	5/1987	Reichle	6,009,390 A	12/1999	Gupta et al.
4,690,822 A	9/1987	Uemura	6,009,690 A	1/2000	Rosenberg et al.
4,713,243 A	12/1987	Schiraldi et al.	6,051,253 A	4/2000	Zettler et al.
4,744,976 A	5/1988	Snipes et al.	6,071,970 A	6/2000	Mueller et al.
4,764,378 A	8/1988	Keitn et al.	6,077,538 A	6/2000	Merrill et al.
4,765,989 A	8/1988	Wong et al.	6,090,411 A	7/2000	Pillay et al.
4,774,074 A	9/1988	Snipes	6,093,420 A	7/2000	Baichwal
4,774,092 A	9/1988	Hamilton	6,096,339 A	8/2000	Ayer et al.
4,783,337 A	11/1988	Wong et al.	6,117,453 A	9/2000	Seth et al.
4,806,337 A	2/1989	Snipes et al.	6,120,802 A	9/2000	Breitenbach et al.
RE33,093 E	10/1989	Schiraldi et al.	6,133,241 A	10/2000	Bok et al.
4,880,585 A	11/1989	Klimesch et al.	6,183,781 B1	2/2001	Burke
4,892,778 A	1/1990	Theeuwes et al.	6,228,863 B1	5/2001	Palermo et al.
4,892,889 A	1/1990	Kirk	6,235,825 B1	5/2001	Yoshida et al.
4,940,556 A	7/1990	MacFarlane et al.	6,238,697 B1	5/2001	Kumar et al.
4,954,346 A	9/1990	Sparta et al.	6,245,357 B1	6/2001	Edgren et al.
4,957,668 A	9/1990	Plackard et al.	6,248,737 B1	6/2001	Buschmann et al.
4,957,681 A	9/1990	Klimesch et al.	6,254,887 B1	7/2001	Miller et al.
4,960,814 A	10/1990	Wu et al.	6,261,599 B1	7/2001	Oshlack
4,992,278 A	2/1991	Khanna	6,290,990 B1	9/2001	Grabowski et al.
4,992,279 A	2/1991	Palmer et al.	6,306,438 B1	10/2001	Oshlack et al.
5,004,601 A	4/1991	Snipes	6,309,668 B1	10/2001	Bastin et al.
5,051,261 A	9/1991	McGinity	6,318,650 B1	11/2001	Breitenbach et al.
5,073,379 A	12/1991	Klimesch et al.	6,322,819 B1	11/2001	Burnside et al.
5,082,668 A	1/1992	Wong et al.	6,326,027 B1	12/2001	Miller et al.
5,126,151 A	6/1992	Bodor et al.	6,335,035 B1	1/2002	Drizen et al.
5,139,790 A	8/1992	Snipes	6,337,319 B1	1/2002	Wang
5,145,944 A	9/1992	Steinmann	6,340,475 B2	1/2002	Shell et al.
5,149,538 A	9/1992	Granger et al.	6,344,215 B1	2/2002	Bettman et al.
5,169,645 A	12/1992	Shukla et al.	6,344,535 B1	2/2002	Timmermann et al.
5,190,760 A	3/1993	Baker	6,348,469 B1	2/2002	Seth
5,198,226 A	3/1993	MacFarlane et al.	6,355,656 B1	3/2002	Zeitlin et al.
5,200,197 A	4/1993	Wright et al.	6,375,957 B1	4/2002	Kaiko et al.
5,211,892 A	5/1993	Gueret	6,375,963 B1	4/2002	Repka et al.
5,225,417 A	7/1993	Dappen	6,387,995 B1	5/2002	Sojka
5,227,157 A	7/1993	McGinity et al.	6,399,100 B1	6/2002	Clancy et al.
5,229,164 A	7/1993	Pins et al.	6,419,954 B1	7/2002	Chu et al.
5,273,758 A	12/1993	Royce	6,436,441 B1	8/2002	Sako et al.
5,326,852 A	7/1994	Fujikake	6,461,644 B1	10/2002	Jackson et al.
5,350,741 A	9/1994	Takada	6,488,939 B1	12/2002	Zeidler et al.
5,378,462 A	1/1995	Boedecker et al.	6,488,962 B1	12/2002	Berner et al.
5,387,420 A	2/1995	Mitchell	6,488,963 B1	12/2002	McGinity et al.
5,427,798 A	6/1995	Ludwig et al.	6,534,089 B1	3/2003	Ayer et al.
RE34,990 E	7/1995	Khanna et al.	6,547,977 B1	4/2003	Yan et al.
5,458,887 A	10/1995	Chen et al.	6,547,997 B1	4/2003	Breitenbach et al.
5,460,826 A	10/1995	Merrill et al.	6,562,375 B1	5/2003	Sako et al.
5,472,943 A	12/1995	Crain et al.	6,569,506 B1	5/2003	Jerde et al.
5,508,042 A	4/1996	Oshlack et al.	6,572,889 B1	6/2003	Guo
5,552,159 A	9/1996	Mueller et al.	6,592,901 B2	7/2003	Durig et al.
5,556,640 A	9/1996	Ito et al.	6,623,754 B2	9/2003	Guo et al.
5,562,920 A	10/1996	Demmer et al.	6,635,280 B2	10/2003	Shell et al.
5,591,452 A	1/1997	Miller et al.	6,696,088 B2	2/2004	Oshlack et al.
5,593,694 A	1/1997	Hayashida et al.	6,699,503 B1	3/2004	Sako et al.
5,601,842 A	2/1997	Bartholomaeus	6,723,340 B2	4/2004	Gusler et al.
5,620,697 A	4/1997	Tormala et al.	6,723,343 B2	4/2004	Kugelmann
5,679,685 A	10/1997	Cincotta et al.	6,733,783 B2	5/2004	Oshlack et al.
5,681,517 A	10/1997	Metzger	6,753,009 B2	6/2004	Luber et al.
5,707,636 A	1/1998	Rodriguez et al.	6,821,588 B1	11/2004	Hammer et al.
5,741,519 A	4/1998	Rosenberg et al.	6,979,722 B2	12/2005	Hamamoto et al.
5,792,474 A	8/1998	Rauchfuss	7,074,430 B2	7/2006	Miller et al.
5,801,201 A	9/1998	Graudums et al.	7,129,248 B2	10/2006	Chapman et al.
			7,141,250 B2	11/2006	Oshlack et al.
			7,157,103 B2	1/2007	Sackler
			7,176,251 B1	2/2007	Bastioli et al.
			RE39,593 E	4/2007	Buschmann et al.

(56)

References Cited

U.S. PATENT DOCUMENTS

7,201,920 B2	4/2007	Kumar et al.	2004/0010000 A1	1/2004	Ayer et al.
7,214,385 B2	5/2007	Gruber	2004/0011806 A1	1/2004	Luciano et al.
7,230,005 B2	6/2007	Shafer et al.	2004/0052731 A1	3/2004	Hirsh et al.
7,300,668 B2	11/2007	Pryce et al.	2004/0052844 A1	3/2004	Hsiao et al.
7,332,182 B2	2/2008	Sackler	2004/0081694 A1	4/2004	Oshlack
7,388,068 B2	6/2008	Falk et al.	2004/0091528 A1	5/2004	Rogers et al.
7,399,488 B2	7/2008	Hirsh et al.	2004/0126428 A1	7/2004	Hughes et al.
7,510,726 B2	3/2009	Kumar et al.	2004/0131671 A1	7/2004	Zhang et al.
7,674,799 B2	3/2010	Chapman et al.	2004/0156899 A1	8/2004	Louie-Helm et al.
7,674,800 B2	3/2010	Chapman et al.	2004/0170567 A1	9/2004	Sackler
7,683,072 B2	3/2010	Chapman et al.	2004/0170680 A1	9/2004	Oshlack et al.
7,776,314 B2	8/2010	Bartholomaeus et al.	2004/0185105 A1	9/2004	Berner et al.
7,842,307 B2	11/2010	Oshlack et al.	2004/0213845 A1	10/2004	Sugihara et al.
7,851,482 B2	12/2010	Dung et al.	2004/0213848 A1	10/2004	Li et al.
7,939,543 B2	5/2011	Kupper	2005/0015730 A1	1/2005	Gunturi et al.
7,968,119 B2	6/2011	Farrell	2005/0031546 A1	2/2005	Bartholomaeus et al.
7,994,364 B2	8/2011	Fischer et al.	2005/0058706 A1	3/2005	Bartholomaeus et al.
8,075,872 B2	12/2011	Arkenau-Maric	2005/0063214 A1	3/2005	Takashima
8,101,630 B2	1/2012	Kumar et al.	2005/0089475 A1	4/2005	Gruber
8,114,383 B2	2/2012	Bartholomaeus et al.	2005/0089569 A1	4/2005	Bar-Shalom
8,114,384 B2	2/2012	Arkenau et al.	2005/0095291 A1	5/2005	Oshlack et al.
8,114,838 B2	2/2012	Marchionni	2005/0106249 A1	5/2005	Hwang et al.
8,192,722 B2	6/2012	Arkenau-Maric et al.	2005/0112067 A1	5/2005	Kumar et al.
8,202,542 B1	6/2012	Mehta et al.	2005/0127555 A1	6/2005	Gusik et al.
8,309,060 B2	11/2012	Bartholomeus et al.	2005/0152843 A1	7/2005	Bartholomaeus et al.
8,309,122 B2	11/2012	Kao et al.	2005/0181046 A1	8/2005	Oshlack et al.
8,323,889 B2	12/2012	Arkenau-Maric et al.	2005/0186139 A1	8/2005	Bartholomaeus et al.
8,329,216 B2	12/2012	Kao et al.	2005/0191244 A1	9/2005	Bartholomaeus et al.
8,337,888 B2	12/2012	Wright et al.	2005/0191352 A1	9/2005	Hayes
8,383,152 B2	2/2013	Jans et al.	2005/0192333 A1	9/2005	Hinze et al.
8,420,056 B2	4/2013	Arkenau-Maric et al.	2005/0214223 A1	9/2005	Bartholomaeus et al.
8,445,023 B2	5/2013	Guimbarteau et al.	2005/0220877 A1	10/2005	Patel
8,722,086 B2	5/2014	Arkenau-Maric et al.	2005/0222188 A1	10/2005	Chapman et al.
8,858,963 B1	10/2014	Devarakonda et al.	2005/0236741 A1	10/2005	Arkenau et al.
9,192,578 B2	11/2015	McGinity et al.	2005/0245556 A1	11/2005	Brogman et al.
2001/0038852 A1	11/2001	Kolter et al.	2005/0266084 A1	12/2005	Li et al.
2002/0012701 A1	1/2002	Kolter et al.	2006/0002859 A1	1/2006	Arkenau et al.
2002/0015730 A1	2/2002	Hoffmann et al.	2006/0002860 A1	1/2006	Bartholomaeus et al.
2002/0051820 A1	5/2002	Shell et al.	2006/0004034 A1	1/2006	Hinze et al.
2002/0114838 A1	8/2002	Ayer et al.	2006/0009478 A1	1/2006	Friedman et al.
2002/0132359 A1	9/2002	Waterman	2006/0017916 A1	1/2006	Clarke et al.
2002/0132395 A1	9/2002	Iyer et al.	2006/0039864 A1	2/2006	Bartholomaeus et al.
2002/0176888 A1	11/2002	Bartholomaeus et al.	2006/0073102 A1	4/2006	Huaihung et al.
2002/0187192 A1	12/2002	Joshi et al.	2006/0099250 A1	5/2006	Tian et al.
2002/0192277 A1	12/2002	Oshlack et al.	2006/0104909 A1	5/2006	Vaghefi
2003/0008409 A1	1/2003	Spearmen et al.	2006/0182801 A1	8/2006	Breder et al.
2003/0015814 A1	1/2003	Krull et al.	2006/0188447 A1	8/2006	Arkenau-Maric et al.
2003/0017532 A1	1/2003	Biswas et al.	2006/0193782 A1	8/2006	Bartholomaeus et al.
2003/0021546 A1	1/2003	Sato	2006/0193914 A1	8/2006	Ashworth et al.
2003/0044458 A1	3/2003	Wright et al.	2006/0194759 A1	8/2006	Eidelson
2003/0044464 A1	3/2003	Ziegler et al.	2006/0194826 A1	8/2006	Oshlack et al.
2003/0064099 A1	4/2003	Oshlack et al.	2006/0240105 A1	10/2006	DeVane et al.
2003/0068276 A1	4/2003	Hughes et al.	2006/0240110 A1	10/2006	Kiick et al.
2003/0068370 A1	4/2003	Sackler et al.	2006/0269603 A1	11/2006	Brown Miller et al.
2003/0068371 A1	4/2003	Oshlack et al.	2007/0003616 A1	1/2007	Arkenau-Maric et al.
2003/0068375 A1	4/2003	Wright et al.	2007/0003617 A1	1/2007	Fischer et al.
2003/0068392 A1	4/2003	Sackler	2007/0020188 A1	1/2007	Sackler
2003/0069263 A1	4/2003	Breder et al.	2007/0020335 A1	1/2007	Chen et al.
2003/0077297 A1	4/2003	Chen et al.	2007/0042044 A1	2/2007	Fischer et al.
2003/0091630 A1	5/2003	Louie-Helm et al.	2007/0048228 A1	3/2007	Arkenau-Maric et al.
2003/0092724 A1	5/2003	Huaihung et al.	2007/0065365 A1	3/2007	Kugelmann et al.
2003/0104052 A1	6/2003	Berner et al.	2007/0092573 A1	4/2007	Joshi et al.
2003/0104053 A1	6/2003	Gusler et al.	2007/0183979 A1	8/2007	Arkenau-Maric et al.
2003/0118641 A1	6/2003	Maloney et al.	2007/0183980 A1	8/2007	Arkenau-Maric et al.
2003/0124185 A1	7/2003	Oshlack et al.	2007/0184117 A1	8/2007	Gregory et al.
2003/0125347 A1	7/2003	Anderson et al.	2007/0190142 A1	8/2007	Breitenbach et al.
2003/0129230 A1	7/2003	Baichwal et al.	2007/0196396 A1	8/2007	Pilgaonkar et al.
2003/0133985 A1	7/2003	Louie-Helm et al.	2007/0196481 A1	8/2007	Amidon et al.
2003/0143269 A1	7/2003	Oshlack et al.	2007/0224129 A1	9/2007	Guimbarteau et al.
2003/0152622 A1	8/2003	Louie-Helm et al.	2007/0231268 A1	10/2007	Emigh et al.
2003/0158242 A1	8/2003	Kugelmann	2007/0259045 A1	11/2007	Mannion et al.
2003/0175326 A1	9/2003	Thombre	2007/0264327 A1	11/2007	Kumar et al.
2003/0198677 A1	10/2003	Pryce Lewis et al.	2007/0269505 A1	11/2007	Flath et al.
2003/0215508 A1	11/2003	Davis et al.	2007/0292508 A1	12/2007	Szamosi et al.
2003/0232895 A1	12/2003	Omidian et al.	2008/0020032 A1	1/2008	Crowley et al.
			2008/0063725 A1	3/2008	Guimbarteau et al.
			2008/0069871 A1	3/2008	Vaughn et al.
			2008/0075669 A1	3/2008	Soscia et al.
			2008/0075768 A1	3/2008	Vaughn et al.

(56)

References Cited

U.S. PATENT DOCUMENTS

2008/0081290	A1	3/2008	Wada et al.
2008/0085304	A1	4/2008	Baichwal et al.
2008/0131503	A1	6/2008	Holm et al.
2008/0145429	A1	6/2008	Leyenecker et al.
2008/0152595	A1	6/2008	Emigh et al.
2008/0181932	A1	7/2008	Bortz et al.
2008/0220079	A1	9/2008	Chen
2008/0233178	A1	9/2008	Reidenberg et al.
2008/0234352	A1	9/2008	Fischer et al.
2008/0247959	A1	10/2008	Bartholomäus et al.
2008/0248113	A1	10/2008	Bartholomäus et al.
2008/0280975	A1	11/2008	Badul
2008/0311049	A1	12/2008	Arkenau-Maric et al.
2008/0311187	A1	12/2008	Ashworth et al.
2008/0311197	A1	12/2008	Arkenau-Maric et al.
2008/0311205	A1	12/2008	Habib et al.
2008/0312264	A1	12/2008	Arkenau-Maric et al.
2008/0317695	A1	12/2008	Everaert et al.
2008/0317854	A1	12/2008	Arkenau et al.
2009/0004267	A1	1/2009	Arkenau-Maric et al.
2009/0005408	A1	1/2009	Arkenau-Maric et al.
2009/0011016	A1	1/2009	Cailly-Dufestel et al.
2009/0017121	A1	1/2009	Berner et al.
2009/0022798	A1	1/2009	Rosenberg et al.
2009/0081287	A1	3/2009	Wright et al.
2009/0081290	A1	3/2009	McKenna et al.
2009/0117191	A1	5/2009	Brown Miller et al.
2009/0202634	A1	8/2009	Jans et al.
2009/0215808	A1	8/2009	Yum et al.
2009/0232887	A1	9/2009	Odidi et al.
2009/0253730	A1	10/2009	Kumar et al.
2009/0317355	A1	12/2009	Roth et al.
2009/0318395	A1	12/2009	Schramm et al.
2010/0015223	A1	1/2010	Cailly-Deufestel et al.
2010/0035886	A1*	2/2010	Cincotta A61K 9/0019 514/250
2010/0047345	A1	2/2010	Crowley et al.
2010/0092553	A1	4/2010	Guimberteau et al.
2010/0098758	A1	4/2010	Bartholomäus et al.
2010/0099696	A1	4/2010	Soscia et al.
2010/0104638	A1	4/2010	Dai et al.
2010/0151028	A1	6/2010	Ashworth et al.
2010/0168148	A1	7/2010	Wright et al.
2010/0172989	A1	7/2010	Roth et al.
2010/0203129	A1	8/2010	Anderson et al.
2010/0221322	A1	9/2010	Bartholomäus et al.
2010/0249045	A1	9/2010	Babul
2010/0260833	A1	10/2010	Bartholomäus et al.
2010/0280047	A1	11/2010	Kolter et al.
2010/0291205	A1	11/2010	Downie et al.
2010/0297229	A1	11/2010	Sesha
2011/0020451	A1	1/2011	Bartholomäus et al.
2011/0020454	A1	1/2011	Lamarca Casado
2011/0038930	A1	2/2011	Barnscheid et al.
2011/0082214	A1	4/2011	Faure et al.
2011/0092515	A1	4/2011	Qiu et al.
2011/0097404	A1	4/2011	Oshlack et al.
2011/0129535	A1	6/2011	Mantelle
2011/0159100	A1	6/2011	Andersen et al.
2011/0187017	A1	8/2011	Haupts
2011/0245783	A1	10/2011	Stinchcomb et al.
2011/0262496	A1*	10/2011	Desai A61K 31/135 424/400
2012/0034171	A1	2/2012	Arkenau-Maric et al.
2012/0059065	A1	3/2012	Barnscheid et al.
2012/0065220	A1	3/2012	Barnscheid et al.
2012/0077879	A1	3/2012	Vasanthavada et al.
2012/0107250	A1	5/2012	Bartholomäus et al.
2012/0108622	A1	5/2012	Wright et al.
2012/0135071	A1	5/2012	Bartholomäus et al.
2012/0136021	A1	5/2012	Barnscheid et al.
2012/0141583	A1	6/2012	Mannion et al.
2012/0202838	A1	8/2012	Ghosh et al.
2012/0225901	A1	9/2012	Leyendecker et al.
2012/0231083	A1	9/2012	Carley et al.

2012/0251637	A1	10/2012	Bartholomäus et al.
2012/0321716	A1	12/2012	Vachon et al.
2013/0028970	A1	1/2013	Schwier et al.
2013/0090349	A1	4/2013	GeiLer et al.
2013/0129825	A1	5/2013	Billoet et al.
2013/0129826	A1	5/2013	GeiLer et al.
2013/0171075	A1	7/2013	Arkenau-Maric et al.
2013/0209557	A1	8/2013	Barnscheid
2013/0225625	A1	8/2013	Barnscheid et al.
2013/0251643	A1	9/2013	Bartholomäus et al.
2013/0289062	A1	10/2013	Kumar et al.
2013/0303623	A1	11/2013	Barnscheid et al.
2013/0330409	A1	12/2013	Mohammad
2014/0010874	A1	1/2014	Sackler
2014/0079780	A1	3/2014	Arkenau Maric et al.
2014/0080858	A1	3/2014	Bartholomäus et al.
2014/0080915	A1	3/2014	Bartholomäus et al.
2014/0094481	A1	4/2014	Fleischer et al.
2014/0112984	A1	4/2014	Arkenau-Maric et al.
2014/0112989	A1	4/2014	Bartholomäus et al.
2014/0170079	A1	6/2014	Arkenau Maric et al.
2014/0186440	A1	7/2014	Han et al.
2014/0356426	A1	12/2014	Barnscheid et al.
2014/0356428	A1	12/2014	Barnscheid et al.
2014/0378498	A1	12/2014	Devarakonda et al.
2015/0017250	A1	1/2015	Wenig et al.
2015/0030677	A1	1/2015	Adjei et al.
2015/0064250	A1	3/2015	Ghebre-Sellassie et al.
2015/0079150	A1	3/2015	Fischer et al.
2015/0118300	A1	4/2015	Haswani et al.
2015/0118302	A1	4/2015	Haswani et al.
2015/0118303	A1	4/2015	Haswani et al.
2015/0374630	A1	12/2015	Arkenau Maric et al.
2016/0175256	A1	6/2016	Bartholomäus et al.
2016/0184297	A1	6/2016	Arkenau-Maric et al.
2016/0256456	A1	9/2016	Caruso et al.
2016/0263037	A1	9/2016	Arkenau Maric et al.
2016/0361308	A1	12/2016	Bartholomäus et al.
2016/0367549	A1	12/2016	Bartholomäus et al.
2017/0027886	A1	2/2017	Bartholomäus et al.

FOREIGN PATENT DOCUMENTS

AR	049562	A1	8/2006
AR	053304	A1	5/2007
AR	054222	A1	6/2007
AR	054328	A1	6/2007
AU	769807	B2	3/2001
AU	2003237944	A1	12/2003
AU	2003274071	A1	5/2004
AU	2003278133	A1	5/2004
AU	2003279317	A1	5/2004
AU	2004264666	B2	2/2005
AU	2004264667	A1	2/2005
AU	2004308653	B2	4/2005
AU	2005259476	B2	1/2006
AU	2005259478	B2	1/2006
AU	2006210145	A1	8/2006
AU	2006210145	B2	8/2006
AU	2009207796	A1	7/2009
AU	2009243681	A1	11/2009
AU	2006311116	B2	1/2013
BR	P10413318	A	10/2006
BR	P10413361	A	10/2006
BR	P10513300	A	5/2008
BR	P10606145	A2	2/2009
CA	0722109	A	11/1965
CA	2082573	C	5/1993
CA	2577233	A1	10/1997
CA	2650637	A1	10/1997
CA	2317747	A1	7/1999
CA	2343234	A1	3/2000
CA	2352874	A1	6/2000
CA	2414349	A1	1/2002
CA	2456322	A1	2/2003
CA	2502965	A1	5/2004
CA	2503155	A1	5/2004
CA	2534925	A1	2/2005
CA	2534932	A1	2/2005

(56)

References Cited

FOREIGN PATENT DOCUMENTS

CA	2489855	A1	4/2005	DK	1658054	T3	10/2007
CA	2551231	A1	7/2005	DK	1515702	T3	1/2009
CA	2572352	A1	1/2006	EC	SP066345	A	8/2006
CA	2572491	A1	1/2006	EP	0008131	A1	2/1980
CA	2595954	A1	7/2006	EP	0043254	A1	1/1982
CA	2229650	C	8/2006	EP	0008131	B1	12/1982
CA	2594713	A1	8/2006	EP	0177893	A2	4/1986
CA	2595979	A1	8/2006	EP	0216453	A2	4/1987
CA	2625055	A1	4/2007	EP	0226061	A2	6/1987
CA	2713128	A1	7/2009	EP	0228417	A1	7/1987
CA	2723438	A1	11/2009	EP	0229652	A2	7/1987
CA	2595954	C	1/2011	EP	0232877	A2	8/1987
CH	689109	A5	10/1998	EP	0239973	A2	10/1987
CL	20162004		5/2005	EP	0240906	A2	10/1987
CL	20172004		5/2005	EP	0261616	A2	3/1988
CL	200403308		9/2005	EP	0261616	A3	3/1988
CL	200500952		11/2005	EP	0270954	A1	6/1988
CL	200501624		12/2005	EP	0277289	A1	8/1988
CL	200501625		6/2006	EP	0293066	A2	11/1988
CL	424-2013		3/2012	EP	0328775	A1	8/1989
CL	437-2013		3/2012	EP	0228417	B1	9/1990
CN	87102755	A	10/1987	EP	0229652	B1	10/1991
CN	1135175	A	11/1996	EP	0477135	A1	3/1992
CN	1473562	A	2/2004	EP	0277289	B1	4/1992
CN	1980643	A	4/2005	EP	0293066	B1	4/1993
CN	101010071	A	6/2005	EP	0270954	B1	5/1993
CN	1671475	A	9/2005	EP	0544144	A1	6/1993
CN	101022787	A	1/2006	EP	0583726	A2	2/1994
CN	1863513	A	11/2006	EP	0598606	A1	5/1994
CN	1863514	A	11/2006	EP	0636370	A1	2/1995
CN	1917862	A	2/2007	EP	0641195	A1	3/1995
CN	1942174	A	4/2007	EP	0647448	A1	4/1995
CN	101011395	A	8/2007	EP	0654263	A1	5/1995
CN	101027044	A	8/2007	EP	0661045	A1	7/1995
CN	101057849	A	10/2007	EP	0675710	A1	10/1995
CN	101484135	A	11/2007	EP	0682945	A2	11/1995
CN	101091721		12/2007	EP	0693475	A1	1/1996
CN	101111232	A	1/2008	EP	0820693	A1	1/1996
CN	101175482	A	9/2008	EP	0696598	A1	2/1996
CN	101370485	A	2/2009	EP	0216453	B1	3/1996
CN	101394839	A	3/2009	EP	0583726	B1	11/1996
CN	101652128	A	2/2010	EP	0756480	A1	2/1997
DE	2530563	A1	1/1977	EP	0760654	A1	3/1997
DE	4229085	A1	3/1994	EP	0761211	A1	3/1997
DE	4309528	A1	9/1994	EP	0780369	A1	6/1997
DE	4446470	A1	6/1996	EP	0785775	A1	7/1997
DE	69400215	T2	10/1996	EP	0809488	A1	12/1997
DE	19522899	C1	12/1996	EP	0820698	A1	1/1998
DE	2808505	A1	1/1997	EP	0820753	A2	1/1998
DE	19753534	A1	6/1999	EP	0857062	A2	8/1998
DE	19800689	C1	7/1999	EP	0864324	A1	9/1998
DE	19800698	A1	7/1999	EP	0864326	A2	9/1998
DE	19822979	A1	12/1999	EP	0598606	B1	6/1999
DE	69229881	T2	12/1999	EP	0675710	B1	8/1999
DE	19855440	A1	6/2000	EP	0980894	A1	2/2000
DE	19856147	A1	6/2000	EP	0988106	A1	3/2000
DE	19940740	A1	3/2001	EP	1014941	A1	7/2000
DE	19960494	A1	6/2001	EP	1070504	A1	1/2001
DE	10036400	A1	6/2002	EP	1127871	A1	8/2001
DE	69429710	T2	8/2002	EP	1138321	A2	10/2001
DE	10250083	A1	12/2003	EP	1152026	A1	11/2001
DE	10250084	A1	5/2004	EP	1138321	A3	1/2002
DE	10250087	A1	5/2004	EP	1166776	A2	1/2002
DE	10250088	A1	5/2004	EP	1201233	A1	5/2002
DE	10336400	A1	3/2005	EP	0661045	B1	7/2002
DE	10361596	A1	9/2005	EP	1250045	A2	10/2002
DE	102004019916	A1	11/2005	EP	1251120	A1	10/2002
DE	102004020220	A1	11/2005	EP	1293127	A2	3/2003
DE	102004032049	A1	1/2006	EP	1293195	A1	3/2003
DE	102004032051	A1	1/2006	EP	1293196	A2	3/2003
DE	102004032103	A1	1/2006	EP	1127871	B1	9/2003
DE	102005005446	A1	8/2006	EP	1201233	B1	12/2004
DE	102005005449	A1	8/2006	EP	1251120	B1	12/2004
DE	102007011485	A1	9/2008	EP	1492506	B1	1/2005
DK	1658055	T3	7/2007	EP	1166776	B1	2/2005
				EP	1502592	A1	2/2005
				EP	1658054	A1	2/2005
				EP	1658055	A1	2/2005
				EP	1515702	B1	3/2005

(56) References Cited

FOREIGN PATENT DOCUMENTS

EP	1527775	A1	4/2005	KR	20100111303	A	10/2010
EP	1558221	A1	8/2005	KR	20110016921	A	2/2011
EP	1558257	A1	8/2005	MX	2007000008	A	3/2007
EP	1560585	B1	8/2005	MX	2007000009	A	3/2007
EP	1611880	A2	1/2006	MX	2007009393	A	8/2007
EP	1658054	B1	5/2006	MX	2010008138	A	8/2010
EP	1138321	B1	1/2007	MX	2010012039	A	11/2010
EP	1740161	A2	1/2007	NO	20061054	A	3/2006
EP	1658055	B1	3/2007	NO	20070578	A	1/2007
EP	1765303	A1	3/2007	NO	20074412	A	11/2007
EP	1786403	A1	5/2007	NZ	528302	A	2/2007
EP	1558221	B1	6/2007	PT	1699440	E	12/2004
EP	1842533	A2	10/2007	PT	1658054	E	5/2006
EP	1845955	A1	10/2007	PT	1658055	E	7/2007
EP	1845956	A1	10/2007	PT	1515702	E	12/2008
EP	1859789	A1	11/2007	RU	2131244	C1	6/1999
EP	1980245	A1	10/2008	RU	2198197	C2	2/2003
EP	1897545	A1	12/2008	RU	2220715	C2	1/2004
EP	2131830	A2	12/2009	RU	2396944	C2	7/2004
EP	2246063	A1	11/2010	RU	2326654	C2	9/2005
EP	2249811	A1	11/2010	RU	2339365	C2	12/2007
EP	2273983	A1	1/2011	RU	2354357	C2	12/2007
EP	2402004	A2	1/2012	RU	2007103712	A	9/2008
ES	2336571	T3	12/2004	RU	2007103707	A	11/2008
ES	2260042	T3	11/2006	RU	2007132975	A	4/2009
ES	2285497	T3	11/2007	RU	2567723	C2	11/2015
ES	2288621	T3	1/2008	SI	1515702	T1	4/2009
ES	2289542	T3	2/2008	SI	1699440	T1	11/2009
ES	2315505	T3	4/2009	SK	10612003	A3	1/2004
GB	1147210	A	4/1969	SU	1759445	A1	9/1992
GB	1567727	A	5/1980	TW	1254634	B	5/2006
GB	2047095	A	11/1980	WO	WO 1980/000841	A1	5/1980
GB	2057878	A	4/1981	WO	WO 1989/005624	A1	6/1989
GB	2238478	A	6/1991	WO	WO 1990/003776	A1	4/1990
HR	20070456	T3	6/2007	WO	WO 1993/006723	A1	4/1993
HR	20070272	T3	11/2007	WO	WO 93/10765	A1	6/1993
JP	S36-022895		11/1961	WO	WO 1993/010758	A1	6/1993
JP	S55162714	A	12/1980	WO	WO 1993/011749	A1	6/1993
JP	S5659708	A	5/1981	WO	WO 1993/023017	A1	11/1993
JP	S56169622	A	12/1981	WO	WO 1994/006414	A1	3/1994
JP	S62240061	A	10/1987	WO	WO 1994/008567	A1	4/1994
JP	H0249719	A	2/1990	WO	WO 1995/017174	A1	6/1995
JP	03-501737	A	4/1991	WO	WO 1995/020947	A1	8/1995
JP	H0517566	A	1/1993	WO	WO 1995/022319	A1	8/1995
JP	H06507645	A	9/1994	WO	WO 1995/030422	A1	11/1995
JP	08053331	A	2/1996	WO	WO 1996/000066	A1	1/1996
JP	8-505076	A	6/1996	WO	WO 1996/003979	A1	2/1996
JP	H09508410	A	8/1997	WO	WO 1996/014058	A1	5/1996
JP	H1057450	A	3/1998	WO	WO 1997/000673	A1	1/1997
JP	2002524150	A	8/2002	WO	WO 1997/033566	A2	9/1997
JP	2002-275175	A	9/2002	WO	WO 1997/049384	A1	12/1997
JP	2003125706	A	5/2003	WO	WO 1998/035655	A3	2/1998
JP	2003526598	A	9/2003	WO	WO 1998/020073	A2	5/1998
JP	2005506965	A	3/2005	WO	WO 1998/028698	A1	7/1998
JP	2005515152	A	5/2005	WO	WO 1998/035655	A2	8/1998
JP	2005534664	A	11/2005	WO	WO 1998/051758	A1	11/1998
JP	2007501201	A	1/2007	WO	WO 1999/012864	A1	3/1999
JP	2007501202	A	1/2007	WO	WO 1999/032120	A1	7/1999
JP	2007513147	A	5/2007	WO	WO 1999/044591	A1	9/1999
JP	2007533692	A	11/2007	WO	WO 1999/045887	A2	9/1999
JP	2008024603	A	2/2008	WO	WO 1999/048481	A1	9/1999
JP	2008504327	A	2/2008	WO	WO 2000/013647	A1	3/2000
JP	2008528654	A	7/2008	WO	WO 2000/033835	A1	6/2000
JP	2009523833	A	6/2009	WO	WO 2000/040205	A2	7/2000
JP	2009531453	A	9/2009	WO	WO 2001/008661	A2	2/2001
JP	2009537456	A	10/2009	WO	WO 2001/012230	A1	2/2001
JP	2011504455	A	2/2011	WO	WO 2001/015667	A1	3/2001
JP	2011506493	A	3/2011	WO	WO 2001/052651	A2	7/2001
JP	2013536810	A	9/2013	WO	WO 2001/058451	A1	8/2001
JP	2014505736	A	3/2014	WO	WO 2001/097783	A1	12/2001
JP	2014528437	A	10/2014	WO	WO 2002/026061	A1	4/2002
KR	1020060069832	A	6/2006	WO	WO 2002/026262	A2	4/2002
KR	20070039041	A	4/2007	WO	WO 2002/026928	A1	4/2002
KR	20070111510	A	11/2007	WO	WO 2002/035991	A2	5/2002
KR	20090085312	A	8/2009	WO	WO 2002/071860	A1	9/2002
				WO	WO 2002/088217	A1	11/2002
				WO	WO 2002/094254	A2	11/2002
				WO	WO 2003/006723	A1	1/2003
				WO	WO 2003/013433	A2	2/2003

(56) References Cited

FOREIGN PATENT DOCUMENTS

WO WO 2003/013476 A1 2/2003
 WO WO 2003/013479 A1 2/2003
 WO WO 2003/013538 A1 2/2003
 WO WO 2003/015531 A2 2/2003
 WO WO 2003/018015 A1 3/2003
 WO WO 2003/024426 A1 3/2003
 WO WO 2003/024430 A1 3/2003
 WO WO 2003/026624 A1 4/2003
 WO WO 2003/026743 A2 4/2003
 WO WO 2003/028698 A1 4/2003
 WO WO 2003/028990 A1 4/2003
 WO WO 2003/031546 A1 4/2003
 WO WO 2003/035029 A1 5/2003
 WO WO 2003/035053 A1 5/2003
 WO WO 2003/035054 A1 5/2003
 WO WO 2003/035177 A2 5/2003
 WO WO 2003/039561 A1 5/2003
 WO WO 2003/049689 A2 6/2003
 WO WO 2003/053417 A2 7/2003
 WO WO 2003/068392 A1 8/2003
 WO WO 2003/070191 A1 8/2003
 WO WO 2003/092648 A1 11/2003
 WO WO 2003/094812 A1 11/2003
 WO WO 2003/105808 A1 12/2003
 WO WO 2004/004693 A1 1/2004
 WO WO 2004/043967 A1 2/2004
 WO WO 2004/026262 A2 4/2004
 WO WO 2004/026263 A2 4/2004
 WO WO 2004/026280 A2 4/2004
 WO WO 2004/037230 A1 5/2004
 WO WO 2004/037259 A1 5/2004
 WO WO 2004/037260 A1 5/2004
 WO WO 2004/066910 A2 8/2004
 WO WO 2004/078212 A1 9/2004
 WO WO 2004/084869 A1 10/2004
 WO WO 2004/093801 A2 11/2004
 WO WO 2004/093819 A2 11/2004
 WO WO 2004/098567 A2 11/2004
 WO WO 2004/100894 A2 11/2004
 WO WO 2005/016313 A1 2/2005
 WO WO 2005/016314 A1 2/2005
 WO WO 2005/032524 A2 4/2005
 WO WO 2005/041968 A2 5/2005
 WO WO 2005/053587 A1 6/2005
 WO WO 2005/053656 A1 6/2005
 WO WO 2005/055981 A2 6/2005
 WO WO 2005/060942 A1 7/2005
 WO WO 2005/063214 A1 7/2005
 WO WO 2005/065646 A2 7/2005
 WO WO 2005/066183 A1 7/2005
 WO WO 2005/079760 A1 9/2005
 WO WO 2005/102286 A1 11/2005
 WO WO 2005/102294 A2 11/2005
 WO WO 2005/102294 A3 11/2005
 WO WO 2005/105036 A1 11/2005
 WO WO 2006/002883 A1 1/2006
 WO WO 2006/002884 A1 1/2006
 WO WO 2006/002886 A1 1/2006
 WO WO 2006/002884 B1 3/2006
 WO WO 2006/039692 A2 4/2006
 WO WO 2006/058249 A2 6/2006
 WO WO 2006/082097 A1 8/2006
 WO WO 2006/082099 A1 8/2006
 WO WO 2006/105615 A1 10/2006
 WO WO 2006/128471 A2 12/2006
 WO WO 2007/005716 A2 1/2007
 WO WO 2007/008752 A2 1/2007
 WO WO 2007/014061 A2 2/2007
 WO WO 2007/048233 A1 5/2007
 WO WO 2007/053698 A2 5/2007
 WO WO 2007/085024 A2 7/2007
 WO WO 2007/085024 A3 7/2007
 WO WO 2007/103105 A2 9/2007
 WO WO 2007/103286 A2 9/2007
 WO WO 2007/112273 A2 10/2007

WO WO 2007/112285 A2 10/2007
 WO WO 2007/112286 A2 10/2007
 WO WO 2007/131357 A1 11/2007
 WO WO 2008/023261 A1 2/2008
 WO WO 2008/033523 A1 3/2008
 WO WO 2008/069941 A2 6/2008
 WO WO 2008/086804 A2 7/2008
 WO WO 2008/107149 A2 9/2008
 WO WO 2008/107149 A3 9/2008
 WO WO 2008/109462 A2 9/2008
 WO WO 2008/132707 A1 11/2008
 WO WO 2008/142627 A2 11/2008
 WO WO 2008/148798 A2 12/2008
 WO WO 2009/005803 A1 1/2009
 WO WO 2009/014534 A1 1/2009
 WO WO 2009/034541 A2 3/2009
 WO WO 2009/034541 A3 3/2009
 WO WO 2009/034541 A9 3/2009
 WO WO 2009/035474 A1 3/2009
 WO WO 2009/051819 A1 4/2009
 WO WO 2009/076764 A1 6/2009
 WO WO 2009/092601 A1 7/2009
 WO WO 2009/110005 A2 9/2009
 WO WO 2009/112273 A2 9/2009
 WO WO 2009/135680 A1 11/2009
 WO WO 2010/022193 A2 2/2010
 WO WO 2010/044842 A1 4/2010
 WO WO 2010/057036 A2 5/2010
 WO WO 2010/066034 A1 6/2010
 WO WO 2010/069050 A1 6/2010
 WO WO 2010/083843 A1 7/2010
 WO WO 2010/083894 A1 7/2010
 WO WO 2010/088911 A1 8/2010
 WO WO 2010/105672 A1 9/2010
 WO WO 2010/140007 A2 12/2010
 WO WO 2010/140007 A9 12/2010
 WO WO 2010/149169 A2 12/2010
 WO WO 2011/008298 A2 1/2011
 WO WO 2011/009602 A1 1/2011
 WO WO 2011/009603 A1 1/2011
 WO WO 2011/009604 A1 1/2011
 WO WO 2011/095314 A2 8/2011
 WO WO 2011/095314 A3 8/2011
 WO WO 2011/128630 A2 10/2011
 WO WO 2011/154414 A1 12/2011
 WO WO 2012/028317 A1 3/2012
 WO WO 2012/028318 A1 3/2012
 WO WO 2012/028319 A1 3/2012
 WO WO 2012/061779 A1 5/2012
 WO WO 2012/076907 A2 6/2012
 WO WO 2012/119727 A1 9/2012
 WO WO 2012/166474 A1 12/2012
 WO WO 2013/003845 A1 1/2013
 WO WO 2013/017234 A1 2/2013
 WO WO 2013/017242 A1 2/2013
 WO WO 2013/030177 A1 3/2013
 WO WO 2013/050539 A2 4/2013
 WO WO 2013/072395 A1 5/2013
 WO WO 2013/084059 A1 6/2013
 WO WO 2013/127830 A1 9/2013
 WO WO 2013/127831 A1 9/2013
 WO WO 2013/128276 A2 9/2013
 WO WO 2013/156453 A1 10/2013
 WO WO 2013/167735 A1 11/2013
 WO WO 2014/059512 A1 4/2014
 WO WO 2014/190440 A1 12/2014
 WO WO 2014/191396 A1 12/2014
 WO WO 2014/191397 A1 12/2014
 WO WO 2015/004245 A1 1/2015
 WO WO 2015/103379 A1 7/2015

OTHER PUBLICATIONS

Almeida, A. et al., Ethylene vinyl acetate as matrix for oral sustained release dosage forms produced via hot-melt extrusion, European Journal of Pharmaceutics and Biopharmaceutics 77 (2011) 297-305.

(56)

References Cited

OTHER PUBLICATIONS

- Almeida, A. et al., Sustained release from hot-melt extruded matrices based on ethylene vinyl acetate and polyethylene oxide, *European Journal of Pharmaceutics and Biopharmaceutics* 82 (2012) 526-533.
- Andre et al., "O-Demethylation of Opioid Derivatives With Methane Sulfonic Acid/Methoinine: Application to the Synthesis of Naloxone and Analogues" *Synthetic Comm.* 22(16), pp. 2313-2327, 1992.
- Apicella A. et al., *Biomaterials*, vol. 14, No. 2, pp. 83-90, 1993.
- Application of a modelling system in the formulation of extended release hydrophilic matrices, Reprinted from *Pharmaceutical Technology Europe*, Jul. 2006.
- Application of Opadry II, complete film coating system, on mefformin HCl extended release matrices containing Polyox water soluble resin, *Colorcon* Apr. 2009.
- Arnold C., "Teen Abuse of Painkiller OxyContin on the Rise," www.npr.org, Dec. 19, 2005.
- Augustine, R.L., Catalytic Hydrogenation of a, B-Unsaturated Ketones. III The Effect of Quantity and Type of Catalysts, *J. Org. Chem.* 28(1), pp. 152-155, Abstract 1963.
- Avis, Kenneth, *Parenteral Preparations*. Chapter 85. pp. 1518-1541 In Remington's *Pharmaceutical Sciences*, 17th Ed, 1985.
- Bailey, F.E., et al., "Some properties of polyethylene oxide) in aqueous solution," *Journal of Applied Polymer Science*, vol. 1, Issue No. 1, pp. 56-62, 1959.
- Bauer et al. *Lehrbuch der Pharmazeutischen Technologie*. Eight Edition 2006. Stuttgart, pp. 343-352.
- Bauer et al. *Lehrbuch der Pharmazeutischen Technologie*. Sixth Edition 1999. Stuttgart, pp. IX-XV, Table of contents. (Full English translation attached).
- Bauer, Kurt H., et al., *Coated Pharmaceutical Dosage Forms—Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials*, 1st edition, 1998, CRC Press, Medpharm Scientific Publishers. (Preface, Table of Content, List of Abbreviations, Explanation of Terms only).
- Baum et al., "The impact of the addition of naloxone on the use and abuse of pentazocine", *Public Health Reports*, Jul.-Aug. 1987, vol. 102, No. 4, p. 426-429.
- Bingwen et al, 2008, p. 367. (full translation attached).
- Block, Lawrence. *Medicated Applications*. Chapter 88. In Remington's *Pharmaceutical Sciences*, 17th Ed, 1985.
- Borquist et al., "Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments," *J. Controlled Release*, 97: 453-465 (2004).
- Braun, et al. A study of Bite Force. Part 2: Relationship to Various cephalometric Measurements. *Angel Orthodontist*, vol. 65 (5) pp. 373-377, 1995.
- Brown, The Dissolution Procedure: Development and Validation, heading "Study Design", "Time Points" US Pharmacopoeia (USP), vol. 31(5), General Chapter 1092, pp. 1-15, 2006.
- Bruce et al, Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid, *European Journal of Pharmaceutics and Biopharmaceutics*, 59 (2005) 85-97.
- Caraballo, *Journal of Controlled Release*, vol. 69, pp. 345-355, 2000.
- Carbopol 71G, retrieved Mar. 10, 2014 from <http://www.lubrizol.com/LifeScience/Products/Carbopol71G-NF.html>.
- Cawello, "Parameters for Compartment-free Pharmacokinetics—Standardization of Study Design, Data Analysis and Reporting" 1999, pp. XI-XIII (table of contents).
- Chibuzor et al. "Formulation Development and Evaluation of Drug Release Kinetics from Colon-Targeted Ibuprofen Tablets Based on Eudragit RL 100-Chitosan Interpolyelectrolyte Complexes," *Hindawi Publ. Corporation ISRN Pharmaceutics*, vol. 2013, Article ID 838403.
- Committee for Proprietary Medicinal Products. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. 2001. pp. 1-18.
- Coppens et al., "Hypromellose, Ethylcellulose, and Polyethylene Oxide Use in Hot Melt Extrusion"; *Pharmaceutical Technology*, 62-70, Jan. 2005.
- Cornish, P. "Avoid the Crush": hazards of medication administration in patients with dysphagia ora feeding tube, *CMA Media Inc., CMAJ*. 172(7), pp. 871-872, 2005.
- Costa et al. "Modeling and comparison of dissolution profiles"; *European Journal of Pharmaceutical Sciences* 13 (2001) 123-33.
- Crowley M.M. et al., "Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion," *Biomaterials* 23, 2002, pp. 4241-4248.
- Crowley MM, *Drug Dev Ind Pharm.* Sep. 2007; 33(9):909-26. (Abstract only).
- Cuesov, 1999, pp. 351-352.
- Dachille et al., "High-pressure Phase Transformations in Laboratory Mechanical Mixers and Mortars", *Nature*, vol. 186, Apr. 2, 1960, pp. 34 and 71.
- Dachille, F. et al., "High-Pressure Phase Transformation in Laboratory Mechanical Mixers and Mortars", 1960., *Nature*, vol. 186, pp. 1-2 (abstract).
- Davies, et al; *European Journal of Pharmaceutics and Biopharmaceutics*, 67, 2007, pp. 268-276.
- Dean, D.A., E.R. Evans, I.H. Hall, *Pharmaceutical Packaging Technology*, Taylor & Francis, 1st Edition, Nov. 30, 2000 (Publisher description dated Oct. 22, 2010).
- Deighan, C.J. et al., Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse, *Q.J. Med.* vol. 93, 2000, pp. 29-33.
- DeJong (*Pharmaceutisch Weekblad Scientific Edition*) 1987, p. 24-28.
- Dezheimer, *Terahertz Spectroscopy: Principles and Applications* (Optical Science and Engineering Series), CRC; 1 edition 2007. (Table of content only).
- Dierickx et al., "Co-extrusion as manufacturing technique for fixed-dose combination mini-matrices," *European Journal of Pharmaceutics and Biopharmaceutics* 81 (2012), 683-689.
- Disanto, Anthony. Bioavailability and Bioequivalency Testing. Chapter 77. In Remington's *Pharmaceutical Sciences*, 17th Ed, 1985.
- Dow Chemical Company, "Using Dow Excipients for Controlled Release of Drugs in Hydrophilic Matrix Systems", Sep. 2006, pp. 1-36.
- Dow Excipients Chem. of Poly. Water Soluble-Resin 2004, pp. 1-2.
- Dow Technical Data, POLYOX WSR Solid Dosage Formulation via Melt Extrusion, Feb. 2003, pp. 1-3.
- Efentakis M et al. "Evaluation of High Molecular Weight Poly(Oxyethylene) (Polyox) Polymer: Studies of Flow Properties and Release Rates of Furosemide and Captopril from controlled-Release hard Gelatin Capsules", *Pharmaceutical Development and Technology*, 5 (3), pp. 339-346, 2000.
- Eggleston, "The seat of the emetic action of various drugs," *J. Pharmacol. Exp. Ther.* 7, 225-253 (1915).
- El-Egaakey, Adel et al, "Hot extruded dosage forms Part I Technology and dissolution kinetics of polymeric matrices" *Pharmaceutica Acta Helvetica*, vol. 46, pp. 31-53, Mar. 19, 1970.
- El-Sherbiny I.M. et al "Preparation, characterization, swelling and in vitro drug release behaviour of poly[N-acryloylglycine-chitosan] interpolymeric pH and thermally-responsive hydrogels", *European Polymer Journal*, vol. 41, pp. 2584-2591, 2005.
- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 1, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.
- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 2, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.
- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 3, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.
- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 4, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.
- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 5, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.

(56)

References Cited

OTHER PUBLICATIONS

- Encyclopedia of Pharmaceutical Technology, Third Edition, vol. 6, edited by James Swarbrick PharmaceuTech, Inc., Pinehurst, North Carolina, USA (Table of Contents only), Oct. 25, 2006.
- Encyclopedia of Pharmacological Technology, Informa Healthcare, 1st Ed., 1996, vol. 14 (Table of Content only).
- Erskine, Jr., Clyde. Quality Assurance and Control. Chapter 83. pp. 1487-1491 In Remington's Pharmaceutical Sciences, 17th Ed, 1985.
- Eudragit NE40D web page from Evonik website; downloaded Feb. 24, 2015.
- Eudragit RS PO web page from Evonik website; downloaded Feb. 24, 2015.
- European Pharmacopeia 5.0; Glyceryl behenate monograph; dated Jan. 2005; downloaded Feb. 24, 2015.
- European Pharmacopoeia 2.9.40 "Uniformity of Dosage Units", 2006, pp. 3370-3373.
- European Pharmacopoeia 5.0, 2.9.8 "Resistance to Crushing of Tablets", 2005, p. 235.
- European Pharmacopoeia, Third Edition Supplement 2000, Council of Europe, Strasbourg, 2000, pp. 85-107.
- European Pharmacopoeia, Third Edition, Council of Europe, Strasbourg, 1997, pp. 127-152.
- European Search Report and Opinion Application No. 12002708. 1-1219, dated Sep. 24, 2012.
- European Search Report and Opinion Application No. 14176277. 3-1460, dated Dec. 15, 2014.
- European Search Report and Opinion, Application No. 11006253. 6-2112, dated Dec. 16, 2011.
- European Search Report and Opinion, Application No. 11006254. 4-2112, dated Dec. 16, 2011.
- European Search Report and Opinion, Application No. 11008131. 2-1219, dated Feb. 24, 2012.
- European Search Report and Opinion, Application No. 11009129. 5-2112, dated Apr. 10, 2012.
- European Search Report and Opinion, Application No. 12001296. 8-1219, dated Jun. 26, 2012.
- European Search Report and Opinion, Application No. 12001301. 6-1219, dated Jun. 26, 2012.
- European Search Report and Opinion, Application No. 12003743. 7-1219, dated Sep. 24, 2012.
- European Search Report and Written Opinion for EP Application No. 13169658.5, dated Aug. 6, 2013.
- European Search Report and Written Opinion for EP Application No. 13169659.3, dated Aug. 6, 2013.
- European Search Report and Written Opinion for EP Application No. 13176309.9-1460, dated Oct. 9, 2013.
- European Search Report and Written Opinion for EP Application No. 13197503.9-1460, dated Feb. 18, 2014.
- European Search Report and Written Opinion for EP Application No. 13425151.1-1460, dated Mar. 11, 2014.
- European Search Report and Written Opinion for EP Application No. 14169801.9-1455 dated Oct. 20, 2014.
- Evaluation of Verapamil HCl (240 mg) Extended Release Matrix Formulation Using USP Apparatus III in Biorelevant Dissolution Media, Jul. 2009.
- Evonik Industries, Eudragit Application Guidelines, 10th Edition, 2008, (Table of Contents only).
- Evonik Rohm GmbH product brochure: EUDRAGIT acrylic polymers for solid oral dosage forms (2009).
- Extended European Search Report and Opinion for Application No. EP 15153679.4-1455, dated Jun. 30, 2015.
- Extended European Search Report and Opinion for Application No. EP 15165064.5-1455, dated Oct. 16, 2015.
- Extended European Search Report and Opinion for Application No. EP 15165065.2-1455, dated Nov. 2, 2015.
- Extended European Search Report and Opinion for Application No. EP 15165067.8-1455, dated Nov. 2, 2015.
- Extended European Search Report and Opinion for Application No. EP 15165069.4-1455, dated Nov. 2, 2015.
- Extended European Search Report and Opinion for Application No. EP 15165070.2-1455, dated Nov. 2, 2015.
- Extended European Search Report and Opinion for Application No. EP 15184634.2-1455, dated Mar. 3, 2016.
- Fell J.T., et al., "Determination of Tablet Strength by the Diametral-Compression Test" Journal of Pharmaceutical Sciences, vol. 59, No. 5, May 1970, pp. 688-691.
- Follonier N. et al., "Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs," Drug Development and Industrial Pharmacy, 20(8), pp. 1323-1339, 1994.
- Follonier, N. et al., "Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials" Journal of Controlled Release 36, pp. 243-250, 1995.
- Formulation of Polyox ER Matrices for a Highly Soluble Active, Colorcon Jul. 2009.
- Foye, W., Principles of Medicinal Chemistry; Analgesics pp. 241-242, at 241 (1989).
- Foye, W., Principles of Medicinal Chemistry; Structural Features and Pharmacologic Activity, pp. 63-66 at 65 (1989).
- Freed et al., "pH Control of Nucleophilic/electrophilic oxidation", International Journal of Pharmaceutics, vol. 357, pp. 180-188 (2008).
- Giles R. et al. Plastic Packaging Materials. Chapter 81. pp. 1473-1477 In Remington's Pharmaceutical Sciences, 17th Ed, 1985.
- Goodman and Gilman, "The Pharmacological Basis of Therapeutics, Seventh Edition", MacMillan Publishing Company, Table of Contents. 1985.
- Goodman and Gilman, 1985, 7th edition, chapter 22, 491-530.
- Goodman and Gilman, 1985, 7th edition, chapter 23, 533-579.
- Graham N. B., Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, p. 263-291 Chapter 17, 1992.
- Griffin W., "Classification of Surface-Active Agents by HLB" Journal of the Society of Cosmetic Chemists, Atlas Powder Company, 1949, pp. 311-326.
- Griffith, et al. "Tablet Crushing and the Law: The Implications for Nursing" Professional Nurse 19(1), pp. 41-42, 2003.
- Gryczke et al., "Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion", Colloids and surfaces., B, Biointerfaces, Elsevier, Amsterdam, NL, vol. 86, No. 2, Apr. 5, 2011, pp. 275-284.
- Guidance for Industry—Bioavailability and Bioequivalence—Studies for Orally Administered Drug Products—General Considerations, FDA, BP, Announced in the Federal Register: vol. 68, No. 53/Mar. 19, 2003.
- Guidance for Industry—Statistical Approaches to Establishing Bioequivalence, FDA, BP, Jan. 2001.
- Handbook of Pharmaceutical Excipients, 1986, American Pharmaceutical Association, Washington, DC and London (Table of Content Only).
- Handbuch der Kunststoff-Extrusionstechnik 1, "Grundlagen" in Chapter 1.2 "Klassifizierung von Extrudern", pp. 3-7. 1989. (Full english translation attached).
- Hanning C.D. et al. "The Morphine Hydrogel Suppository. A New Sustained release Rectal Preparation", British Journal of Anaesthesia, 61, pp. 221-227, 1988.
- Hartauer, Kerry J. "Influence of Peroxide Impurities in Povidone and Crospovidone on the Stability of Raloxife" Pharma. Dev. & Tech, 5 (3) 303-310 (2000).
- Henriest D. et al. In vitro and in vivo evaluation of starch-based hot stage extruded double matrix systems. Journal of Controlled Release. 2001, vol. 75, pp. 391-400.
- Hoepfner et al. Fiedler Encyclopedia of Excipients. Sixth Edition, 2007, Aulendorf, Germany; Table of Contents only.
- Hong S. et al. Dissolution kinetics and physical characterization of three-layered tablet with poly(ethylene oxide) core matrix capped by Carbopol. Int. J. Pharmacol. 2008, vol. 356, pp. 121-129.
- Inert gas—Wikipedia, Dec. 2009, pp. 1-3.
- Investigation of a Directly Compressible Metformin HCl 500mg Extended Release Formulation Based on Hypromellose, Colorcon Jul. 2009.

(56)

References Cited

OTHER PUBLICATIONS

- James, A. "The legal and clinical implications of crushing tablet medication", *Nurse Times* 100(50), 28-33, 2004.
- Janicki S. et al. "Slow-Release Microballs: Method of Preparation", *Acta Pharm. Technol.* 33 (3) 154-155, 1987.
- Jannetto, P. et al., "Oxycodone: Recognition and Pharmacogenomics," *Toxicology News*, Mar. 2003, 1-7.
- Kalant H. et al., *Death in Amphetamine Users: Causes and Rates*, *CMA Journal*, vol. 112 (Feb. 8, 1975): 299-304.
- Katz N. et al. "Challenges in the development of prescription opioid abuse-deterrent formulations", *Clin. J. Pain*, 23(8): 648-660 (Oct. 2007).
- Kim C.-J. "Drug Release from Compressed Hydrophilic Polyox-WSR Tablets" *J Pharm. Sciences* 1995, 84(3): pp. 303-306.
- Kim N et al. "Preparation and Evaluation of Eudragit Gels. V. Rectal Gel Preparations for Sustained Release and Avoidance of First-Pass Metabolism of Lidocaine", *Chem. Pharm Bull.* 1992, 40(10), 2800-2804.
- King et al. *Oral Solid Dosage Forms*. Chapter 90. pp. 163-1632 In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- King, R., "Tablets, Capsules, and Pills" *Remington's Pharmaceutical Sciences*, pp. 1553-1593, Ch. 89, 1980, 16th Edition.
- King, *Remington's Pharmaceutical Sciences* 17th ed., Chapter 78, p. 1418 (1985).
- Knevel, Adelbert. *Separation*. Chapter 78. pp. 1432-1442 In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Kolter, K., "Compression Behaviour of Kollidon SR," *APV/ APGI* 2002, Florence, Apr. 11, 2002.
- Kondrat, T., "Technology dosage forms" *Moscow* 1991, p. 96.
- Lee, Y.-S. et al., *Principles of Terahertz Science and Technology (Lecture Notes in Physics)*, Springer; 1 edition 2008. (Table of Contents Only).
- Lenindzer, A., "The molecular basis of the structure and functions of cells" *Moscow* 1974, p. 68.
- Levina et al., "The Effect of Ultrasonic Vibration on the Compaction Characteristics of Ibuprofen" *Drug Development and Industrial Pharmacy*, vol. 28, No. 5, pp. 495-514, 2002.
- Levina M. et al "The Effect of Ultrasonic Vibration on the Compaction Characteristics of Paracetamol", *Journal of Pharmaceutical Sciences*, vol. 89, No. 6, pp. 705-723, Jun. 2000.
- Li et al, "Characterization of Poly(Ethylene Oxide) as a Drug Carrier in Hot-Melt Extrusion", *Drug Development and Industrial Pharmacy*, vol. 32, No. 8, Jan. 1, 2006, pp. 991-1002.
- Lieberman, Herbert A., *Pharmaceutical Dosage Forms, Tablets*, Second Edition, Revised and Expanded, 1990. Volume 2 (Cover and Table of Content only).
- Lintner, Carl. *Stability of Pharmaceutical Products*. Chapter 82. pp. 1478-1486 In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Liu J. et al., "Properties of Lipophilic Matrix Tablets Containing Phenylpropanolamine Hydrochloride Prepared by Hot-Melt Extrusion", *EJPB*, 52 (2001), pp. 181-190.
- Lockhart H. et al, "Packaging of Pharmaceuticals and Health Care Products"; Blackie Academic & Professional; First Edition 1996. (Table of contents only).
- Longer et al. *Sustained-Release Drug Delivery Systems*. Chapter 92. pp. 1611-1661 in *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Madorsky S.L. "Thermal degradation of Polyethylene Oxide and Polypropylene Oxide", *Journal of Polymer Science*, pp. 183-194 vol. 36, No. 3, Mar. 1959.
- Maggi et al., "Dissolution behavior of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study" *Biomaterials*, 2002, 23, 1113-1119.
- Maggi L. et al, "High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage form", 2000, *International Journal of Pharmaceutics*, 195 pp. 229-238.
- Maggi, C. *Therapeutic Potential of Capsaicin-like Molecules*. *Life Sciences*, vol. 51, pp. 1777-1781, 1992.
- Mank R. et al., "Darstellung wirkstoffhaltiger Extrusionsformlinge auf der Basis von Thermoplasten. Teil 1: Untersuchung zur Wirkstoffliberation" *Pharmazie* 44, H. 11, pp. 773-776, 1989. English language translation of relevant paragraph provided.
- Mank R., "Darstellung wirkstoffhaltiger Extrusionsformlinge auf der Basis von Thermoplasten. Teil 2: Untersuchungen zur Optimierung der Wirkstofffreigabe" *Pharmazie* 45, H. 8, pp. 592-593 1990. English language translation of relevant paragraph provided.
- Marques, *Tablet breaking force*, 2008.
- Matos, Dr. Rick, Ph.D—Letter Jan. 6, 2011.
- McGary, C.W., Jr. "Degradation of Poly(ethylene Oxide)", *Journal of Polymer Science* vol. XLVI, 1960, pp. 51-57.
- McGinity et al., *Hot-Melt Extrusion as a Pharmaceutical Process*, *American Pharmaceutical Review*, vol. 4 (2), pp. 25-36, 2001.
- McGinity, J.W.—Letter of Jan. 26, 2009, pp. 1-4.
- McNeill M. et al. Properties controlling the diffusion and release of water-soluble solutes from poly(ethylene oxide) hydrogels. 4. Extended constant rate release from partly-coated spheres. *Journal Biomater. Sci. Polymer. Ed.* 1996, vol. 7, pp. 953-963.
- Mesiha M.S. et al "A Screening Study of Lubricants in Wet Powder Passes Suitable for extrusion-spheronization", *Drug Development and Industrial Pharmacy*, 19(8), pp. 943-959, 1993.
- Metformin Hydrochloride 1000 mg Extended Release Tablets, *Lubrizol Advanced Materials, Inc.*, Nov. 20, 2009, Previous Edition Dec. 19, 2008.
- Metformin Hydrochloride 750 mg Extended Release Tablets, *Lubrizol Advanced Materials, Inc.*, Sep. 2010.
- Miles, R.E. et al., *Terahertz Frequency Detection and Identification of Materials and Objects (NATO Science for Peace and Security Series B: Physics and Biophysics)*, Springer; 1 edition 2007. (Table of contents).
- Miller "To crush or not to crush? What to consider before giving medications to a patient with a tube or who has trouble swallowing", *Nursing*, pp. 50-52, Feb. 2000.
- Mises à jour cumulatives, *Vidal*, Jan./Oct. 2002 (full translation attached).
- Mitchell, "Oral Dosage Forms That Should Not Be Crushed: 2000 Update" *Hospital Pharmacy* 35(5), 553-557, 2000.
- Monolithic: retrieved from internet: <http://meriam-webster.com/dictionary/monolithic>. Retrieved on Sep. 2, 2015.
- Moorman-Li, R. et al, "A Review of Abuse-Deterrent Opioids for Chronic Nonmalignant Pain." *Pharmacy and Therapeutics*, vol. 37 No. 7, Jul. 2012, pp. 412-421.
- Morissette et al. *Advanced Drug Delivery Review* 26 (2004), 275-300.
- Moroni A. et al, "Application of Poly(Oxyethylene) Homopolymers in Sustained release Solid Formulations" *Drug Development and Industrial Pharmacy*, 21(12) pp. 1411-1428, 1995.
- Mullins, John. *Ophthalmic Preparations*. Chapter 87. pp. 1553-1563; In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Munjal M. et al., "Polymeric Systems for Amorphous Delta⁹—Tetrahydrocannabinol Produced by a Hot-Melt Method. Part II: Effect of Oxidation Mechanisms and Chemical Interactions on Stability" *Journal of Pharmaceutical Sciences* vol. 95 No. 11, Wiley InterScience, 2006, pp. 2473-2485.
- Munsell Color Company, "The Munsell Book of Color: Glossy Collection", X-Rite, Originally published in 1966, pp. 1-7.
- Nairn, J.G., *Solutions, Emulsion, Suspensions and Extractives*. Chapter 84. pp. 1492-1517, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Note for Guidance on Stability Testing, *EMA*, Aug. 2003, pp. 1-20.
- Note for Guidance on the Investigation of Bioavailability and Bioequivalence, *EMA*, London, Jul. 26, 2001 (CPMP/EWP/QWP/1401/98).
- Ohnishi N. et al., Effect of the Molecular Weight of Polyethylene Glycol on the Bioavailability of Indomethacin Sustained-Release suppositories Prepared with Solid Dispersion, *Chem. Pharm. Bull.* 35(8), pp. 3511-3515, 1987.
- Oliveira et al., "Production and characterization of laminar coextrudates at room temperature in the absence of solvents," *AAPS Annual Meeting and Exposition*, Oct. 14-18, 2012, Chicago, USA.

(56)

References Cited

OTHER PUBLICATIONS

- Oxicotin: Balancing Risks and Benefits, United States Senate, Hearing, Feb. 12, 2002.
- Oxycodon (Oxygesic): Missbrauch, Abhängigkeit und tödliche Folgen durch Injection zerstoßener Retardtabletten, Deutsches Ärzteblatt, vol. 36, A2326-A2326, Sep. 5, 2003.
- Ozeki T. et al. "Control of Medicine Release From Solid Dispersion Through Poly(ethylene oxide)-Carboxyvinylpolymer Interaction", *International Journal of Pharmaceutics*, 165, 1998, pp. 239-244.
- Ozeki T. et al. "Controlled Release From Solid Dispersion Composed of Poly(ethylene oxide)—Carbopol Interpolymer Complex With Various Cross-Linking Degrees of Carbopol", *Journal of Controlled Release*, 63, 2000, pp. 287-295.
- Ozeki T. et al., "Control of medicine release from solid dispersion composed of the poly(ethylene oxide)-carboxyvinylpolymer interpolymer complex by varying molecular weight of poly(ethylene oxide)" *Journal of Controlled Release* 58, pp. 87-95, 1999.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2009/003290 dated Jul. 9, 2009.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2010/004459 dated Dec. 1, 2010.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2013/053894 dated Mar. 22, 2013.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2013/057851 dated Jun. 12, 2013.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2013/059728 dated Aug. 6, 2013.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2014/064830 dated Aug. 6, 2014.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2014/075618 dated Feb. 11, 2015.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2014/0777748 dated Feb. 12, 2015.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2015/060377 dated Jul. 23, 2015.
- PCT International Search Report and Written Opinion for PCT Application No. PCT/EP2015/061343 dated Jul. 21, 2015.
- PCT Second Written Opinion for PCT Application No. PCT/EP2013/053893 dated Feb. 21, 2014.
- PCT Second Written Opinion for PCT Application No. PCT/EP2013/057851 dated Apr. 15, 2014.
- Pentoxifylline 400 mg Extended Release Tablets, Lubrizol Advanced Materials, Inc., Mar. 3, 2011, Previous Edition Nov. 19, 2009.
- Perez-Marcos, B., Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices, *International Journal of Pharmaceutics*, 67 (1991) 113-121.
- Pharm. Research, Official Journal of the American Association of Pharmaceutical Scientists, Oct. 1991, 8(10), S-192.
- Pharm. Research, Official Journal of the American Association of Pharmaceutical Scientists, Sep. 1989, 6(9), S-98.
- Phillips, G. Briggs. Sterilization. Chapter 79. pp. 1443-1454, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Physico-mechanical Characterization of Polyox for Table Manufacture, Colorcon Jul. 2009.
- Pillay V. et al. A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. *Journal of Controlled Release*, 2000, vol. 67, pp. 67-78.
- Pinto, Joao F. et al., "Evaluation of the Potential Use of Poly(ethylene oxide) as Tablet- and Extrudate-Forming Material," *AAPS PharmSci*, 2004; 6 (2), Article 15, pp. 1-10, (<http://www.aapspharmsci.org>).
- Piringer, O.G. and A.L. Baner, Plastic Packaging: Interactions with Food and Pharmaceuticals, Wiley VCH, 2nd Completely Revised Edition, Feb. 13, 2008. (Table of Contents only).
- Polyox water soluble resins 2003. <http://www.dow.com/webapps/lit/litorder.asp?filepath=polyox/pdfs/noreg/326-00002.pdf>.
- Polyox water-soluble resins (Dow Mar. 2002); see http://msds-search.dow.com/PublishedLiteratureDOWCOM/dh_0031/0901b80380031a4a.pdf?filepath=/326-00001.pdf&fromPage=GetDoc.
- Polyox WSR-303, retrieved Mar. 10, 2014 from URL http://www.dow.com/dowwolff/en/industrial_solutions/polymers/polyethylene.
- Polyox, Colorcon, Application Data (Apr. 2009) downloaded from http://www.colorcon.com/literature/marketing/mr/Extended%20Release/POLYOX/English/ads_PEO_Antioxidant.pdf.
- Pontier, C. et al, "Use of cycles of compression to characterize the behavior of apatitic phosphate powders," *Journal of the European Ceramic Society* 22 (2002), 1205-1216.
- Porter, S. Coating of Pharmaceutical Dosage Forms. Chapter 91. pp. 1633-1643 In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Prapaitrakul W. et al, "Release of Chlorpheniramine Maleate from Fatty Acid Ester Matrix disks Prepared by Melt-extrusion" *J. Pharm. Pharmacol.* 43, pp. 377-381, 1991.
- Proeschel, P.A. et al., "Task-dependence of activity / bite-force Relations and its impact on estimation of chewing force from EMG"; *J. Dent. Res.*, vol. 81, No. 7, pp. 464-468, 2002.
- Purdue News, "Purdue Pharma Provides Update on Development of New Abuse-Resistant Pain medications; FDA Cites Patient Needs as First Priority; New Drug Application Delayed," www.headaches.about.com, Jun. 18, 2002, pp. 1-6.
- Quintavalle et al., "Preparation of sustained release co-extrudates by hot-melt extrusion and mathematical modelling of in vitro/in vivo drug release profiles," *European Journal of Pharmaceutical Sciences* 33 (2008), 282-293.
- Radko S. et al., *Applied and Theoretical Electrophoresis* 5, pp. 79-88, 1995.
- Ravin, L. Preformulation. Chapter 76, pp. 1409-1423, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Remington, The Science and Practice of Pharmacy, 19th ed., vol. II, p. 1457 (1995) (providing a table of FDA-approved commercially marketed salts).
- Repka M. et al., Bioadhesive Properties of Hydroxypropylcellulose Topical Films Produced by Hot-Melt Extrusion, *Journal of Controlled Release*, 70 (2001), pp. 341-351.
- Repka Ma, *Drug Dev Ind Pharm.* Oct. 2007; 33(10):1043. (Abstract).
- Rippi M. et al., The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets, *Eur J Pharm Biopharm.* vol. 46, 1998, pp. 339-345.
- Rippie E.G. et al, "Regulation of Dissolution Rate by Pellet Geometry" *Journal of Pharmaceutical Sciences*, Vol. 58, No. 4, pp. 428-431, Apr. 1969.
- Rippie, E. Powders. Chapter 89, pp. 1585-1602, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Ritschel et al. Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung. 2nd Edition, 2002, Ch 6, pp. 515-519. (Full English translation attached).
- Ritschel et al. Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung. 2nd Edition, 2002, Ch 6, pp. 69-82 and 115-136.
- Ritschel et al. Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung. 2nd Edition, 2002, Table of content.
- Rosiaux et al. "Ethanol-resistant ethylcellulose/guar gum coatings—Importance for formulation parameters" *European Journal of Pharmaceutics and Bioharmaceutics*, vol. 85, No. 3, (Jul. 25, 2013), pp. 1250-1258.
- Rowe C et al. Handbook of Pharmaceutical Excipients. Sixth Edition. 2009, Edition Cantor Verlag Aulendorf, pp. V-IX, Table of Contents.
- Rowe C et al., Handbook of Pharmaceutical Excipients, 7th Edition, 2012, Table of Contents.
- Saleem et al. "Formulation and Evaluation of Tramadol hydrochloride Rectal Suppositories," *Indian J. Pharm Sci.* Sep.-Oct. 2008; 70(5), 640-644.

(56)

References Cited

OTHER PUBLICATIONS

- Salomies et al., "Determination of Oxycodone Hydrochloride in Oral Solutions by High-Performance Thin-Layer Chromatography/Densitometry," *Journal of AOAC International*, 83: 1497-1501 (2000).
- Satish et al. "Formulation and Characterization of Matrix and Triple Layer Matrix Tablets for Controlled Delivery of Tramadol Hydrochloride," *International Journal of Pharmaceutical Sciences*; 5(4) (2013) 458-464.
- Sax et al., *Hawley's Condensed Chemical Dictionary*, 11th ed., 1987, p. 1233, definition of "wax".
- Scheirs J., et al. "Characterizing the Solid-State Thermal Oxidation of Poly (ethylene oxide) Powder", pp. 2014-2019, *Polymer*, vol. 32, No. 11, 1991.
- Schier et al. "Fatality from Administration of Labetalol and Crushed Extended-Release Nifedipine" *The Annals of Pharmacotherapy* vol. 37, 1420-1423, Oct. 2003.
- Schroeder J., et al. *Granulierung hydrophober Wirkstoffe im Planetwalzenextruder*, *Pharm. Ind.* 2003, vol. 65, No. 4, 367-372. (Full English translation attached).
- Sciarra et al. *Aerosols*. Chapter 93., pp. 1662-1677, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Search result conducted on <http://www.unitconversion.org/force/new-tons-to-kiloponds-convesion.html>, on Jul. 5, 2011 (Conversion of 18.8 kiloponds to newtons).
- Shivanand P. et al., "Factors Affecting Release of KCl From Melt extruded Polyethylene Disks", *Pharmaceutical Research*, Oct. 1991, vol. 8, No. 10, p. S-192.
- Sidhu et al., "Watch for nonpsychotropics causing psychiatric side effects," *Current Psychiatry*, vol. 7, No. 4, 2008, 61-74.
- Siegel, P. *Tonicity, Osmolality, and Osmolarity*. Chapter 80. pp. 1454-1472 In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- Silver, J. "Painkiller OxyContin most commonly abused prescription drug on the streets of Western Pennsylvania", *Pittsburg Post-Gazette*, Apr. 8, 2001.
- Spassov et al., *Stereochemistry of Diastereomeric 3-Dialkylaminopropanols and O-Derivatives*, *J.f. prakt. Chemie*, 323:5, 793-800 (1981).
- Sprockel O.L et al. "Permeability of Cellulose Polymers: Water Vapour Transmission Rates", *J. Pharma. Pharmacol.* 42, pp. 152-157, 1990.
- Sreenivasa, B. et al, Design and Evaluation of Ethylene Vinyl Acetate Sintered Matrix Tablets, *Indian Journal of Pharmaceutical Sciences*, Sep.-Oct. 2003, 65(5): 496-502.
- Stafford J., *überzogene feste Formen*, 1991, 347-68. (English translation attached).
- Strang, Abuse of buprenorphie (Temgesic) by snorting, Letter to the editor, *British Med. J.*, 302: 969 (1991).
- Stringer J.L., et al "Diffusion of small molecular weight drugs in radiation-crosslinked of ethylene oxide) hydrogels", *Journal of Controlled Release* 42, pp. 195-202, 1996.
- Summers et al; "Influence of Crystal Form on Tensile Strength of Compacts of Pharmaceutical Materials" *Journal of Pharmaceutical Sciences*, vol. 66, No. 8, Aug. 1977, pp. 1172-1175.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 1, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 10, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 11, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 12, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 13, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 14, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 15, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 16, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 18, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 19, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 2, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 20, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 3, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 4, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 5, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 6, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 7, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 8, table of contents.
- Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, 1988, 1st edition, vol. 9, table of contents.
- Tablet, www.docstoc.com (2011).
- The Merck Index, 14th Ed. (2006) No. 0006360 Nalefene.
- The Merck Index, 14th Ed. (2006) No. 0006362 Naloxone.
- The Merck Index, 14th Ed. (2006) No. 0006363 Naltrexone.
- The Merck Index, 14th Ed. (2006) No. 0006959 Oxycodone.
- Third Party Observations filed with EPO for Patent EP658055B1, Feb. 2, 2009, pp. 1-8.
- Thoma V.K. et al. "Bestimmung der In-vitro-Freigabe von schwach basischen Wirkstoffen aus Retardarzneiformen", pp. 299-301, *Pharm. Ind.* 51, Nr. 3, 1989.
- Tikhonov, A. et al, *Biopharmacy. The Manual for Students of Pharmaceutical Universities and Departments*, 2003, pp. 40-41, Kharkov, Ukraine (Full English translation attached).
- Tipler, et al, *Physics for Scientists and Engineers*, vol. I, 6th Edition, pp. 234-235, 2003.
- Tompkins et al., "Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone," *Psychopharma.*, 210: 471-480 (2010).
- Tramadol Hydrochloride 100 mg Extended Release Tablets, *Lubrizol Advanced Materials, Inc.*, Sep. 2010.
- Tranquilan-Aranilla et al., "Kappa-carrageenan-polyethylene oxide hydrogel blends prepared by gamma irradiation," *Radiation Physics and Chemistry* vol. 55, pp. 127-131, 1999.
- Turco et al. *Intravenous Admixtures*. Chapter 86. pp. 1542-1552, In *Remington's Pharmaceutical Sciences*, 17th Ed, 1985.
- US Pharmacopoeia, Chapter 1217, Aug. 12, 2008.
- Varma et al, Factors Affecting Mechanism and Kinetics of Drug Release from Matrix-Based Oral Controlled Drug Delivery Systems, *Am. J. Drug Deliv.* 2004: 2 (1): 43-57.
- Verhoeven et al., "Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot-melt extrusion: in vitro and in vivo evaluations," *European Journal of Pharmaceutics and Biopharmaceutics* 72 (2009) 463-470.
- Verhoeven, et al. "Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hotmelt extrusion: in vitro and in vivo evaluation," *European Journal of Pharmaceutics and Biopharmaceutics*, 63 (2006) 320-330.
- Vippagunta et al. *Crystalline Solids*, *Advanced Drug Delivery Review* 48 (2001), 3-26.
- Vynckier et al., "Hot-melt co-extrusion for the production of fixed-dose combination products with a controlled release ethylcellulose matrix core," *International Journal of Pharmaceutics* 464 (2014), 65-74.
- Wade and Weller, "Handbook of Pharmaceutical Excipients: 2nd Edition", The American Pharmaceutical Association and the Pharmaceutical Press, Washington and London, Table of Contents pp. v-vi, 1994.

(56)

References Cited

OTHER PUBLICATIONS

- Wagner, *Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe—Scharfstoffdrogen*, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-N.Y., 1982, pp. 82-92 (Full English translation attached).
- Wagner, *Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe—Scharfstoffdrogen*, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-N.Y., 1982, Table of Content.
- Waltimo, et al., “A novel bite force recorder and maximal isometric bite force values for healthy young adults”, *Scandinavian Journal of Dental Research* 1993; 101: 171-175.
- Waltimo, et al., “Maximal bite force and its association with signs and symptoms of craniomandibular disorders in young Finnish non-patients”, *Acta Odontol Scand* 53 (1995): 254-258.
- Waterman et al., “Stabilization of Pharmaceuticals to Oxidative Degradation”, *Pharmaceutical Development and Technology*, vol. 7(1), pp. 1-32, (2002).
- Waters et al., “Intravenous Quetiapine-Cocaine Use (“Q-Ball”)”, Letter to the Editor, *Am. J. Psychiatry*, 164(1): pp. 173-174 (2007).
- Weiss, U., “Derivatives of Morphine. I 14-Dihydroxydihydromorphinone,” *J. Am. Chem. Soc.* 77, pp. 5891-5892, Nov. 20, 1955.
- West, Anthony R., *Solid state chemistry and its applications*, Wiley, New York, 1988, pp. 358 and 365.
- Wikipedia-Dextromethorphan Aug. 12, 2013 (and attached related English-language entry dated Dec. 11, 2013).
- Woodburn, K.R. et al., *Vascular complications of injecting drug misuse*, *Br. J. of Surgery*, vol. 83, 1996, pp. 1329-1334.
- Wu N, et al. Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights, *J Control Release*. Feb. 16, 2005;102(3):569-581.
- Yang et al., “Zero-Order Release Kinetics from a Self-Correcting Floatable Asymmetric Configuration Drug Delivery System”, *Journal of Pharmaceutical Sciences*, vol. 85, No. 2, Feb. 1996, pp. 170-173.
- Yang, et al; “Characterization of Compressibility and Compactibility of Poly(ethylene oxide) Polymers for Modified Release Application by Compaction Simulator”, *Journal of Pharmaceutical Sciences*, vol. 85, No. 10, pp. 1085-1090, Oct. 1996.
- Yarbrough et al, Letters to Nature “Extraordinary effects of mortar-and-pestle grinding on microstructure of sintered alumina gel”, *Nature* 322, pp. 347-349 (Abstract only) (Jul. 24, 1986).
- Yeh et al., *Stability of Morphine in Aqueous Solution III: Kinetics of Morphine Degradation in Aqueous Solution*, Wiley Subscription Services, Inc., *Journal of Pharmaceutical Sciences*, 50(1): 35-42 (1961).
- Zeeshan, F and N. Bukhari, “Development and Evaluation of a Novel Modified-Release Pellet-Based Tablet System for the Delivery of Loratadine and Pseudoephedrine Hydrochloride as Model Drugs,” *AAPS PharmaSciTech* 11(2); 910-916 (available on-line May 22, 2010).
- Zhang et al., “Properties of Sustained-Release Tablets Prepared by Hot-Melt Extrusion” *Pharmaceutical Development and Technology*, 1999, 4(2), 241-250.
- Linz et al. “Cebiranopadol: A Novel Potent Analgesic Nociception/Orphanin FQ Peptide and Opioid Receptor Agonist,” *J Pharmacol. Exp. Ther.* 2014; 349: 535-548; available online Apr. 8, 2014.
- Decision of the United States District Court for the Southern District of New York, in *In re Endo Pharmaceuticals Inc. and Grünenthal GmbH v. Amneal Pharmaceuticals, LLC et al.*, Findings of Fact and Conclusions of Law, District Judge Thomas P. Griesa, New York, New York, Jan. 14, 2014.
- Decision of the United States District Court for the Southern District of New York, in *In re Oxycontin Antitrust Litigation, Purdue Pharma LP v. Teva Pharmaceuticals, LLC et al.*, Findings of Fact and Conclusions of Law, District Judge Sidney H. Stein, New York, New York, Jan. 14, 2014.
- U.S. Court of Appeals, Federal Circuit, *Purdue Pharma L.P. v. Epic Pharma, LLC*, 117 USPQ2d 1733 (Fed. Cir. 2016).
- Al-Angari, A. et al. “The compaction properties of polyethylene glycols,” *J Pharm. Pharmacol.* (1985) 37:151-153.
- Al-Nasassrah et al., “The effect of an increase in chain length on the mechanical properties of polyethylene glycols,” *European Journal of Pharmaceutics and Biopharmaceutics* 46 (1998) 31-38.
- Anderson, S.L. et al., “A Model for Antiplasticization. In Polystyrene,” *Macromolecules* 28:2944-54 (1995).
- Back, D.M. et al., “Ethylene Oxide Polymers”, in *Kirk-Othmer Encyclopedia of Chemical Technology*. 2000, John Wiley & Sons, Inc., vol. 10, 673-696.
- Bailey, F.E., et al., “High Molecular Weight Polymers of Ethylene Oxide” *Solution Properties Industrial and Engineering Chemistry*, 1958, 50(1): 8-11.
- Balogh, E., “Tastes in a Tastes of Paprika,” in *Taste: Proceedings of the Oxford Symposium on Food and Cookery* 28 (Tom Jaine Ed.) 1988, pp. 25-40.
- Baumann, T., “Pain Management,” *Pharmacotherapy: A Pathophysiologic Approach* (J.T. DiPiro et al. eds., McGraw-Hill 4th ed. 1999), Ch. 56, 1014-1026.
- Baumrucker, S.J., “OxyContin, the Media, and Law Enforcement”, *American Journal of Hospice & Palliative Care*, 18:3 (May/Jun. 2001), 154-156.
- Choi, S., et al., “Development of a Directly Compressible Poly(Ethylene Oxide) Matrix for the Sustained-Release of Dihydrocodeine Bitartrate”, *Drug Development and Industrial Pharmacy*, vol. 29, No. 10, pp. 1045-1052, 2003.
- Choi, S., et al., “Hydrophilic Matrix Formulations of Dihydrocodeine Bitartrate with Polyethylene Oxide by Direct Compression,” *Proceedings of the 29th Annual Meeting of the Controlled Release Society*, in collaboration with the Korea Society for Biomaterials, Minneapolis, 1st Edition, 2002, 984-985.
- Ciccone, P. E., “Attempted Abuse of Concerta,” *Letters to the Editor, J. Am. Acad. Child Adolesc. Psychiatry*, 41:7 (Jul. 2002).
- Controversies in ADHD: A Breakfast Symposium—Concerta.
- Crowley, M. et al., *Pharmaceutical Applications of Hot-Melt Extrusion: Part I. Drug Dev. & Indus. Pharmacy* (2007) 33:909-926.
- Crowley, M. et al., “Properties of Hot-Melt Extruded CPM Tablets Using Hydrophilic Polymers,” poster presentation, (2000).
- Crowley, M., “Physicochemical and Mechanical Characterization of Hot-Melt Extruded Dosage Forms.” Dissertation presented to the Faculty of the Graduate School of The University of Texas at Austin. (May 2003).
- Crowley, M., et al., “Evaluation of a Hot Melt Extrusion Technique using a Hydrophilic Thermal Polymer and Retardant for the Preparation of Extended Release Chlorpheniramine Maleate Tablets,” in *American Association of Pharmaceutical Scientists: Indianapolis, IN* (2000).
- Crowley0000001-Crowley0000127.
- Davies, N. “Sustained Release and Enteric Coated NSAIDs: Are They Really GI Safe?” *J. Pharm. & Pharmaceut. Sci.*, 2(1):5-14, 1999.
- Declaration of Dr. James W. McGinity, dated Oct. 28, 2009; online, retrieved from: http://www.accessdata.fda.gov/dmgsatfda_docs/labeV2013/021121s032tbl.pdf.
- Dimitrov, M. et al., “Study of Verapamil hydrochloride release from compressed hydrophilic Polyox-Wsr tablets.” *Int’l J Pharmaceutics* (1999) 189:105-111.
- Dittmer, D.K., et al., “Glue-Sniffing Neuropathies,” *Canadian Family Physician* 39:1965-1971 (1993).
- Donnelly, C.L., “ADHD Medications: Past and Future,” *Behavioral Health Management*, May/Jun., 2002, 28 & 30.
- Dow, “Material Safety Data Sheet: POLYOX(TM) WSR 30” (effective date: Sep. 18, 2001).
- Dow, “POLYOX Water-Soluble Resins: Degradation of Water-Soluble Resins,” *Technical Data* (Oct. 2002).
- Drug Bank “Oxymorphone,” 2015; online, available at: www.dmgbank.ca/chugs/db01192 printed Jul. 1, 2015.
- Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.* (S.D.N.Y. 2015)—Redacted Version.
- FDA News Release, “FDA approves abuse-deterrent labeling for reformulated OxyContin,” Apr. 16, 2013, available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm>.

(56)

References Cited

OTHER PUBLICATIONS

- FDA, "Notice of Determination that OxyContin Drug Products Covered by NDA 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness." Federal Register, vol. 78, No. 75, Apr. 18, 2013, 23273-23274.
- Final Draft Labeling for Concerta Extended-Release Tablets Attachment to Approval Letter (2000); available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/211211bl.pdf.
- Greenhill, L.L., et al., "Practice Parameter for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults," J. Am. Acad. Child Adolesc. Psychiatry, 41:2 Supplement, 26S-49S (Feb. 2002).
- Griffith, D., "Potential new ADHD drug creating lots of big hopes," Sacramento Bee (California), Oct. 30, 2002.
- Huang, H. et al., "Preparation of Controlled Release Oral Dosage Forms by Low Temperature Melt Extrusion," AAPS PharmSci. 2000 2(S1).
- Jaffe, S.L., "Failed Attempts at Intranasal Abuse of Concerta," Letters to the Editor, J. Am. Acad. Child Adolesc. Psychiatry, 41:1 (Jan. 2002).
- Janssen Pharmaceuticals, Inc. Concerta Labeling Revisions, Dec. 12, 2013; online, retrieved from: http://www.accessdata.fda.gov/dmgsatfda_docs/label/2013/021121s0321bl.pdf.
- Joint Claim Construction and Prehearing Statement, dated Jul. 11, 2014. *Janssen Pharmaceuticals, Inc. and Grünenthal GMBH v. Actavis Elizabeth LLC and Alkem Laboratories Limited*, Civil Action No. 2:13-cv-04507 CCC-MF (D.N.J.), *Janssen Pharmaceuticals, Inc. and Grünenthal GMBH v. Roxane Laboratories, Inc.*, Civil Action No. 2:13-cv-06929 CCC-MF (D.N.J.), and *Janssen Pharmaceuticals, Inc. and Grünenthal GMBH v. Alkem Laboratories Limited*, Civil Action No. 2:13-cv-07803 CCC-MF (D.N.J.).
- Kibbe, Coloring Agents, in Handbook of Pharmaceutical Excipients (3d ed. 2000).
- Kidokoro, M. et al., "Properties of Tablets Containing Granulations of Ibuprofen and Acrylic Copolymers Prepared by Thermal Processes," Pharm Dev. and Tech., 6:263-275 (2001).
- Kinjo, N. et al., "Antiplasticization in the Slightly Plasticized Poly(vinyl chloride)," Polymer Journal 4(2):143-153 (1973).
- Larhib, H. et al., "Compressing polyethylene glycols: the effect of compression pressure and speed," Int 'l J Pharmaceutics (1997) 147: 199-205.
- Lieberman, H., et al., Pharmaceutical Dosage Forms: Tablets, vol. 2, Ch. 5: Granulation Technology and Tablet Characterization (1990), Table of contents and 245-348.
- Lyons et al., "Twitch Interpolation in the Assessment of the Maximum Force-Generating Capacity of the Jaw-Closing Muscles in Man," Arch. Oral. Biol. 41:12, 1161-1168 (1996).
- Makki, A. et al., Eds., A Dictionary of American Idioms, 4th Ed. Barron's, New York (2004), 342-343.
- Markovitz, H., et al. "Calculations of Entanglement Coupling Spacings in Linear Polymers." Journal of Physical Chemistry, 1962. 66(8): 1567-1568.
- McCrum, N., et al., Principles of Polymer Engineering. 2nd ed., New York: Oxford University Press. 447(1997), Chapter 7, 296-351.
- McGinity, J.W. et al., "Melt-Extruded Controlled-Release Dosage Forms" in Pharmaceutical Extrusion Technology, Ghebressellassie, I. and Martin, C., Eds., Marcel Dekker, Inc., New York, 2003, Chapter 10, 183-208.
- McQuay, H. et al. "Methods of Therapeutic Trials," Textbook of Pain 1125-1138 (P.D. Wall & R. Melzack eds., Elsevier 4th ed. 1999), Table of Contents and 1125-1138.
- Miura et al., "Comparison of Maximum Bite Force and Dentate Statue Between Healthy and Frail Elderly Persons," J. Oral Rehabilitation, vol. 28 (2001), pp. 592-595.
- Miyagawa, Y. et al., "Controlled-release of diclofenac sodium from wax matrix granulate," Int 'l J. Pharmaceutics (1996) 138:215-224.
- National Drug Intelligence Center Information Bulletin "OxyContin Diversion and Abuse" Jan. 2001.
- Payne, H. et al., Denatonium Benzoate as a Bitter Aversive Additive in Ethylene Glycol and Methanol-Based Automotive Products, SAE Technical Paper 930589, Abstract (1993).
- Pilpel, N., et al. "The effect of temperature on the tensile strength and disintegration of paracetamol and oxytetracycline tablets," J Pharm Pharmac., 29:389-392 (1977).
- POLYOX Water-Soluble Resins NF in Pharmaceutical Applications, Dow Chemical Company, Aug. 2002.
- Purdue Pharma LP Material Safety Data Sheet, OxyContin Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, Version Sep. 10, 2016; available at www.purduepharma.com/msds/oxycontin_msds.pdf.
- Rauwendaal, Chris, PHD, Responsive Expert Report of Chris Rauwendaal, Ph.D. Regarding Expert Report of Michael M. Crowley, Ph.D., dated Jul. 17, 2015.
- Repka, M. et al. Pharmaceutical Applications of Hot-Melt Extrusion: Part II. Drug Dev. & Indus. Pharmacy (2007) 33:1043-1057.
- Saravanan, M. et al., "The Effect of Tablet Formulation and Hardness on in Vitro Release of Cephalexin from Eudragit L100 Based Extended Release Tablets," Biol. Pharm. Bull. (2002) 25(4):541-545.
- Seitz, J.A.; et al., "Evaluation of the Physical Properties of Compressed Tablets 1: Tablet Hardness and Friability," J. of Pharm. Sci., 54:1353-1357 (1965).
- Shah, et al., "Some Effects of Humidity and Heat on the Tableting Properties of Microcrystalline Cellulose Formulations 1," J. of Pharm. Sci., 57:181-182 (1967).
- Singhal, et al., Handbook of Indices of Food Quality and Authenticity (1997), "Capsicum" p. 398-299.
- Smith, K.L. et al. "High Molecular Weight Polymers of Ethylene Oxide—Plastic Properties." Industrial and Engineering Chemistry, 1958. 50(1): 12-16.
- Tapentadol Pre-Review Report, Expert Committee on Drug Dependence Thirty-Fifth Meeting Hammamet, Tunisia, Jun. 4-8, 2012, available at http://www.who.int/medicines/areas/quality_safety/5.2/tapentadolpre-review.pdf.
- Tiwari, D., et al., "Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations." AAPS PharmSci, 1999. 1(3): Article 13.
- Wilkins, J.N., "Pharmacotherapy of Schizophrenia Patients with Comorbid Substance Abuse," Schizophrenia Bulletin, 23:215-228 (1997).
- World Health Org., Cancer Pain Relief With a Guide to Opioid Availability (2d ed. 1996).
- Yin, T.P., et al., "Viscoelastic Properties of Polyethylene Oxide in Rubber-Like State." Journal of Physical Chemistry, 1961. 65(3): 534-538.
- Zacny, J. et al. Drug & Alcohol Dependence (2003) 69:215-232.
- Zhang, F., "Hot-Melt Extrusion as a Novel Technology to Prepare Sustained-Release Dosage Forms," Dissertation University of Texas at Austin, Dec. 1999.
- USP Expert Council, US Pharmacopoeia, Chapter 1092, 2007, 1-15.
- M. Xu et al., "Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology," Int. J. Pharm. 478 (2015) 318-327.
- Baxter, J.L. et al., "Hydrodynamics-induced variability in the USP apparatus II dissolution test," International Journal of Pharmaceutics 292 (2005) 17-28.
- Bellmann et al., "Development of an advanced in vitro model of the stomach and its evaluation versus human gastric psychology." Food Research International 88 (2016) 191-198.
- Cuesov, Drug Production Technology, Khar'kov, 1999, pp. 351-352. (Full translation attached.).
- Efentakis et al, Effects of Excipients on Swelling and Drug Release from Compressed Matrices, in Drug Development and Industrial Pharmacy 23(1):107-112, Jan. 1997, Abstract.
- Extended European Search Report for Application No. EP 16183922.0-1460, dated Oct. 31, 2016.
- Koziolek, M. et al., "Development of a bio-relevant dissolution test device simulating mechanical aspects present in the fed stomach," European Journal of Pharmaceutical Sciences 57 (2014) 250-256.
- Meyer et al., "Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms," FDA ACPS Meeting, Oct. 2005, p. 1-4.

(56)

References Cited

OTHER PUBLICATIONS

Remington, Chapter 45, pp. 996-1035. (Full Translation Attached).
Schilling, et al., "Novel application of hot-melt extrusion for the preparation of monolithic matrices containing enteric-coated particles." International Journal of Pharmaceutics 400 (2010) 34-31.
Dabbagh, et al. "Release of Propranolol Hydrochloride from Matrix Tablets Containing Sodium Carboxymethylcellulose and Hydroxypropylmethylcellulose"; 1999; Pharmaceutical Development and Technology, 4(3), 313-324.
COMPAP 90 technical data sheet Mar. 2014; 1 page.

* cited by examiner

FIG. 1

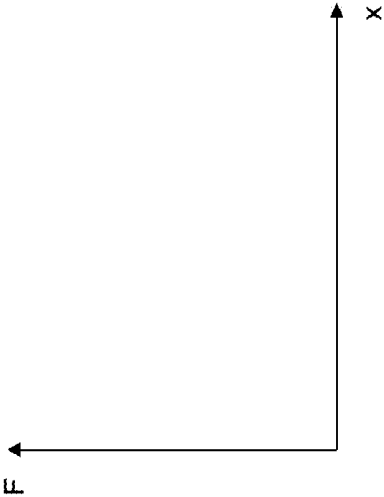
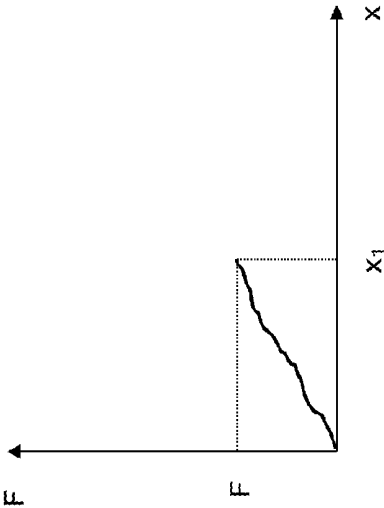
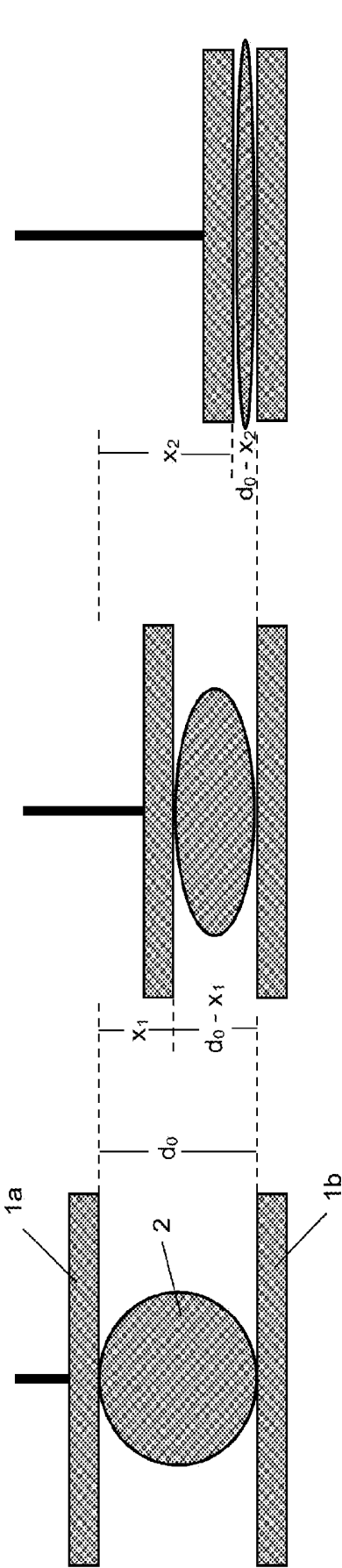


FIG. 2

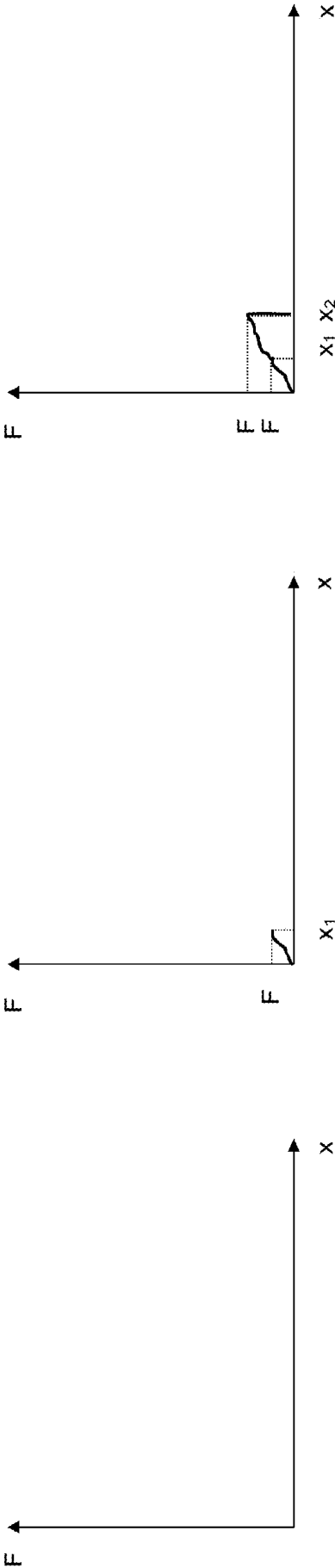
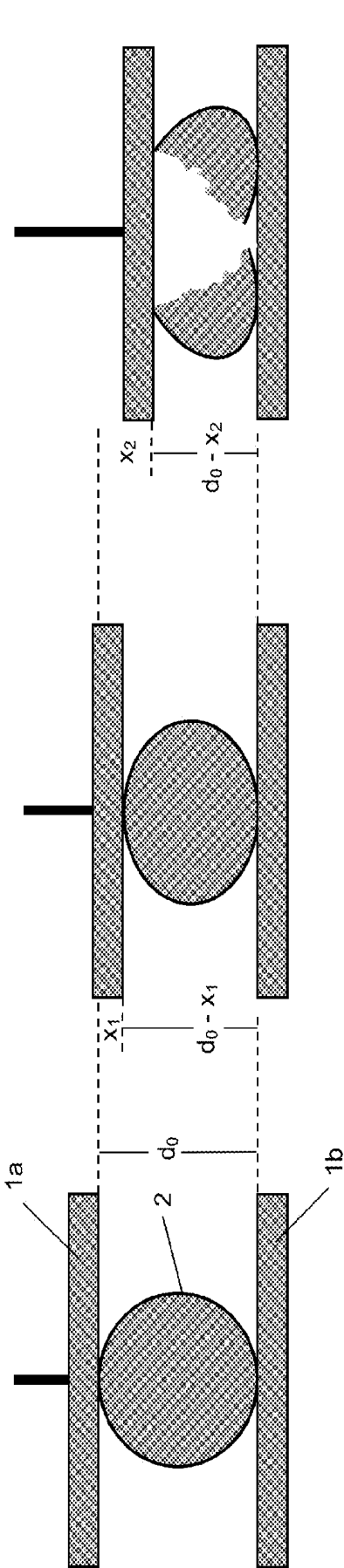


FIG. 3

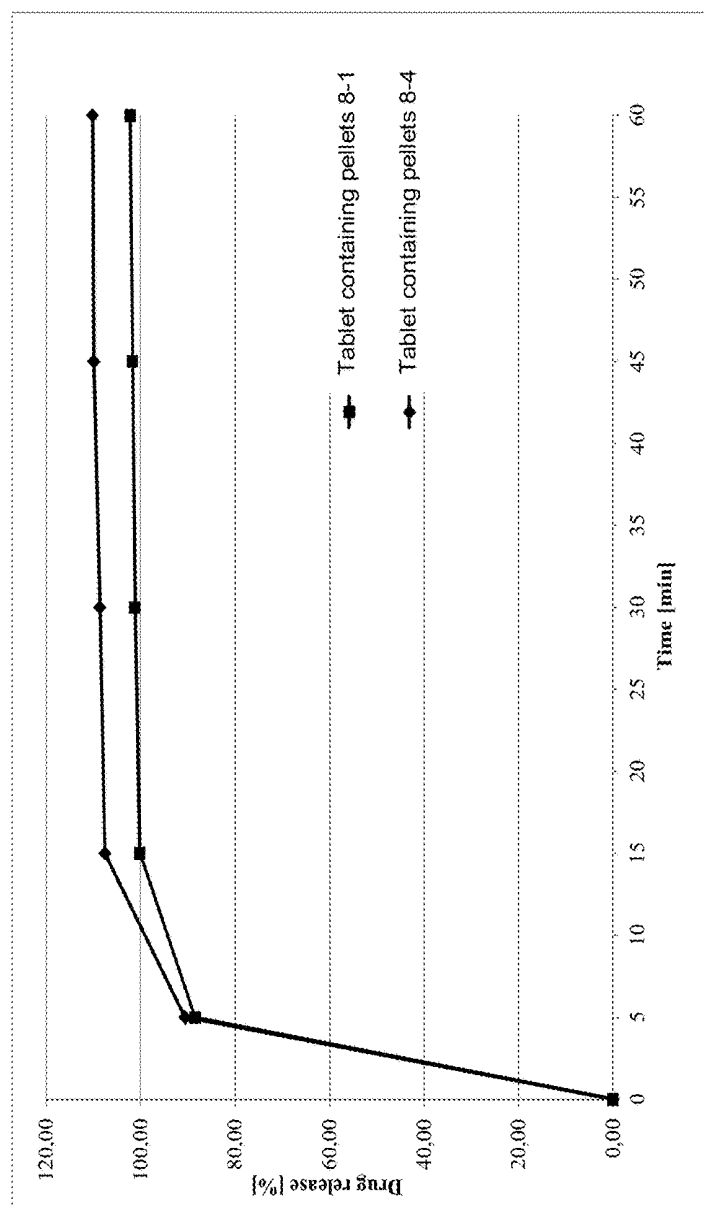
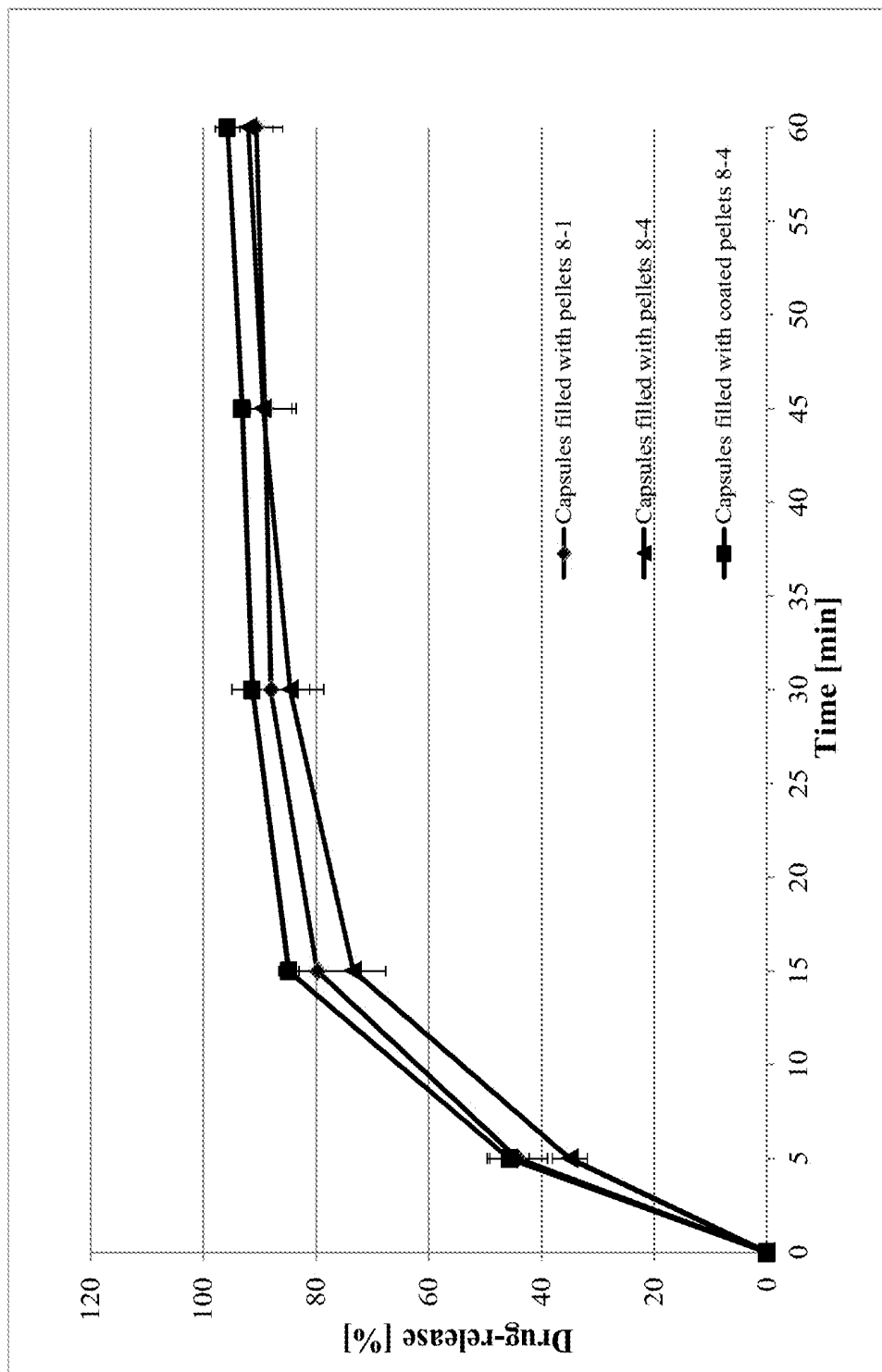


FIG. 4



TAMPER-RESISTANT DOSAGE FORM WITH IMMEDIATE RELEASE AND RESISTANCE AGAINST SOLVENT EXTRACTION

This application is a continuation of U.S. Nonprovisional application Ser. No. 15/135,649, filed Apr. 22, 2016, which, in turn, claims priority of European Patent Application No. 15 165 064.5, filed on Apr. 24, 2015, the entire contents of which patent applications are incorporated herein by reference.

The invention relates to a tamper-resistant pharmaceutical dosage form comprising a multitude of particles which comprise a pharmacologically active compound, a polyalkylene oxide, and a disintegrant; wherein the pharmacologically active compound is dispersed in a matrix comprising the polyalkylene oxide and the disintegrant; wherein the content of the disintegrant is more than 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; wherein the content of the polyalkylene oxide is at least 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; and wherein the dosage form provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

A large number of pharmacologically active substances have a potential for being abused or misused, i.e. they can be used to produce effects which are not consistent with their intended use. Thus, e.g. opioids which exhibit an excellent efficacy in controlling severe to extremely severe pain, are frequently abused to induce euphoric states similar to being intoxicated. In particular, active substances which have a psychotropic effect are abused accordingly.

To enable abuse, the corresponding dosage forms, such as tablets or capsules are crushed, for example ground by the abuser, the active substance is extracted from the thus obtained powder using a preferably aqueous liquid and after being optionally filtered through cotton wool or cellulose wadding, the resultant solution is administered parenterally, in particular intravenously. This type of dosage results in an even faster diffusion of the active substance compared to the oral abuse, with the result desired by the abuser, namely the kick. This kick or these intoxication-like, euphoric states are also reached if the powdered dosage form is administered nasally, i.e. is sniffed.

Various concepts for the avoidance of drug abuse have been developed.

It has been proposed to incorporate in dosage forms aversive agents and/or antagonists in a manner so that they only produce their aversive and/or antagonizing effects when the dosage forms are tampered with. However, the presence of such aversive agents is principally not desirable and there is a need to provide sufficient tamper-resistance without relying on aversive agents and/or antagonists.

Another concept to prevent abuse relies on the mechanical properties of the pharmaceutical dosage forms, particularly an increased breaking strength (resistance to crushing). The major advantage of such pharmaceutical dosage forms is that comminuting, particularly pulverization, by conventional means, such as grinding in a mortar or fracturing by means of a hammer, is impossible or at least substantially impeded. Thus, the pulverization, necessary for abuse, of the dosage forms by the means usually available to a potential abuser is prevented or at least complicated.

Such pharmaceutical dosage forms are useful for avoiding drug abuse of the pharmacologically active compound contained therein, as they may not be powdered by conventional

means and thus, cannot be administered in powdered form, e.g. nasally. The mechanical properties, particularly the high breaking strength of these pharmaceutical dosage forms renders them tamper-resistant. In the context of such tamper-resistant pharmaceutical dosage forms it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, WO 2006/082099, and WO2009/092601.

These dosage forms secured against abuse are distinguished by a controlled, preferably retarded release of the active substance which has abuse potential. However, a rapid release of the active substance is necessary for numerous therapeutic applications, for example pain relief using active substances with abuse potential.

WO 2008/033523 discloses a pharmaceutical composition that may include a granulate which may at least include one active pharmaceutical ingredient susceptible to abuse. The particle contains both an alcohol soluble and alcohol insoluble and at least partially water soluble material. Both materials are granulated in the presence of alcohol and water. The granulate may also include a coating on the granulate exhibiting crush resistance. Material deposition on the granule is performed using an alcohol based solvent.

WO 2008/107149 (US 2009/004267) discloses multiparticulate dosage forms with impeded abuse containing, one or more active substances having abuse potential, at least one synthetic or natural polymer, and at least one disintegrant, with the individual particles of the pharmaceutical dosage form having a breaking strength of at least 500 N and a release of the active substance of at least 75% after 45 minutes. The exemplified capsules provide rapid release of the pharmacologically active compound. The disintegrant is preferably not contained in the particulates. When it is contained in the particulates, its content is rather low. The reference does not contain any information that besides its disintegrating effect a disintegrant may have any beneficial effect with respect to tamper resistance such as resistance against solvent extraction.

WO 2010/140007 discloses dosage forms comprising melt-extruded particles comprising a drug, wherein said melt-extruded particles are present as a discontinuous phase in a matrix. The dosage forms provide prolonged release of the drug.

WO 2013/017242 and WO 2013/017234 disclose a tamper-resistant tablet comprising a matrix material in an amount of more than one third of the total weight of the tablet; and a plurality of particulates in an amount of less than two thirds of the total weight of the tablet; wherein said particulates comprise a pharmacologically active compound and a polyalkylene oxide; and form a discontinuous phase within the matrix material. The matrix material may comprise a disintegrant. The reference does not contain any information that besides its disintegrating effect a disintegrant may have any beneficial effect with respect to tamper resistance such as resistance against solvent extraction.

WO2014/190440 relates to an immediate release orally administrable abuse-deterrent pharmaceutical formulation comprising: at least one pharmaceutically active ingredient susceptible to abuse; at least one gelling polymeric compound selected from the group consisting of: polysaccharides, sugars, sugar derived alcohols, starches, starch derivatives, cellulose derivatives, Carrageenan, pectin, sodium alginate, gellan gum, xanthan gum, poloxamer, carbopol, polyox, povidone, hydroxypropyl methylcellulose, hypermellose, and combinations thereof; at least one disintegrant and optionally at least one surfactant, wherein said formu-

lation exhibit properties related to deterring the abuse, via injection or nasal inhalation when being tampered and exposed to aqueous, alcoholic, acidic and basic media.

US 2010/0092553 discloses solid multiparticle oral pharmaceutical forms whose composition and structure make it possible to avoid misuse. The microparticles have an extremely thick coating layer which assures the modified release of the drug and simultaneously imparts crushing resistance to the coated microparticles so as to avoid misuse.

The properties of these tamper-resistant dosage forms, however, are not satisfactory in every respect. There is a need for tamper-resistant dosage forms that possess crush resistance and release the pharmacologically active compound as quick as possible (immediate release), i.e. should show a gradual increase reaching 85% to 100% at 30 to 45 minutes or earlier. When trying to tamper the dosage form in order to prepare a formulation suitable for abuse by intravenous administration, the liquid part of the formulation that can be separated from the remainder by means of a syringe should be as less as possible, e.g. should contain not more than 10 wt.-% of the pharmacologically active compound originally contained in the dosage form.

It is an object according to the invention to provide tamper-resistant pharmaceutical dosage forms that provide rapid release of the pharmacologically active compound and that have advantages compared to the tamper-resistant pharmaceutical dosage forms of the prior art.

This object has been achieved by the patent claims.

The invention relates to a tamper-resistant pharmaceutical dosage form, preferably for oral administration, comprising a multitude of particles which comprise a pharmacologically active compound, a polyalkylene oxide, and a disintegrant; wherein the pharmacologically active compound is dispersed in a matrix comprising the polyalkylene oxide and the disintegrant; wherein the content of the disintegrant is more than 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; wherein the content of the polyalkylene oxide is at least 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles; and wherein the dosage form provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

It has been surprisingly found that tamper-resistant dosage forms can be provided that on the one hand provide immediate release of the pharmacologically active compound and that on the other hand provide improved tamper-resistance, particularly with respect to resistance against solvent extraction.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the behavior of the particles contained in the pharmaceutical dosage form according to the invention when being subjected to a breaking strength test, in particular their deformability.

FIG. 2 illustrates the behavior of conventional particles when being subjected to a breaking strength test.

FIG. 3 provides in vitro dissolution data of tablets containing pellets.

FIG. 4 provides in vitro dissolution data of capsules containing pellets.

As used herein, the term "pharmaceutical dosage form" refers to a pharmaceutical entity comprising a pharmacologically active compound and which is actually administered to, or taken by, a patient, preferably orally.

Preferably, the pharmaceutical dosage form according to the invention is a capsule or a tablet. The particles that are contained in the pharmaceutical dosage form and/or the pharmaceutical dosage form as such may be film-coated.

The pharmaceutical dosage form may be compressed or molded in its manufacture, and it may be of almost any size, shape, weight, and color. Most pharmaceutical dosage forms are intended to be swallowed as a whole and accordingly, preferred pharmaceutical dosage forms according to the invention are designed for oral administration. However, alternatively pharmaceutical dosage forms may be dissolved in the mouth, chewed, or dissolved or dispersed in liquid or meal before swallowing, and some may be placed in a body cavity. Thus, the pharmaceutical dosage form according to the invention may alternatively be adapted for buccal, lingual, rectal or vaginal administration. Implants are also possible.

In a preferred embodiment, the pharmaceutical dosage form according to the invention preferably can be regarded as a MUPS formulation (multiple unit pellet system). In a preferred embodiment, the pharmaceutical dosage form according to the invention is monolithic. In another preferred embodiment, the pharmaceutical dosage form according to the invention is not monolithic. In this regard, monolithic preferably means that the pharmaceutical dosage form is formed or composed of material without joints or seams or consists of or constitutes a single unit.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains all ingredients in a dense compact unit which in comparison to capsules has a comparatively high density. In another preferred embodiment, the pharmaceutical dosage form according to the invention contains all ingredients in a capsule which in comparison to dense compact unit has a comparatively low density.

An advantage of the pharmaceutical dosage forms according to the invention is that the same particles may be mixed with excipients in different amounts to thereby produce pharmaceutical dosage forms of different strengths. Another advantage of the pharmaceutical dosage forms according to the invention is that the different particles may be mixed with one another to thereby produce pharmaceutical dosage forms of different properties, e.g. different release rates, different pharmacologically active ingredients, and the like.

The pharmaceutical dosage form according to the invention has preferably a total weight in the range of 0.01 to 1.5 g, more preferably in the range of 0.05 to 1.2 g, still more preferably in the range of 0.1 g to 1.0 g, yet more preferably in the range of 0.2 g to 0.9 g, and most preferably in the range of 0.3 g to 0.8 g. In a preferred embodiment, the total weight of the pharmaceutical dosage form is within the range of 500±450 mg, more preferably 500±300 mg, still more preferably 500±200 mg, yet more preferably 500±150 mg, most preferably 500±100 mg, and in particular 500±50 mg. In another preferred embodiment, the total weight of the pharmaceutical dosage form is within the range of 600±450 mg, more preferably 600±300 mg, still more preferably 600±200 mg, yet more preferably 600±150 mg, most preferably 600±100 mg, and in particular 600±50 mg. In still another preferred embodiment, the total weight of the pharmaceutical dosage form is within the range of 700±450 mg, more preferably 700±300 mg, still more preferably 700±200 mg, yet more preferably 700±150 mg, most preferably 700±100 mg, and in particular 700±50 mg. In yet another preferred embodiment, the total weight of the pharmaceutical dosage form is within the range of 800±450 mg, more preferably 800±300 mg, still more preferably 800±200 mg,

yet more preferably 800 ± 150 mg, most preferably 800 ± 100 mg, and in particular 800 ± 50 mg.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is a round pharmaceutical dosage form, preferably having a diameter of e.g. 11 mm or 13 mm. Pharmaceutical dosage forms of this embodiment preferably have a diameter in the range of 1 mm to 30 mm, in particular in the range of 2 mm to 25 mm, more in particular 5 mm to 23 mm, even more in particular 7 mm to 13 mm; and a thickness in the range of 1.0 mm to 12 mm, in particular in the range of 2.0 mm to 10 mm, even more in particular from 3.0 mm to 9.0 mm, even further in particular from 4.0 mm to 8.0 mm.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is an oblong pharmaceutical dosage form, preferably having a length of e.g. 17 mm and a width of e.g. 7 mm. In preferred embodiments, the pharmaceutical dosage form according to the invention has a length of e.g. 22 mm and a width of e.g. 7 mm; or a length of 23 mm and a width of 7 mm; whereas these embodiments are particularly preferred for capsules. Pharmaceutical dosage forms of this embodiment preferably have a lengthwise extension (longitudinal extension) of 1 mm to 30 mm, in particular in the range of 2 mm to 25 mm, more in particular 5 mm to 23 mm, even more in particular 7 mm to 20 mm; a width in the range of 1 mm to 30 mm, in particular in the range of 2 mm to 25 mm, more in particular 5 mm to 23 mm, even more in particular 7 mm to 13 mm; and a thickness in the range of 1.0 mm to 12 mm, in particular in the range of 2.0 mm to 10 mm, even more in particular from 3.0 mm to 9.0 mm, even further in particular from 4.0 mm to 8.0 mm.

The pharmaceutical dosage forms according to the invention can optionally be provided, partially or completely, with a conventional coating. The pharmaceutical dosage forms according to the invention are preferably film coated with conventional film coating compositions. Suitable coating materials are commercially available, e.g. under the trademarks Opadry® and Eudragit®.

Examples of suitable materials include cellulose esters and cellulose ethers, such as methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), sodium carboxymethylcellulose (Na-CMC), poly(meth)acrylates, such as aminoalkylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers; vinyl polymers, such as polyvinylpyrrolidone, polyvinyl alcohol, polyvinylacetate; and natural film formers.

In a particularly preferred embodiment, the coating is water-soluble. In a preferred embodiment, the coating is based on polyvinyl alcohol, such as polyvinyl alcohol-partially hydrolyzed, and may additionally contain polyethylene glycol, such as macrogol 3350, and/or pigments. In another preferred embodiment, the coating is based on hydroxypropylmethylcellulose, preferably hypromellose type 2910 having a viscosity of 3 to 15 mPas.

The coating can be resistant to gastric juices and dissolve as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the pharmaceutical dosage form according to the invention passes through the stomach undissolved and the active compound is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

The coating can also be applied e.g. to improve the aesthetic impression and/or the taste of the pharmaceutical

dosage forms and the ease with which they can be swallowed. Coating the pharmaceutical dosage forms according to the invention can also serve other purposes, e.g. improving stability and shelf-life. Suitable coating formulations comprise a film forming polymer such as, for example, polyvinyl alcohol or hydroxypropyl methylcellulose, e.g. hypromellose, a plasticizer such as, for example, a glycol, e.g. propylene glycol or polyethylene glycol, an opacifier, such as, for example, titanium dioxide, and a film smoother, such as, for example, talc. Suitable coating solvents are water as well as organic solvents. Examples of organic solvents are alcohols, e.g. ethanol or isopropanol, ketones, e.g. acetone, or halogenated hydrocarbons, e.g. methylene chloride. Coated pharmaceutical dosage forms according to the invention are preferably prepared by first making the cores and subsequently coating said cores using conventional techniques, such as coating in a coating pan.

The subjects to which the pharmaceutical dosage forms according to the invention can be administered are not particularly limited. Preferably, the subjects are animals, more preferably human beings.

The pharmaceutical dosage form according to the invention contains a plurality of particles. The particles comprise a pharmacologically active compound, a polyalkylene oxide and a disintegrant. Preferably, the pharmacologically active compound is dispersed in the polyalkylene oxide and the disintegrant.

For the purpose of the specification, the term "particle" refers to a discrete mass of material that is solid, e.g. at 20° C. or at room temperature or ambient temperature. Preferably a particle is solid at 20° C. Preferably, the particles are monoliths. Preferably, the pharmacologically active compound and the polyalkylene oxide are intimately homogeneously distributed in the particles so that the particles do not contain any segments where either pharmacologically active compound is present in the absence of polyalkylene oxide or where polyalkylene oxide is present in the absence of pharmacologically active compound.

When the particles are film coated, the polyalkylene oxide is preferably homogeneously distributed in the core of the pharmaceutical dosage form, i.e. the film coating preferably does not contain polyalkylene oxide, but optionally polyalkylene glycol that differs from polyalkylene oxide in its lower molecular weight. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the polyalkylene oxide contained in the core.

The particles are of macroscopic size, typically the average diameter is within the range of from 100 μ m to 1500 μ m, preferably 200 μ m to 1500 μ m, more preferably 300 μ m to 1500 μ m, still more preferably 400 μ m to 1500 μ m, most preferably 500 μ m to 1500 μ m, and in particular 600 μ m to 1500 μ m.

Preferably, the content of the particles in the pharmaceutical dosage forms according to the invention is at most 65 wt.-%, more preferably at most 60 wt.-%, still more preferably at most 55 wt.-%, yet more preferably at most 50 wt.-%, most preferably at most 45 wt.-% and in particular at most 40 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the content of the particles in the pharmaceutical dosage forms according to the invention is at least 2.5 wt.-%, at least 3.0 wt.-%, at least 3.5 wt.-% or at least 4.0 wt.-%; more preferably at least 4.5 wt.-%, at least 5.0 wt.-%, at least 5.5 wt.-% or at least 6.0 wt.-%; most preferably at least 6.5 wt.-%, at least 7.0 wt.-%, at least 7.5 wt.-% or at least 8.0 wt.-%; and in particular at least 8.5 wt.-%, at least

9.0 wt.-%, at least 9.5 wt.-% or at least 10 wt.-%; based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 10 ± 7.5 wt.-%, more preferably 10 ± 5.0 wt.-%, still more preferably 10 ± 4.0 wt.-%, yet more preferably 10 ± 3.0 wt.-%, most preferably 10 ± 2.0 wt.-%, and in particular 10 ± 1.0 wt.-%, based on the total weight of the pharmaceutical dosage form. In another preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 15 ± 12.5 wt.-%, more preferably 15 ± 10 wt.-%, still more preferably 15 ± 8.0 wt.-%, yet more preferably 15 ± 6.0 wt.-%, most preferably 15 ± 4.0 wt.-%, and in particular 15 ± 2.0 wt.-%, based on the total weight of the pharmaceutical dosage form. In still another preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 20 ± 17.5 wt.-%, more preferably 20 ± 15 wt.-%, still more preferably 20 ± 12.5 wt.-%, yet more preferably 20 ± 10 wt.-%, most preferably 20 ± 7.5 wt.-%, and in particular 20 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form. In yet another preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 25 ± 17.5 wt.-%, more preferably 25 ± 15 wt.-%, still more preferably 25 ± 12.5 wt.-%, yet more preferably 25 ± 10 wt.-%, most preferably 25 ± 7.5 wt.-%, and in particular 25 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form. In another preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 30 ± 17.5 wt.-%, more preferably 30 ± 15 wt.-%, still more preferably 30 ± 12.5 wt.-%, yet more preferably 30 ± 10 wt.-%, most preferably 30 ± 7.5 wt.-%, and in particular 30 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form. In still another preferred embodiment, the content of the particles in the pharmaceutical dosage forms according to the invention is within the range of 35 ± 17.5 wt.-%, more preferably 35 ± 15 wt.-%, still more preferably 35 ± 12.5 wt.-%, yet more preferably 35 ± 10 wt.-%, most preferably 35 ± 7.5 wt.-%, and in particular 35 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form.

The shape of the particles is not particularly limited. As the particles are preferably manufactured by hot-melt extrusion, preferred particles present in the pharmaceutical dosage forms according to the invention are generally cylindrical in shape. The diameter of such particles is therefore the diameter of their circular cross section. The cylindrical shape is caused by the extrusion process according to which the diameter of the circular cross section is a function of the extrusion die and the length of the cylinders is a function of the cutting length according to which the extruded strand of material is cut into pieces of preferably more or less predetermined length.

The suitability of cylindrical, i.e. a spherical particles for the manufacture of the pharmaceutical dosage forms according to the invention is unexpected. Typically, the aspect ratio is regarded as an important measure of the spherical shape. The aspect ratio is defined as the ratio of the maximal diameter (d_{max}) and its orthogonal Feret-diameter. For aspherical particles, the aspect ratio has values above 1. The smaller the value the more spherical is the particle. Aspect ratios below 1.1 are typically considered satisfactory, aspect ratios above 1.2, however, are typically considered not suitable for the manufacture of conventional pharmaceutical dosage forms. The inventors have surprisingly found that

when manufacturing the pharmaceutical dosage forms according to the invention, even particles having aspect ratios above 1.2 can be processed without difficulties and that it is not necessary to provide spherical particles. In a preferred embodiment, the aspect ratio of the particles is at most 1.40, more preferably at most 1.35, still more preferably at most 1.30, yet more preferably at most 1.25, even more preferably at most 1.20, most preferably at most 1.15 and in particular at most 1.10. In another preferred embodiment, the aspect ratio of the particles is at least 1.10, more preferably at least 1.15, still more preferably at least 1.20, yet more preferably at least 1.25, even more preferably at least 1.30, most preferably at least 1.35 and in particular at least 1.40.

The particles in the pharmaceutical dosage forms according to the invention are of macroscopic size, i.e. typically have an average particle size of at least 50 μm , more preferably at least 100 μm , still more preferably at least 150 μm or at least 200 μm , yet more preferably at least 250 μm or at least 300 μm , most preferably at least 400 μm or at least 500 μm , and in particular at least 550 μm or at least 600 μm .

Preferred particles have an average length and average diameter of 1000 μm or less. When the particles are manufactured by extrusion technology, the "length" of particles is the dimension of the particles that is parallel to the direction of extrusion. The "diameter" of particles is the largest dimension that is perpendicular to the direction of extrusion.

Particularly preferred particles have an average diameter of less than 1000 μm , more preferably less than 800 μm , still more preferably of less than 650 μm . Especially preferred particles have an average diameter of less than 700 μm , particularly less than 600 μm , still more particularly less than 500 μm , e.g. less than 400 μm . Particularly preferred particles have an average diameter in the range 200 to 1000 μm , more preferably 400 to 800 μm , still more preferably 450 to 700 μm , yet more preferably 500 to 650 μm , e.g. 500 to 600 μm . Further preferred particles have an average diameter of between 300 μm and 400 μm , of between 400 μm and 500 μm , or of between 500 μm and 600 μm , or of between 600 μm and 700 μm or of between 700 μm and 800 μm .

Preferred particles that are present in the pharmaceutical dosage forms according to the invention have an average length of less than 1000 μm , preferably an average length of less than 800 μm , still more preferably an average length of less than 650 μm , e.g. a length of 800 μm , 700 μm , 600 μm , 500 μm , 400 μm or 300 μm . Especially preferred particles have an average length of less than 700 μm , particularly less than 650 μm , still more particularly less than 550 μm , e.g. less than 450 μm . Particularly preferred particles therefore have an average length in the range 200-1000 μm , more preferably 400-800 μm , still more preferably 450-700 μm , yet more preferably 500-650 μm , e.g. 500-600 μm . The minimum average length of the microparticles is determined by the cutting step and may be, e.g. 500 μm , 400 μm , 300 μm or 200 μm .

In a preferred embodiment, the particles have (i) an average diameter of 1000 ± 300 μm , more preferably 1000 ± 250 μm , still more preferably 1000 ± 200 μm , yet more preferably 1000 ± 150 μm , most preferably 1000 ± 100 μm , and in particular 1000 ± 50 μm ; and/or (ii) an average length of 1000 ± 300 μm , more preferably 1000 ± 250 μm , still more preferably 1000 ± 200 μm , yet more preferably 1000 ± 150 μm , most preferably 1000 ± 100 μm , and in particular 1000 ± 50 μm .

The size of particles may be determined by any conventional procedure known in the art, e.g. laser light scattering, sieve analysis, light microscopy or image analysis.

Preferably, the plurality of particles that is contained in the pharmaceutical dosage form according to the invention has an arithmetic average weight, in the following referred to as "aaw", wherein at least 70%, more preferably at least 75%, still more preferably at least 80%, yet more preferably at least 85%, most preferably at least 90% and in particular at least 95% of the individual particles contained in said plurality of particles has an individual weight within the range of $aaw \pm 30\%$, more preferably $aaw \pm 25\%$, still more preferably $aaw \pm 20\%$, yet more preferably $aaw \pm 15\%$, most preferably $aaw \pm 10\%$, and in particular $aaw \pm 5\%$. For example, if the pharmaceutical dosage form according to the invention contains a plurality of 100 particles and aaw of said plurality of particles is 1.00 mg, at least 75 individual particles (i.e. 75%) have an individual weight within the range of from 0.70 to 1.30 mg ($1.00 \text{ mg} \pm 30\%$).

In a preferred embodiment, the particles are not film coated.

In another preferred embodiment, the particles are film coated. It has been surprisingly found that when the particles are film coated, the disintegration time and/or the drug release from the pharmaceutical dosage forms can be further accelerated, which is particularly significant for pharmaceutical dosage forms with immediate drug release.

The particles according to the invention can optionally be provided, partially or completely, with a conventional coating. The particles according to the invention are preferably film coated with conventional film coating compositions. Suitable coating materials are commercially available, e.g. under the trademarks Opadry® and Eudragit®.

When the particles are film coated, the content of the dried film coating is preferably at most 5 wt.-%, more preferably at most 4 wt.-%, still more preferably at most 3.5 wt.-%, yet more preferably at most 3 wt.-%, most preferably at most 2.5 wt.-%, and in particular at most 2 wt.-%, based on the total weight of the particles. In a particularly preferred embodiment, the weight increase based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles (uncoated starting material) is within the range of from 3.0 to 4.7 wt.-%, more preferably 3.1 to 4.6 wt.-%, still more preferably 3.2 to 4.5 wt.-%, yet more preferably 3.3 to 4.4 wt.-%, most preferably 3.4 to 4.3 wt.-%, and in particular 3.5 to 4.2 wt.-%.

The tamper-resistant pharmaceutical dosage form according to the invention comprises a multitude of particles which comprise a pharmacologically active compound. The particles contain at least a pharmacologically active compound, a polyalkylene oxide and a disintegrant. Preferably, however, the particles contain additional pharmaceutical excipients such as antioxidants and plasticizers.

The pharmacologically active compound is dispersed in a matrix comprising the polyalkylene oxide and the disintegrant. In other words, the polyalkylene oxide and the disintegrant form a matrix in which the pharmacologically active compound is embedded.

The pharmacologically active compound is not particularly limited. Preferably, the pharmacologically active compound is an opioid.

In a preferred embodiment, the particles and the pharmaceutical dosage form, respectively, contain only a single pharmacologically active compound. In another preferred embodiment, the particles and the pharmaceutical dosage form, respectively, contain a combination of two or more pharmacologically active compounds.

Preferably, pharmacologically active compound is an active ingredient with potential for being abused. Active ingredients with potential for being abused are known to the person skilled in the art and comprise e.g. tranquilizers, stimulants, barbiturates, narcotics, opioids or opioid derivatives.

Preferably, the pharmacologically active compound exhibits psychotropic action.

Preferably, the pharmacologically active compound is selected from the group consisting of opiates, opioids, stimulants, tranquilizers, and other narcotics.

In a preferred embodiment, the pharmacologically active compound is an opioid. According to the ATC index, opioids are divided into natural opium alkaloids, phenylpiperidine derivatives, diphenylpropylamine derivatives, benzomorphan derivatives, oripavine derivatives, morphinan derivatives and others.

In another preferred embodiment, the pharmacologically active compound is a stimulant. Stimulants are psychoactive drugs that induce temporary improvements in either mental or physical functions or both. Examples of these kinds of effects may include enhanced wakefulness, locomotion, and alertness. Preferred stimulants are phenylethylamine derivatives. According to the ATC index, stimulants are contained in different classes and groups, e.g. psychoanaleptics, especially psychostimulants, agents used for ADHD and nootropics, particularly centrally acting sympathomimetics; and e.g. nasal preparations, especially nasal decongestants for systemic use, particularly sympathomimetics.

The following opiates, opioids, stimulants, tranquilizers or other narcotics are substances with a psychotropic action, i.e. have a potential of abuse, and hence are preferably contained in the pharmaceutical dosage form and the particles, respectively: alfentanil, allobarbitol, allylprodine, alphaprodine, alprazolam, amfepramone, amphetamine, amphetaminil, amobarbital, anileridine, apocodeine, axomadol, barbital, bemidone, benzyl-morphine, bezitramide, bromazepam, brotizolam, buprenorphine, butobarbital, butorphanol, camazepam, carfentanil, cathine/D-norpseudoephedrine, cebranopadol, chlordiazepoxide, clobazam, clofedanol, clonazepam, clonitazene, clorazepate, clotiazepam, cloxazolam, cocaine, codeine, cyclobarbitol, cyclorphan, cyrenorphine, delorazepam, desomorphine, dex-amphetamine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphine, diazepam, dihydrocodeine, dihydromorphine, dihydromorphone, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, dronabinol, eptazocine, estazolam, ethoheptazine, ethylmethylthiambutene, ethyl loflazepate, ethylmorphine, etonitazene, etorphine, fexeladol, fencamfamine, fenethylline, fenpipramide, fenproporex, fentanyl, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethyl-morphinan, ketazolam, ketobemidone, levacetylmethadol (LAAM), levomethadone, levorphanol, levophenacymorphane, levoxemacin, lisdexamfetamine dimesylate, lofentanil, lopraxolam, lorazepam, lormetazepam, mazindol, medazepam, mefenorex, meperidine, meprobamate, metapone, meptazinol, metazocine, methylmorphine, metamphetamine, metha-done, methaqualone, 3-methylfentanyl, 4-methylfentanyl, methylphenidate, methylpheno-barbital, methypylon, metopon, midazolam, modafinil, morphine, myrophine, nabilone, nalbuphene, nalorphine, narceine, nicomorphine, nimetazepam, nitrazepam, nordazepam, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxazepam, oxazolam, oxycodone, oxymorphone,

Papaver somniferum, papaveretum, pemoline, pentazocine, pentobarbital, pethidine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phenobarbital, phentermine, pinazepam, pipradrol, piritramide, prazepam, profadol, proheptazine, 5 promedol, properidine, propoxyphene, pseudoephedrine, remifentanyl, secbutabarbital, secobarbital, sufentanil, tapentadol, temazepam, tetrazepam, tilidine (cis and trans), tramadol, triazolam, vinylbital, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, (1R,2R)-3-(3-dimethyl-10 amino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-15 1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethyl amino methyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethyl aminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl) 25 propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethyl amino methyl-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-dimethyl aminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethyl amino methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethyl amino methyl-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, in each case the 40 corresponding derivatives thereof, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, e.g. ethers, esters or amides, and in each case the physiologically acceptable compounds thereof, in particular the acid or base addition salts thereof and solvates, e.g. hydrochlorides.

In a preferred embodiment, the pharmacologically active compound is selected from the group consisting of DPI-125, M6G (CE-04-410), ADL-5859, CR-665, NRP290 and sebacoyl dinalbuphine ester.

In a preferred embodiment, the pharmacologically active compound is an opioid selected from the group consisting of oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, tramadol, tapentadol, cebranopadol and the 55 physiologically acceptable salts thereof.

In another preferred embodiment, the pharmacologically active compound is a stimulant selected from the group consisting of amphetamine, dex-amphetamine, dexamphenidate, atomoxetine, caffeine, ephedrine, phenylpropanolamine, phenylephrine, fencamphamin, fenozolone, fenetylline, methylenedioxymethamphetamine (MDMA), methylenedioxypropylvalerone (MDPV), prolintane, lisdex- 60 amphetamine, mephedrone, methamphetamine, methylphenidate, modafinil, nicotine, pemoline, phenylpropanolamine, propylhexedrine, dimethylamylamine, and pseudoephedrine.

In a particularly preferred embodiment, the pharmacologically active compound is methylphenidate.

In another particularly preferred embodiment, the pharmacologically active compound is lisdexamfetamine.

In another particularly preferred embodiment, the pharmacologically active compound is dexmethylphenidate.

The pharmacologically active compound may be present in form of a physiologically acceptable salt, e.g. physiologically acceptable acid addition salt.

Physiologically acceptable acid addition salts comprise the acid addition salt forms which can conveniently be obtained by treating the base form of the active ingredient with appropriate organic and inorganic acids. Active ingredients containing an acidic proton may be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. The term addition salt also comprises the hydrates and solvent addition forms which the active ingredients are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

In a preferred embodiment, the pharmacologically active compound is amphetamine aspartate monohydrate.

In another preferred embodiment, the pharmacologically active compound is dextroamphetamine saccharate.

In another preferred embodiment, the pharmacologically active compound is dextroamphetamine sulfate.

It has been surprisingly found that the content of the pharmacologically active compound in the pharmaceutical dosage form and in the particles, respectively, can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

The pharmacologically active compound is present in the pharmaceutical dosage form in a therapeutically effective amount. The amount that constitutes a therapeutically effective amount varies according to the active ingredients being used, the condition being treated, the severity of said condition, the patient being treated, and the frequency of administration.

The content of the pharmacologically active compound in the pharmaceutical dosage form is not limited. The dose of the pharmacologically active compound which is adapted for administration preferably is in the range of 0.1 mg to 500 mg, more preferably in the range of 1.0 mg to 400 mg, even more preferably in the range of 5.0 mg to 300 mg, and most preferably in the range of 10 mg to 250 mg. In a preferred embodiment, the total amount of the pharmacologically active compound that is contained in the pharmaceutical dosage form is within the range of from 0.01 to 200 mg, more preferably 0.1 to 190 mg, still more preferably 1.0 to 180 mg, yet more preferably 1.5 to 160 mg, most preferably 2.0 to 100 mg and in particular 2.5 to 80 mg.

Preferably, the content of the pharmacologically active compound is at least 0.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the content of the pharmacologically active compound is within the range of from 0.01 to 80 wt.-%, more preferably 0.1 to 50 wt.-%, still more preferably 1 to 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the content of pharmacologically active compound is within the range of from 0.50±0.45 wt.-%, or 0.75±0.70 wt.-%, or 1.00±0.90 wt.-%, or 1.25±1.20 wt.-%, or 1.50±1.40 wt.-%, or 1.75±1.70 wt.-%, or 2.00±1.90 wt.-%, or 2.25±2.20 wt.-%, or 2.50±2.40

wt.-%; more preferably 0.50±0.40 wt.-%, or 0.75±0.60 wt.-%, or 1.00±0.80 wt.-%, or 1.25±1.10 wt.-%, or 1.50±1.25 wt.-%, or 1.75±1.50 wt.-%, or 2.00±1.75 wt.-%, or 2.25±2.00 wt.-%, or 2.50±2.25 wt.-%; still more preferably 0.50±0.35 wt.-%, or 0.75±0.50 wt.-%, or 1.00±0.70 wt.-%, or 1.25±1.00 wt.-%, or 1.50±1.15 wt.-%, or 1.75±1.30 wt.-%, or 2.00±1.50 wt.-%, or 2.25±1.90 wt.-%, or 2.50±2.10 wt.-%; yet more preferably 0.50±0.30 wt.-%, or 0.75±0.40 wt.-%, or 1.00±0.60 wt.-%, or 1.25±0.80 wt.-%, or 1.50±1.00 wt.-%, or 1.75±1.10 wt.-%, or 2.00±1.40 wt.-%, or 2.25±1.60 wt.-%, or 2.50±1.80 wt.-%; even more preferably 0.50±0.25 wt.-%, or 0.75±0.30 wt.-%, or 1.00±0.50 wt.-%, or 1.25±0.60 wt.-%, or 1.50±0.80 wt.-%, or 1.75±0.90 wt.-%, or 2.00±1.30 wt.-%, or 2.25±1.40 wt.-%, or 2.50±1.50 wt.-%; most preferably 0.50±0.20 wt.-%, or 0.75±0.25 wt.-%, or 1.00±0.40 wt.-%, or 1.25±0.50 wt.-%, or 1.50±0.60 wt.-%, or 1.75±0.70 wt.-%, or 2.00±1.10 wt.-%, or 2.25±1.20 wt.-%, or 2.50±1.30 wt.-%; and in particular 0.50±0.15 wt.-%, or 0.75±0.20 wt.-%, or 1.00±0.30 wt.-%, or 1.25±0.40 wt.-%, or 1.50±0.50 wt.-%, or 1.75±0.60 wt.-%, or 2.00±0.70 wt.-%, or 2.25±0.80 wt.-%, or 2.50±0.90 wt.-%; in each case based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the content of pharmacologically active compound is within the range of from 2.0±1.9 wt.-%, or 2.5±2.4 wt.-%, or 3.0±2.9 wt.-%, or 3.5±3.4 wt.-%, or 4.0±3.9 wt.-%, or 4.5±4.4 wt.-%, or 5.0±4.9 wt.-%, or 5.5±5.4 wt.-%, or 6.0±5.9 wt.-%; more preferably 2.0±1.7 wt.-%, or 2.5±2.2 wt.-%, or 3.0±2.6 wt.-%, or 3.5±3.1 wt.-%, or 4.0±3.5 wt.-%, or 4.5±4.0 wt.-%, or 5.0±4.4 wt.-%, or 5.5±4.9 wt.-%, or 6.0±5.3 wt.-%; still more preferably 2.0±1.5 wt.-%, or 2.5±2.0 wt.-%, or 3.0±2.3 wt.-%, or 3.5±2.8 wt.-%, or 4.0±3.1 wt.-%, or 4.5±3.6 wt.-%, or 5.0±3.9 wt.-%, or 5.5±4.4 wt.-%, or 6.0±4.7 wt.-%; yet more preferably 2.0±1.3 wt.-%, or 2.5±1.8 wt.-%, or 3.0±2.0 wt.-%, or 3.5±2.5 wt.-%, or 4.0±2.7 wt.-%, or 4.5±3.2 wt.-%, or 5.0±3.4 wt.-%, or 5.5±3.9 wt.-%, or 6.0±4.1 wt.-%; even more preferably 2.0±1.1 wt.-%, or 2.5±1.6 wt.-%, or 3.0±1.7 wt.-%, or 3.5±2.2 wt.-%, or 4.0±2.4 wt.-%, or 4.5±2.8 wt.-%, or 5.0±2.9 wt.-%, or 5.5±3.4 wt.-%, or 6.0±3.5 wt.-%; most preferably 2.0±0.9 wt.-%, or 2.5±1.4 wt.-%, or 3.0±1.4 wt.-%, or 3.5±1.9 wt.-%, or 4.0±2.1 wt.-%, or 4.5±2.4 wt.-%, or 5.0±2.4 wt.-%, or 5.5±2.9 wt.-%, or 6.0±2.9 wt.-%; and in particular 2.0±0.7 wt.-%, or 2.5±1.2 wt.-%, or 3.0±1.1 wt.-%, or 3.5±1.6 wt.-%, or 4.0±1.8 wt.-%, or 4.5±2.0 wt.-%, or 5.0±1.9 wt.-%, or 5.5±2.4 wt.-%, or 6.0±2.3 wt.-%; in each case based on the total weight of the particles.

In a preferred embodiment, the content of pharmacologically active compound is within the range of from 10±6 wt.-%, more preferably 10±5 wt.-%, still more preferably 10±4 wt.-%, most preferably 10±3 wt.-%, and in particular 10±2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of pharmacologically active compound is within the range of from 15±6 wt.-%, more preferably 15±5 wt.-%, still more preferably 15±4 wt.-%, most preferably 15±3 wt.-%, and in particular 15±2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In a further preferred embodiment, the content of pharmacologically active compound is within the range of from 20±6 wt.-%, more preferably 20±5 wt.-%, still more preferably 20±4 wt.-%, most preferably 20±3 wt.-%, and in particular 20±2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the con-

tent of pharmacologically active compound is within the range of from 25±6 wt.-%, more preferably 25±5 wt.-%, still more preferably 25±4 wt.-%, most preferably 25±3 wt.-%, and in particular 25±2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

The skilled person may readily determine an appropriate amount of pharmacologically active compound to include in a pharmaceutical dosage form. For instance, in the case of analgesics, the total amount of pharmacologically active compound present in the pharmaceutical dosage form is that sufficient to provide analgesia. The total amount of pharmacologically active compound administered to a patient in a dose will vary depending on numerous factors including the nature of the pharmacologically active compound, the weight of the patient, the severity of the pain, the nature of other therapeutic agents being administered etc.

In a preferred embodiment, the pharmacologically active compound is contained in the pharmaceutical dosage form in an amount of 2.5±1 mg, 5.0±2.5 mg, 7.5±5 mg, 10±5 mg, 20±5 mg, 30±5 mg, 40±5 mg, 50±5 mg, 60±5 mg, 70±5 mg, 80±5 mg, 90±5 mg, 100±5 mg, 110±5 mg, 120±5 mg, 130±5 mg, 140±5 mg, 150±5 mg, 160±5 mg, 170±5 mg, 180±5 mg, 190±5 mg, 200±5 mg, 210±5 mg, 220±5 mg, 230±5 mg, 240±5 mg, 250±5 mg, 260±5 mg, 270±5 mg, 280±5 mg, 290±5 mg, or 300±5 mg. In another preferred embodiment, the pharmacologically active compound is contained in the pharmaceutical dosage form in an amount of 2.5±1 mg, 5.0±2.5 mg, 7.5±2.5 mg, 10±2.5 mg, 15±2.5 mg, 20±2.5 mg, 25±2.5 mg, 30±2.5 mg, 35±2.5 mg, 40±2.5 mg, 45±2.5 mg, 50±2.5 mg, 55±2.5 mg, 60±2.5 mg, 65±2.5 mg, 70±2.5 mg, 75±2.5 mg, 80±2.5 mg, 85±2.5 mg, 90±2.5 mg, 95±2.5 mg, 100±2.5 mg, 105±2.5 mg, 110±2.5 mg, 115±2.5 mg, 120±2.5 mg, 125±2.5 mg, 130±2.5 mg, 135±2.5 mg, 140±2.5 mg, 145±2.5 mg, 150±2.5 mg, 155±2.5 mg, 160±2.5 mg, 165±2.5 mg, 170±2.5 mg, 175±2.5 mg, 180±2.5 mg, 185±2.5 mg, 190±2.5 mg, 195±2.5 mg, 200±2.5 mg, 205±2.5 mg, 210±2.5 mg, 215±2.5 mg, 220±2.5 mg, 225±2.5 mg, 230±2.5 mg, 235±2.5 mg, 240±2.5 mg, 245±2.5 mg, 250±2.5 mg, 255±2.5 mg, 260±2.5 mg, or 265±2.5 mg.

In a particularly preferred embodiment, the pharmacologically active compound is tapentadol, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 25 to 100 mg.

In a particularly preferred embodiment, the pharmacologically active compound is oxymorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 5 to 40 mg. In another particularly preferred embodiment, the pharmacologically active compound is oxymorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 10 to 80 mg.

In another particularly preferred embodiment, the pharmacologically active compound is oxycodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically

active compound is preferably contained in the pharmaceutical dosage form in an amount of from 5 to 80 mg.

In still another particularly preferred embodiment, the pharmacologically active compound is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 2 to 52 mg. In another particularly preferred embodiment, the pharmacologically active compound is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 4 to 104 mg.

In yet another particularly preferred embodiment, the pharmacologically active compound is hydrocodone, preferably its bitartrate salt, and the pharmaceutical dosage form is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the pharmaceutical dosage form in an amount of from 2.5 to 10 mg.

The particles present in the pharmaceutical dosage forms according to the invention preferably comprise 3 to 75 wt.-% of pharmacologically active compound, more preferably 5 to 70 wt.-% of pharmacologically active compound, still more preferably 7.5 to 65 wt.-% of pharmacologically active compound, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the content of the pharmacologically active compound is at least 25 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, most preferably at least 45 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the content of the pharmacologically active compound is at most 70 wt.-%, more preferably at most 65 wt.-%, still more preferably at most 60 wt.-%, yet more preferably at most 55 wt.-%, most preferably at most 50 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the content of the pharmacologically active compound is within the range of 35±30 wt.-%, more preferably 35±25 wt.-%, still more preferably 35±20 wt.-%, yet more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of the pharmacologically active compound is within the range of 45±30 wt.-%, more preferably 45±25 wt.-%, still more preferably 45±20 wt.-%, yet more preferably 45±15 wt.-%, most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In still another preferred embodiment, the content of the pharmacologically active compound is within the range of 55±30 wt.-%, more preferably 55±25 wt.-%, still more preferably 55±20 wt.-%, yet more preferably 55±15 wt.-%, most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

The pharmacologically active compound that is included in the preparation of the pharmaceutical dosage forms according to the invention preferably has an average particle

size of less than 500 microns, still more preferably less than 300 microns, yet more preferably less than 200 or 100 microns. There is no lower limit on the average particle size and it may be, for example, 50 microns. The particle size of pharmacologically active compounds may be determined by any technique conventional in the art, e.g. laser light scattering, sieve analysis, light microscopy or image analysis. Generally speaking it is preferable that the largest dimension of the pharmacologically active compound particle be less than the size of the particles (e.g. less than the smallest dimension of the particles).

A skilled person knows how to determine pharmacokinetic parameters such as $t_{1/2}$, T_{max} , C_{max} , AUC and bioavailability. For the purposes of the description, the pharmacokinetic parameters, which may be determined from the blood plasma concentrations of 3-(2-dimethylaminomethylcyclohexyl)phenol, are defined as follows:

C_{max}	maximum measured plasma concentration of the active ingredient after single administration (=average peak plasma level)
t_{max}	interval of time from administration of the active ingredient until C_{max} is reached
AUC	total area of the plasma concentration/time curve including the subarea from the final measured value extrapolated to infinity
$t_{1/2}$	half-life

The above parameters are in each case stated as mean values of the individual values for all investigated patients/test subjects.

A person skilled in the art knows how the pharmacokinetic parameters of the active ingredient may be calculated from the measured concentrations of the active ingredient in the blood plasma. In this connection, reference may be made, for example, to Willi Cawello (ed.) *Parameters for Compartment-free Pharmacokinetics*, Shaker Verlag Aachen (1999).

In a preferred embodiment, the pharmacologically active compound is tapentadol or a physiologically acceptable salt thereof, e.g. the hydrochloride. Preferably, the pharmaceutical dosage form according to the invention provides a mean absolute bioavailability of tapentadol of at least 22%, more preferably at least 24%, still more preferably at least 26%, yet more preferably at least 28%, most preferably at least 30%, and in particular at least 32%. T_{max} of tapentadol is preferably within the range of 1.25±1.20 h, more preferably 1.25±1.00 h, still more preferably 1.25±0.80 h, yet more preferably 1.25±0.60 h, most preferably 1.25±0.40 h, and in particular 1.25±0.20 h. $t_{1/2}$ of tapentadol is preferably within the range of 4.0±2.8 h, more preferably 4.0±2.4 h, still more preferably 4.0±2.0 h, yet more preferably 4.0±1.6 h, most preferably 4.0±1.2 h, and in particular 4.0±0.8 h. Preferably, when normalized to a dose of 100 mg tapentadol, C_{max} of tapentadol is preferably within the range of 90±85 ng/mL, more preferably 90±75 ng/mL, still more preferably 90±65 ng/mL, yet more preferably 90±55 ng/mL, most preferably 90±45 ng/mL, and in particular 90±35 ng/mL; and/or AUC of tapentadol is preferably within the range of 420±400 ng/mL·h, more preferably 420±350 ng/mL·h, still more preferably 420±300 ng/mL·h, yet more preferably 420±250 ng/mL·h, most preferably 420±200 ng/mL·h, and in particular 420±150 ng/mL·h.

In another preferred embodiment, the pharmacologically active compound is oxycodone or a physiologically acceptable salt thereof, e.g. the hydrochloride. Preferably, the pharmaceutical dosage form according to the invention provides a mean absolute bioavailability of oxycodone of at least 40%, more preferably at least 45%, still more prefer-

ably at least 50%, yet more preferably at least 55%, most preferably at least 60%, and in particular at least 70%. T_{max} of oxycodone is preferably within the range of 2.6 ± 2.5 h, more preferably 2.6 ± 2.0 h, still more preferably 2.6 ± 1.8 h, yet more preferably 2.6 ± 0.16 h, most preferably 2.6 ± 1.4 h, and in particular 2.6 ± 1.2 h. $t_{1/2}$ of oxycodone is preferably within the range of 3.8 ± 3.5 h, more preferably 3.8 ± 3.0 h, still more preferably 3.8 ± 2.5 h, yet more preferably 3.8 ± 2.0 h, most preferably 3.8 ± 1.5 h, and in particular 3.8 ± 1.0 h. Preferably, when normalized to a dose of 30 mg oxycodone, C_{max} of oxycodone is preferably within the range of 40 ± 35 ng/mL, more preferably 40 ± 30 ng/mL, still more preferably 40 ± 25 ng/mL, yet more preferably 40 ± 20 ng/mL, most preferably 40 ± 15 ng/mL, and in particular 40 ± 10 ng/mL; and/or AUC of oxycodone is preferably within the range of 270 ± 250 ng/mL·h, more preferably 270 ± 200 ng/mL·h, still more preferably 270 ± 150 ng/mL·h, yet more preferably 270 ± 100 ng/mL·h, most preferably 270 ± 75 ng/mL·h, and in particular 270 ± 50 ng/mL·h.

In still another preferred embodiment, the pharmacologically active compound is hydrocodone or a physiologically acceptable salt thereof, e.g. the bitartrate. T_{max} of hydrocodone is preferably within the range of 1.3 ± 1.2 h, more preferably 1.3 ± 1.0 h, still more preferably 1.3 ± 0.8 h, yet more preferably 1.3 ± 0.6 h, most preferably 1.3 ± 0.4 h, and in particular 1.3 ± 0.2 h. $t_{1/2}$ of hydrocodone is preferably within the range of 3.8 ± 3.5 h, more preferably 3.8 ± 3.0 h, still more preferably 3.8 ± 2.5 h, yet more preferably 3.8 ± 2.0 h, most preferably 3.8 ± 1.5 h, and in particular 3.8 ± 1.0 h.

In yet another preferred embodiment, the pharmacologically active compound is morphine or a physiologically acceptable salt thereof, e.g. the sulfate. Preferably, the pharmaceutical dosage form according to the invention provides a mean absolute bioavailability of morphine of at least 15%, more preferably at least 20%, still more preferably at least 25%, yet more preferably at least 30%, most preferably at least 35%, and in particular at least 40%. T_{max} of morphine is preferably within the range of 0.625 ± 0.60 h, more preferably 0.625 ± 0.50 h, still more preferably 0.625 ± 0.40 h, yet more preferably 0.625 ± 0.30 h, most preferably 0.625 ± 0.20 h, and in particular 0.625 ± 0.15 h. Preferably, when normalized to a dose of 30 mg morphine sulfate, C_{max} of morphine is preferably within the range of 25 ± 20 ng/mL, more preferably 25 ± 15 ng/mL, still more preferably 25 ± 10 ng/mL, yet more preferably 25 ± 5 ng/mL; and/or AUC of morphine is preferably within the range of 50 ± 45 ng/mL·h, more preferably 50 ± 40 ng/mL·h, still more preferably 50 ± 35 ng/mL·h, yet more preferably 50 ± 30 ng/mL·h, most preferably 50 ± 25 ng/mL·h, and in particular 50 ± 20 ng/mL·h.

In still another preferred embodiment, the pharmacologically active compound is amphetamine or a physiologically acceptable salt thereof. T_{max} of amphetamine is preferably within the range of 1.7 ± 1.2 h, more preferably 1.7 ± 1.0 h, still more preferably 1.7 ± 0.8 h, yet more preferably 1.7 ± 0.6 h, most preferably 1.7 ± 0.4 h, and in particular 1.7 ± 0.2 h.

In still another preferred embodiment, the pharmacologically active compound is dex-amphetamine or a physiologically acceptable salt thereof, e.g. the sulfate. T_{max} of dex-amphetamine is preferably within the range of 3.0 ± 2.9 h, more preferably 3.0 ± 2.5 h, still more preferably 3.0 ± 2.1 h, yet more preferably 3.0 ± 1.7 h, most preferably 3.0 ± 1.3 h, and in particular 3.0 ± 0.9 h. $t_{1/2}$ of dex-amphetamine is preferably within the range of 10 ± 6.0 h, more preferably 10 ± 5.0 h, still more preferably 10 ± 4.0 h, yet more preferably 10 ± 3.0 h, most preferably 10 ± 2.0 h, and in particular 10 ± 1.0 h.

The pharmaceutical dosage forms according to the invention may also comprise one or more additional pharmacologically active compounds. The additional pharmacologically active compound may be susceptible to abuse or another pharmaceutical. Additional pharmacologically active compounds may be present within the particles ("intragranular") or within the matrix ("extragranular"). Where an additional pharmacologically active compound is present intragranularly, it may be present either in combination with one or more pharmacologically active compounds within the same particles or in a discrete population of particles alone and separate from any other pharmacologically active compounds present in the pharmaceutical dosage form.

In a preferred embodiment, the pharmaceutical dosage form according to the invention, preferably the particles, comprise an opioid (agonist) as well as an opioid antagonist.

Any conventional opioid antagonist may be present, e.g. naltrexone or naloxone or their pharmaceutically acceptable salts. Naloxone, including its salts, is particularly preferred. The opioid antagonist may be present within the particles or within the matrix. Alternatively, opioid antagonist may be provided in separate particles to the pharmacologically active compounds. The preferred composition of such particles is the same as that described for pharmacologically active compound-containing particles.

The ratio of opioid agonist to opioid antagonist in the pharmaceutical dosage forms according to the invention is preferably 1:1 to 3:1 by weight, for example, 2:1 by weight.

In another preferred embodiment, neither the particles nor the pharmaceutical dosage form comprise any opioid antagonist.

The tamper-resistant pharmaceutical dosage form according to the invention comprises a multitude of particles which comprise a polyalkylene oxide, wherein the content of the polyalkylene oxide is at least 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the polyalkylene oxide is selected from polymethylene oxide, polyethylene oxide and polypropylene oxide, or copolymers thereof. Polyethylene oxide is preferred.

Preferably, the polyalkylene oxide has a weight average molecular weight of at least 500,000 g/mol. In a preferred embodiment, the polyalkylene oxide has a weight average molecular weight (M_w) or viscosity average molecular weight (M_v) of at least 750,000 g/mol, preferably at least 1,000,000 g/mol or at least 2,500,000 g/mol, more preferably in the range of 1,000,000 g/mol to 15,000,000 g/mol, and most preferably in the range of 5,000,000 g/mol to 10,000,000 g/mol. Suitable methods to determine M_w and M_v are known to a person skilled in the art. M_v is preferably determined by rheological measurements, whereas M_w can be determined by gel permeation chromatography (GPC).

Polyalkylene oxide may comprise a single polyalkylene oxide having a particular average molecular weight, or a mixture (blend) of different polymers, such as two, three, four or five polymers, e.g., polymers of the same chemical nature but different average molecular weight, polymers of different chemical nature but same average molecular weight, or polymers of different chemical nature as well as different molecular weight.

For the purpose of the specification, a polyalkylene glycol has a molecular weight of up to 20,000 g/mol whereas a polyalkylene oxide has a molecular weight of more than 20,000 g/mol. In a preferred embodiment, the weight average over all molecular weights of all polyalkylene oxides

that are contained in the pharmaceutical dosage form is at least 200,000 g/mol. Thus, polyalkylene glycols, if any, are preferably not taken into consideration when determining the weight average molecular weight of polyalkylene oxide.

In a preferred embodiment, polyalkylene oxide is homogeneously distributed in the particles according to the invention. Preferably, the pharmacologically active compound and polyalkylene oxide are intimately homogeneously distributed in the particles so that the particles do not contain any segments where either pharmacologically active compound is present in the absence of polyalkylene oxide or where polyalkylene oxide is present in the absence of pharmacologically active compound.

When the particles are film coated, the polyalkylene oxide is preferably homogeneously distributed in the core of the particles, i.e. the film coating preferably does not contain polyalkylene oxide. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the polyalkylene oxide contained in the core.

The polyalkylene oxide may be combined with one or more different polymers selected from the group consisting of polyalkylene oxide, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyvinylpyrrolidone, poly(alk)acrylate, poly(hydroxy fatty acids), such as for example poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (Biopol), poly(hydroxyvaleric acid); polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyamide, polylactide, polyacetal (for example polysaccharides optionally with modified side chains), polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate (Polyactive®), polyanhydride (Polifeprosan), copolymers thereof, block-copolymers thereof (e.g., Poloxamer®), and mixtures of at least two of the stated polymers, or other polymers with the above characteristics.

Preferably, the molecular weight dispersity M_w/M_n of polyalkylene oxide is within the range of 2.5 ± 2.0 , more preferably 2.5 ± 1.5 , still more preferably 2.5 ± 1.0 , yet more preferably 2.5 ± 0.8 , most preferably 2.5 ± 0.6 , and in particular 2.5 ± 0.4 .

The polyalkylene oxide preferably has a viscosity at 25° C. of 30 to 17,600 cP, more preferably 55 to 17,600 cP, still more preferably 600 to 17,600 cP and most preferably 4,500 to 17,600 cP, measured in a 5 wt.-% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2/rotational speed 2 rpm); of 400 to 4,000 cP, more preferably 400 to 800 cP or 2,000 to 4,000 cP, measured on a 2 wt.-% aqueous solution using the stated viscosimeter (spindle no. 1 or 3/rotational speed 10 rpm); or of 1,650 to 10,000 cP, more preferably 1,650 to 5,500 cP, 5,500 to 7,500 cP or 7,500 to 10,000 cP, measured on a 1 wt.-% aqueous solution using the stated viscosimeter (spindle no. 2/rotational speed 2 rpm).

Polyethylene oxide that is suitable for use in the pharmaceutical dosage forms according to the invention is commercially available from Dow. For example, Polyox WSR N-12K, Polyox N-60K, Polyox WSR 301 NF or Polyox WSR 303NF may be used in the pharmaceutical dosage forms according to the invention. For details concerning the properties of these products, it can be referred to e.g. the product specification.

Preferably, the content of the polyalkylene oxide is within the range of from 25 to 80 wt.-%, more preferably 25 to 75

wt.-%, still more preferably 25 to 70 wt.-%, yet more preferably 25 to 65 wt.-%, most preferably 30 to 65 wt.-% and in particular 35 to 65 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In a preferred embodiment, the content of the polyalkylene oxide is at least 30 wt.-%, more preferably at least 35 wt.-%, still more preferably at least 40 wt.-%, yet more preferably at least 45 wt.-% and in particular at least 50 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the overall content of polyalkylene oxide is within the range of 35 ± 8 wt.-%, more preferably 35 ± 6 wt.-%, most preferably 35 ± 4 wt.-%, and in particular 35 ± 2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the overall content of polyalkylene oxide is within the range of 40 ± 12 wt.-%, more preferably 40 ± 10 wt.-%, most preferably 40 ± 7 wt.-%, and in particular 40 ± 3 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In still another preferred embodiment, the overall content of polyalkylene oxide is within the range of 45 ± 16 wt.-%, more preferably 45 ± 12 wt.-%, most preferably 45 ± 8 wt.-%, and in particular 45 ± 4 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In yet another preferred embodiment, the overall content of polyalkylene oxide is within the range of 50 ± 20 wt.-%, more preferably 50 ± 15 wt.-%, most preferably 50 ± 10 wt.-%, and in particular 50 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In a further preferred embodiment, the overall content of polyalkylene oxide is within the range of 55 ± 20 wt.-%, more preferably 55 ± 15 wt.-%, most preferably 55 ± 10 wt.-%, and in particular 55 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In still a further a preferred embodiment, the overall content of polyalkylene oxide is within the range of 60 ± 20 wt.-%, more preferably 60 ± 15 wt.-%, most preferably 60 ± 10 wt.-%, and in particular 60 ± 5 wt.-%. In a still further a preferred embodiment, the overall content of polyalkylene oxide is within the range of 65 ± 20 wt.-%, more preferably 65 ± 15 wt.-%, and most preferably 65 ± 10 wt.-%, and in particular 65 ± 5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the relative weight ratio of the polyalkylene oxide to the pharmacologically active compound is within the range of 30:1 to 1:10, more preferably 20:1 to 1:1, still more preferably 15:1 to 5:1, yet more preferably 14:1 to 6:1, most preferably 13:1 to 7:1, and in particular 12:1 to 8:1.

The tamper-resistant pharmaceutical dosage form according to the invention comprises a multitude of particles which comprise a disintegrant, wherein the content of the disintegrant is more than 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, particularly when the pharmaceutical dosage form is a capsule, the pharmaceutical dosage form contains the entire amount of disintegrant within the particles, i.e. outside the particles there is preferably no disintegrant. Furthermore, the disintegrant is preferably homogeneously distributed in the particles. Preferably, when the particles are coated, the coating does not contain disintegrant.

In another preferred embodiment, particularly when the pharmaceutical dosage form is a tablet, the pharmaceutical dosage form contains the disintegrant within the particles as well as outside the particles. In a preferred embodiment, the nature of disintegrant within the particle is identical with the nature of disintegrant outside the particles. However, different disintegrants inside the particles and outside the particles are also possible in accordance with the invention. Furthermore, the disintegrant is preferably homogeneously distributed in the particles. Preferably, when the particles are coated, the coating does not contain disintegrant.

Suitable disintegrants are known to the skilled person and are preferably selected from the group consisting of polysaccharides, starches, starch derivatives, cellulose derivatives, polyvinylpyrrolidones, acrylates, gas releasing substances, and the mixtures of any of the foregoing.

Preferred starches include but are not limited to "standard starch" (e.g. native maize starch) and pregelatinized starch (e.g. starch 1500).

Preferred starch derivatives include but are not limited to sodium starch glycolate (carboxymethyl starch sodium, e.g. Vivastar).

Preferred cellulose derivatives include but are not limited to croscarmellose sodium (=crosslinked sodium carboxymethylcellulose; e.g. Vivasol®), carmellose calcium (calcium carboxymethylcellulose), carmellose sodium (sodium carboxymethylcellulose), low substituted carmellose sodium (low substituted sodium carboxymethylcellulose; average degree of substitution (DS) 0.20 to 0.40, Mr 80,000 to 600,000 g/mol, CAS 9004-32-4, E 466), low substituted hydroxypropylcellulose (having a content of propyl groups within the range of from 5 to 16%; CAS 9004-64-2).

Preferred acrylates include but are not limited to carbopol.

Preferred polyvinylpyrrolidones include but are not limited to crospovidone (PVP)

Preferred gas releasing substances include but are not limited to sodium bicarbonate.

Preferred disintegrants include but are not limited to crosslinked sodium carboxymethylcellulose (Na-CMC) (e.g. Crosscarmellose, Vivasol®, Ac-Di-Sol®); crosslinked casein (e.g. Esma-Spreng®); polysaccharide mixtures obtained from soybeans (e.g. Emcosoy®); maize starch or pretreated maize starch (e.g. Amijel5; alginic acid, sodium alginate, calcium alginate; polyvinylpyrrolidone (PVP) (e.g. Kollidone®, Polyplasdone®, Polydone®); crosslinked polyvinylpyrrolidone (PVP CI) (e.g. Polyplasdone® XL); starch and pretreated starch such as sodium carboxymethyl starch (=sodium starch glycolate, e.g. Explotab®, Prejel®, Primotab® ET, Starch® 1500, Ulmatryl®, and the mixtures thereof. Crosslinked polymers are particularly preferred disintegrants, especially crosslinked sodium carboxymethylcellulose (Na-CMC) or crosslinked polyvinylpyrrolidone (PVP CI).

Particularly preferred disintegrants are selected from the group consisting of

crosslinked sodium carboxymethylcellulose (Na-CMC)

(e.g. Crosscarmellose, Vivasol®, Ac-Di-Sol®);

crosslinked casein (e.g. Esma-Spreng®);

alginic acid, sodium alginate, calcium alginate;

polysaccharide mixtures obtained from soybeans (e.g. Emcosoy®);

starch and pretreated starch such as sodium carboxymethyl starch (=sodium starch glycolate, e.g. Explotab®, Prejel®, Primotab® ET, Starch® 1500, Ulmatryl®;

maize starch or pretreated maize starch (e.g. Amijel®);

and mixtures of any of the foregoing.

Preferably, the content of the disintegrant is at least 6.0 wt.-%, at least 7.0 wt.-%, at least 8.0 wt.-%, at least 9.0 wt.-%, or at least 10 wt.-%, more preferably at least 12 wt.-%, still more preferably at least 14 wt.-%, yet more preferably at least 15 wt.-%, even more preferably at least 16 wt.-%, most preferably at least 18 wt.-%, and in particular at least 19 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

It has been surprisingly found that the content of disintegrant typically has an optimum at which it provides the best balance of immediate release properties on the one hand and resistance against solvent extraction on the other hand. Said optimum may vary, but preferably is within the range of from about 10 wt.-% to about 20 wt.-%, relative to the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 15 ± 9.0 wt.-%, more preferably 15 ± 8.5 wt.-%, still more preferably 15 ± 8.0 wt.-%, yet more preferably 15 ± 7.5 wt.-%, most preferably 15 ± 7.0 wt.-%, and in particular 15 ± 6.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In still another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 15 ± 6.0 wt.-%, more preferably 15 ± 5.5 wt.-%, still more preferably 15 ± 5.0 wt.-%, yet more preferably 15 ± 4.5 wt.-%, most preferably 15 ± 4.0 wt.-%, and in particular 15 ± 3.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 15 ± 3.0 wt.-%, more preferably 15 ± 2.5 wt.-%, still more preferably 15 ± 2.0 wt.-%, yet more preferably 15 ± 1.5 wt.-%, most preferably 15 ± 1.0 wt.-%, and in particular 15 ± 0.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 20 ± 15 wt.-% or 20 ± 14 wt.-%, more preferably 20 ± 13 wt.-%, still more preferably 20 ± 12 wt.-%, yet more preferably 20 ± 11 wt.-%, most preferably 20 ± 10 wt.-%, and in particular 20 ± 9.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 20 ± 9.0 wt.-%, more preferably 20 ± 8.5 wt.-%, still more preferably 20 ± 8.0 wt.-%, yet more preferably 20 ± 7.5 wt.-%, most preferably 20 ± 7.0 wt.-%, and in particular 20 ± 6.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In still another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 20 ± 6.0 wt.-%, more preferably 20 ± 5.5 wt.-%, still more preferably 20 ± 5.0 wt.-%, yet more preferably 20 ± 4.5 wt.-%, most preferably 20 ± 4.0 wt.-%, and in particular 20 ± 3.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 20 ± 3.0 wt.-%, more preferably 20 ± 2.5 wt.-%, still more preferably 20 ± 2.0 wt.-%, yet more preferably 20 ± 1.5 wt.-%, most preferably 20 ± 1.0 wt.-%, and in

particular 20 ± 0.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In still another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 25 ± 9.0 wt.-%, more preferably 25 ± 8.5 wt.-%, still more preferably 25 ± 8.0 wt.-%, yet more preferably 25 ± 7.5 wt.-%, most preferably 25 ± 7.0 wt.-%, and in particular 25 ± 6.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In still another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 25 ± 6.0 wt.-%, more preferably 25 ± 5.5 wt.-%, still more preferably 25 ± 5.0 wt.-%, yet more preferably 25 ± 4.5 wt.-%, most preferably 25 ± 4.0 wt.-%, and in particular 25 ± 3.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the content of the disintegrant in the pharmaceutical dosage form is within the range of 25 ± 3.0 wt.-%, more preferably 25 ± 2.5 wt.-%, still more preferably 25 ± 2.0 wt.-%, yet more preferably 25 ± 1.5 wt.-%, most preferably 25 ± 1.0 wt.-%, and in particular 25 ± 0.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

When the pharmaceutical dosage form according to the invention contains more than a single disintegrant, e.g. a mixture of two different disintegrants, the above percentages preferably refer to the total content of disintegrants.

Preferably, the relative weight ratio of the polyalkylene oxide to the disintegrant is within the range of 8:1 to 1:5, more preferably 7:1 to 1:4, still more preferably 6:1 to 1:3, yet more preferably 5:1 to 1:2, most preferably 4:1 to 1:1, and in particular 3:1 to 2:1.

Preferably, the relative weight ratio of the pharmacologically active ingredient to the disintegrant is within the range of 4:1 to 1:10, more preferably 3:1 to 1:9, still more preferably 2:1 to 1:8, yet more preferably 1:1 to 1:7, most preferably 1:2 to 1:6, and in particular 1:3 to 1:5.

The pharmaceutical dosage form may contain a single disintegrant or a mixture of different disintegrants. Preferably, the pharmaceutical dosage form contains a single disintegrant.

Preferably, the pharmaceutical dosage form and/or the particles according to the invention additionally comprise a gelling agent, which is preferably a polysaccharide.

While the gelling agent may principally contribute to the overall resistance against solvent extraction of the pharmaceutical dosage form according to the invention, it has been unexpectedly found that one or more disintegrants in comparatively high amounts in combination with one or more gelling agents are of particular advantage in this regard. It has been surprisingly found that the combination of one or more disintegrants in comparatively high amounts with one or more gelling agent is robust against variation of the pharmacologically active ingredient. Thus, according to the present invention exchanging a given pharmacologically active ingredient by another pharmacologically active ingredient does preferably not substantially alter the overall resistance against solvent extraction of the pharmaceutical dosage form according to the invention.

As used herein the term "gelling agent" is used to refer to a compound that, upon contact with a solvent (e.g. water), absorbs the solvent and swells, thereby forming a viscous or semi-viscous substance. Preferred gelling agents are not cross-linked. This substance may moderate pharmacologically active compound release from the particles in both

aqueous and aqueous alcoholic media. Upon full hydration, a thick viscous solution or dispersion is typically produced that significantly reduces and/or minimizes the amount of free solvent which can contain an amount of solubilized pharmacologically active compound, and which can be drawn into a syringe. The gel that is formed may also reduce the overall amount of pharmacologically active compound extractable with the solvent by entrapping the pharmacologically active compound within a gel structure. Thus the gelling agent may play an important role in conferring tamper-resistance to the pharmaceutical dosage forms according to the invention.

Gelling agents include pharmaceutically acceptable polymers, typically hydrophilic polymers, such as hydrogels. Representative examples of gelling agents include gums like xanthan gum, carrageenan, locust bean gum, guar, tragacanth, acaica (gum arabic), karaya, tara and gellan gum; polyethylene oxide, polyvinyl alcohol, hydroxypropylmethyl cellulose, carbomers, poly(uronic) acids and mixtures thereof.

Preferably, the content of the gelling agent, preferably xanthan gum, is at least 1.0 wt.-%, more preferably at least 2.0 wt.-%, still more preferably at least 3.0 wt.-%, most preferably at least 4.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the content of the gelling agent, preferably xanthan gum, is within the range of 5.0 ± 4.5 wt.-%, more preferably 5.0 ± 4.0 wt.-%, still more preferably 5.0 ± 3.5 wt.-%, yet more preferably 5.0 ± 3.0 wt.-%, even more preferably 5.0 ± 2.5 wt.-%, most preferably 5.0 ± 2.0 wt.-%, and in particular 5.0 ± 1.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the relative weight ratio of disintegrant:gelling agent is within the range of from 11:1 to 1:5, more preferably 10:1 to 1:4, still more preferably 9:1 to 1:3, yet more preferably 8:1 to 1:2, even more preferably 7:1 to 1:1, most preferably 6:1 to 2:1, and in particular 5:1 to 3:1.

The pharmaceutical dosage form and/or the particles according to the invention may contain additional pharmaceutical excipients conventionally contained in pharmaceutical dosage forms in conventional amounts, such as antioxidants, preservatives, lubricants, plasticizer, fillers, binders, and the like.

The skilled person will readily be able to determine appropriate further excipients as well as the quantities of each of these excipients. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate the pharmaceutical dosage forms according to the invention are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Preferably, the pharmaceutical dosage form and/or the particles according to the invention further comprise an antioxidant. Suitable antioxidants include ascorbic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, coniferyl benzoate, nordihydroguajaretic acid, gallus acid esters, sodium bisulfite, particularly preferably butylhydroxytoluene or butylhydroxyanisole and α -tocopherol. The antioxidant is preferably present in quantities of 0.01 wt.-% to 10 wt.-%, more preferably of 0.03 wt.-% to 5 wt.-%, most preferably of 0.05 wt.-% to 2.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the pharmaceutical dosage form and/or the particles according to the invention further comprise an acid, preferably citric acid. The amount of acid is preferably in the range of 0.01 wt.-% to 20 wt.-%, more preferably in the range of 0.02 wt.-% to 10 wt.-%, and still more preferably in the range of 0.05 wt.-% to 5 wt.-%, and most preferably in the range of 0.1 wt.-% to 1.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the pharmaceutical dosage form and/or the particles according to the invention further comprise another polymer which is preferably selected from cellulose esters and cellulose ethers, in particular hydroxypropyl methylcellulose (HPMC).

The amount of the further polymer, preferably hydroxypropyl methylcellulose, preferably ranges from 0.1 wt.-% to 30 wt.-%, more preferably in the range of 1.0 wt.-% to 20 wt.-%, most preferably in the range of 2.0 wt.-% to 15 wt.-%, and in particular in the range of 3.5 wt.-% to 10.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the relative weight ratio of the polyalkylene oxide to the further polymer is within the range of $4.5 \pm 2:1$, more preferably $4.5 \pm 1.5:1$, still more preferably $4.5 \pm 1:1$, yet more preferably $4.5 \pm 0.5:1$, most preferably $4.5 \pm 0.2:1$, and in particular $4.5 \pm 0.1:1$. In another preferred embodiment, the relative weight ratio of the polyalkylene oxide to the further polymer is within the range of $8 \pm 7:1$, more preferably $8 \pm 6:1$, still more preferably $8 \pm 5:1$, yet more preferably $8 \pm 4:1$, most preferably $8 \pm 3:1$, and in particular $8 \pm 2:1$. In still another preferred embodiment, the relative weight ratio of the polyalkylene oxide to the further polymer is within the range of $11 \pm 8:1$, more preferably $11 \pm 7:1$, still more preferably $11 \pm 6:1$, yet more preferably $11 \pm 5:1$, most preferably $11 \pm 4:1$, and in particular $11 \pm 3:1$.

In another preferred embodiment, the pharmaceutical dosage form and/or the particles according to the invention do not contain any further polymer besides the polyalkylene oxide and optionally, polyethylene glycol.

In a preferred embodiment, the pharmaceutical dosage form contains at least one lubricant. Preferably, the lubricant is contained in the pharmaceutical dosage form outside the particles, i.e. the particles as such preferably do not contain lubricant. In another preferred embodiment, the pharmaceutical dosage form contains no lubricant. Especially preferred lubricants are selected from

- magnesium stearate and stearic acid;
- glycerides of fatty acids, including monoglycerides, diglycerides, triglycerides, and mixtures thereof; preferably of C_6 to C_{22} fatty acids; especially preferred are partial glycerides of the C_{16} to C_{22} fatty acids such as glycerol behenat, glycerol palmitostearate and glycerol monostearate;
- polyoxyethylene glycerol fatty acid esters, such as mixtures of mono-, di- and triesters of glycerol and di- and monoesters of macrogols having molecular weights within the range of from 200 to 4000 g/mol, e.g., macrogolglycerolcaprylocaprate, macrogolglycerollaurate, macrogolglycerolcocoate, macrogolglycerolli-

- noleate, macrogol-20-glycerolmonostearate, macrogol-6-glycerolcaprylocaprate, macrogolglycerololeate; macrogolglycerolstearate, macrogolglycerolhydroxystearate, and macrogolglycerolrizinoate;
- polyglycolized glycerides, such as the one known and commercially available under the trade name "Labrasol";
- fatty alcohols that may be linear or branched, such as cetylalcohol, stearylalcohol, cetylstearyl alcohol, 2-octyldodecane-1-ol and 2-hexyldecane-1-ol;
- polyethylene glycols having a molecular weight between 10.000 and 60.000 g/mol; and
- natural semi-synthetic or synthetic waxes, preferably waxes with a softening point of at least 50° C., more preferably 60° C., and in particular carnauba wax and bees wax.

Preferably, the amount of the lubricant ranges from 0.01 wt.-% to 10 wt.-%, more preferably in the range of 0.05 wt.-% to 7.5 wt.-%, most preferably in the range of 0.1 wt.-% to 5 wt.-%, and in particular in the range of 0.1 wt.-% to 1 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

Preferably, the pharmaceutical dosage form and/or the particles according to the invention further comprise a plasticizer. The plasticizer improves the processability of the polyalkylene oxide. A preferred plasticizer is polyalkylene glycol, like polyethylene glycol, triacetin, fatty acids, fatty acid esters, waxes and/or microcrystalline waxes. Particularly preferred plasticizers are polyethylene glycols, such as PEG 6000 (Macrogol 6000).

Preferably, the content of the plasticizer is within the range of from 0.5 to 30 wt.-%, more preferably 1.0 to 25 wt.-%, still more preferably 2.5 wt.-% to 22.5 wt.-%, yet more preferably 5.0 wt.-% to 20 wt.-%, most preferably 6 to 20 wt.-% and in particular 7 wt.-% to 17.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the plasticizer is a polyalkylene glycol having a content within the range of 7 ± 6 wt.-%, more preferably 7 ± 5 wt.-%, still more preferably 7 ± 4 wt.-%, yet more preferably 7 ± 3 wt.-%, most preferably 7 ± 2 wt.-%, and in particular 7 ± 1 wt.-%, based based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles. In another preferred embodiment, the plasticizer is a polyalkylene glycol having a content within the range of 10 ± 8 wt.-%, more preferably 10 ± 6 wt.-%, still more preferably 10 ± 5 wt.-%, yet more preferably 10 ± 4 wt.-%, most preferably 10 ± 3 wt.-%, and in particular 10 ± 2 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

In a preferred embodiment, the relative weight ratio of the polyalkylene oxide to the polyalkylene glycol is within the range of $5.4 \pm 2:1$, more preferably $5.4 \pm 1.5:1$, still more preferably $5.4 \pm 1:1$, yet more preferably $5.4 \pm 0.5:1$, most preferably $5.4 \pm 0.2:1$, and in particular $5.4 \pm 0.1:1$. This ratio satisfies the requirements of relative high polyalkylene oxide content and good extrudability.

Plasticizers can sometimes act as a lubricant, and lubricants can sometimes act as a plasticizer.

In preferred compositions of the particles that are preferably hot-melt extruded and that are contained in the pharmaceutical dosage form according to the invention, the pharmacologically active ingredient is an opioid and the polyalkylene oxide is a polyethylene oxide with a weight average molecular weight within the range of from 0.5 to 15 million g/mol. Particularly preferred embodiments A¹ to A⁸ are summarized in the table here below:

[wt.-%]	A ¹	A ²	A ³	A ⁴	A ⁵	A ⁶	A ⁷	A ⁸
opioid	5.5 ± 5.0	5.5 ± 4.5	5.5 ± 4.0	5.5 ± 3.5	5.5 ± 3.0	5.5 ± 2.5	5.5 ± 2.0	5.5 ± 1.5
polyethylene oxide	55 ± 40	55 ± 35	55 ± 30	55 ± 25	55 ± 20	55 ± 15	55 ± 10	55 ± 5
disintegrant	20 ± 15	20 ± 13	20 ± 11	20 ± 9	20 ± 7	20 ± 5	20 ± 4	20 ± 3
optionally, acid	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.5	0.8 ± 0.5	0.8 ± 0.5	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3
optionally, plasticizer	14 ± 13	14 ± 12	14 ± 11	14 ± 10	14 ± 9	14 ± 8	14 ± 7	14 ± 6
optionally, antioxidant	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
optionally, gelling agent	5.0 ± 4.5	5.0 ± 4.0	5.0 ± 3.5	5.0 ± 3.0	5.0 ± 2.5	5.0 ± 2.0	5.0 ± 1.5	5.0 ± 1.0

(all percentages relative to the total weight of the particles).

In the above table, “optionally” in the context of the acid, the plasticizer, the antioxidant and the gelling agent means that these excipients may independently of one another be contained in the particles or not and provided that they are contained in the particles, their content in wt.-% is as specified.

The pharmaceutical dosage form according to the invention preferably contains no antagonists for the pharmacologically active compound, preferably no antagonists against psychotropic substances, in particular no antagonists against opioids. Antagonists suitable for a given pharmacologically active compound are known to the person skilled in the art and may be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof. The pharmaceutical dosage form according to the invention preferably contains no antagonists selected from among the group comprising naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate; and no neuroleptics, for example a compound selected from among the group comprising haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopenthixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

Further, the pharmaceutical dosage form according to the invention preferably also contains no bitter substance. Bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Examples of bitter substances are aromatic oils, such as peppermint oil, *eucalyptus* oil, bitter almond oil, menthol, fruit aroma substances, aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

The pharmaceutical dosage form according to the invention accordingly preferably contains neither antagonists for the pharmacologically active compound nor bitter substances.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is a tablet, wherein the particles are contained in a matrix of a matrix material. In the following, this preferred embodiment is referred to as the “preferred tablet according to the invention”.

The preferred tablet according to the invention comprises subunits having different morphology and properties, namely drug-containing particles and matrix material,

wherein the particles form a discontinuous phase within the matrix material. The particles typically have mechanical properties that differ from the mechanical properties of the matrix material. Preferably, the particles have a higher mechanical strength than the matrix material. The particles within the preferred tablet according to the invention can be visualized by conventional means such as solid state nuclear magnetic resonance spectroscopy, raster electron microscopy, terahertz spectroscopy and the like.

In the preferred tablet according to the invention, the particles are incorporated in a matrix material. From a macroscopic perspective, the matrix material preferably forms a continuous phase in which the particles are embedded as discontinuous phase.

Preferably, the matrix material is a homogenous coherent mass, preferably a homogeneous mixture of solid constituents, in which the particles are embedded thereby spatially separating the particles from one another. While it is possible that the surfaces of particles are in contact or at least in very close proximity with one another, the plurality of particles preferably cannot be regarded as a single continuous coherent mass within the preferred tablet according to the invention.

In other words, the preferred tablet according to the invention comprises the particles as volume element(s) of a first type in which the pharmacologically active compound, the polyalkylene oxide and the disintegrant are contained, preferably homogeneously, and the matrix material as volume element of a second type differing from the material that forms the particles, preferably containing neither pharmacologically active compound nor polyalkylene oxide, but optionally polyethylene glycol which differs from polyethylene oxide in its molecular weight.

A purpose of the matrix material in the preferred tablet according to the invention is to ensure rapid disintegration and subsequent release of the pharmacologically active compound from the disintegrated preferred tablet according to the invention, i.e. from the particles. Thus, the matrix material preferably does not contain any excipient that might have a retardant effect on disintegration and drug release, respectively. Thus, the matrix material preferably does not contain any polymer that is typically employed as matrix material in prolonged release formulations.

The preferred tablet according to the invention preferably comprises the matrix material in an amount of more than one third of the total weight of the preferred tablet according to the invention. Thus, the polyalkylene oxide that is contained in the particles of the preferred tablet according to the invention is preferably not also contained in the matrix material.

Preferably, the pharmacologically active compound which is contained in the particles of the preferred tablet

according to the invention is preferably not also contained in the matrix material. Thus, in a preferred embodiment, the total amount of pharmacologically active compound contained in the preferred tablet according to the invention is present in the particles which form a discontinuous phase within the matrix material; and the matrix material forming a continuous phase does not contain any pharmacologically active compound.

Preferably, the content of the matrix material is at least 35 wt.-%, at least 37.5 wt.-% or at least 40 wt.-%; more preferably at least 42.5 wt.-%, at least 45 wt.-%, at least 47.5 wt.-% or at least 50 wt.-%; still more preferably at least 52.5 wt.-%, at least 55 wt.-%, at least 57.5 wt.-% or at least 60 wt.-%; yet more preferably at least 62.5 wt.-%, at least 65 wt.-%, at least 67.5 wt.-% or at least 60 wt.-%; most preferably at least 72.5 wt.-%, at least 75 wt.-%, at least 77.5 wt.-% or at least 70 wt.-%; and in particular at least 82.5 wt.-%, at least 85 wt.-%, at least 87.5 wt.-% or at least 90 wt.-%; based on the total weight of the preferred tablet according to the invention.

Preferably, the content of the matrix material is at most 90 wt.-%, at most 87.5 wt.-%, at most 85 wt.-%, or at most 82.5 wt.-%; more preferably at most 80 wt.-%, at most 77.5 wt.-%, at most 75 wt.-% or at most 72.5 wt.-%; still more preferably at most 70 wt.-%, at most 67.5 wt.-%, at most 65 wt.-% or at most 62.5 wt.-%; yet more preferably at most 60 wt.-%, at most 57.5 wt.-%, at most 55 wt.-% or at most 52.5 wt.-%; most preferably at most 50 wt.-%, at most 47.5 wt.-%, at most 45 wt.-% or at most 42.5 wt.-%; and in particular at most 40 wt.-%, at most 37.5 wt.-%, or at most 35 wt.-%; based on the total weight of the preferred tablet according to the invention.

In a preferred embodiment, the content of the matrix material is within the range of 40 ± 5 wt.-%, more preferably 40 ± 2.5 wt.-%, based on the total weight of the preferred tablet according to the invention. In another preferred embodiment, the content of the matrix material is within the range of 45 ± 10 wt.-%, more preferably 45 ± 7.5 wt.-%, still more preferably 45 ± 5 wt.-%, and most preferably 45 ± 2.5 wt.-%, based on the total weight of the preferred tablet according to the invention. In still another preferred embodiment, the content of the matrix material is within the range of 50 ± 10 wt.-%, more preferably 50 ± 7.5 wt.-%, still more preferably 50 ± 5 wt.-%, and most preferably 50 ± 2.5 wt.-%, based on the total weight of the preferred tablet according to the invention. In yet another preferred embodiment, the content of the matrix material is within the range of 55 ± 10 wt.-%, more preferably 55 ± 7.5 wt.-%, still more preferably 55 ± 5 wt.-%, and most preferably 55 ± 2.5 wt.-%, based on the total weight of the preferred tablet according to the invention.

Preferably, the matrix material is a mixture, preferably a homogeneous mixture of at least two different constituents, more preferably of at least three different constituents. In a preferred embodiment, all constituents of the matrix material are homogeneously distributed in the continuous phase that is formed by the matrix material.

The pharmaceutical dosage form according to the invention is tamper-resistant.

As used herein, the term "tamper-resistant" refers to pharmaceutical dosage forms that are resistant to conversion into a form suitable for misuse or abuse, particular for nasal and/or intravenous administration, by conventional means such as grinding in a mortar or crushing by means of a hammer. In this regard, the pharmaceutical dosage forms as such may be crushable by conventional means. However, the particles contained in the pharmaceutical dosage forms

according to the invention preferably exhibit mechanical properties such that they cannot be pulverized by conventional means any further. As the particles are of macroscopic size and contain the pharmacologically active compound, they cannot be administered nasally thereby rendering the pharmaceutical dosage forms tamper-resistant. Preferably, when trying to tamper the dosage form in order to prepare a formulation suitable for abuse by intravenous administration, the liquid part of the formulation that can be separated from the remainder by means of a syringe is as less as possible, preferably it contains not more than 20 wt.-%, more preferably not more than 15 wt.-%, still more preferably not more than 10 wt.-%, and most preferably not more than 5 wt.-% of the originally contained pharmacologically active compound. Preferably, this property is tested by (i) dispensing a pharmaceutical dosage form that is either intact or has been manually comminuted by means of two spoons in 5 ml of purified water, (ii) heating the liquid up to its boiling point, (iii) boiling the liquid in a covered vessel for 5 min without the addition of further purified water, (iv) drawing up the hot liquid into a syringe (needle 21 G equipped with a cigarette filter), (v) determining the amount of the pharmacologically active compound contained in the liquid within the syringe.

Further, when trying to disrupt the pharmaceutical dosage forms by means of a hammer or mortar, the particles tend to adhere to one another thereby forming aggregates and agglomerates, respectively, which are larger in size than the untreated particles.

Preferably, tamper-resistance is achieved based on the mechanical properties of the particles so that comminution is avoided or at least substantially impeded. According to the invention, the term comminution means the pulverization of the particles using conventional means usually available to an abuser, for example a pestle and mortar, a hammer, a mallet or other conventional means for pulverizing under the action of force. Thus, tamper-resistance preferably means that pulverization of the particles using conventional means is avoided or at least substantially impeded.

Preferably, the mechanical properties of the particles according to the invention, particularly their breaking strength and deformability, substantially rely on the presence and spatial distribution of polyalkylene oxide, although their mere presence does typically not suffice in order to achieve said properties. The advantageous mechanical properties of the particles according to the invention may not automatically be achieved by simply processing pharmacologically active compound, polyalkylene oxide, and optionally further excipients by means of conventional methods for the preparation of pharmaceutical dosage forms. In fact, usually suitable apparatuses must be selected for the preparation and critical processing parameters must be adjusted, particularly pressure/force, temperature and time. Thus, even if conventional apparatuses are used, the process protocols usually must be adapted in order to meet the required criteria.

In general, the particles exhibiting the desired properties may be obtained only if, during preparation of the particles, suitable components in suitable amounts are exposed to a sufficient pressure at a sufficient temperature for a sufficient period of time.

Thus, regardless of the apparatus used, the process protocols must be adapted in order to meet the required criteria.

Therefore, the breaking strength and deformability of the particles is separable from the composition.

The particles contained in the pharmaceutical dosage form according to the invention preferably have a breaking strength of at least 300 N, at least 400 N, or at least 500 N, preferably at least 600 N, more preferably at least 700 N, still more preferably at least 800 N, yet more preferably at least 1000 N, most preferably at least 1250 N and in particular at least 1500 N.

In order to verify whether a particle exhibits a particular breaking strength of e.g. 300 N or 500 N it is typically not necessary to subject said particle to forces much higher than 300 N and 500 N, respectively. Thus, the breaking strength test can usually be terminated once the force corresponding to the desired breaking strength has been slightly exceeded, e.g. at forces of e.g. 330 N and 550 N, respectively.

The "breaking strength" (resistance to crushing) of a pharmaceutical dosage form and of a particle is known to the skilled person. In this regard it can be referred to, e.g., W. A. Ritschel, *Die Tablette*, 2. Auflage, Editio Cantor Verlag Aulendorf, 2002; H Liebermann et al., *Pharmaceutical dosage forms: Pharmaceutical dosage forms*, Vol. 2, Informa Healthcare; 2 edition, 1990; and *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare; 1 edition.

For the purpose of the specification, the breaking strength is preferably defined as the amount of force that is necessary in order to fracture the particle (=breaking force). Therefore, for the purpose of the specification a particle does preferably not exhibit the desired breaking strength when it breaks, i.e., is fractured into at least two independent parts that are separated from one another. In another preferred embodiment, however, the particle is regarded as being broken if the force decreases by 50% (threshold value) of the highest force measured during the measurement (see below).

The particles according to the invention are distinguished from conventional particles that can be contained in pharmaceutical dosage forms in that, due to their breaking strength, they cannot be pulverized by the application of force with conventional means, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverization, in particular devices developed for this purpose (tablet crushers). In this regard "pulverization" means crumbling into small particles. Avoidance of pulverization virtually rules out oral or parenteral, in particular intravenous or nasal abuse.

Conventional particles typically have a breaking strength well below 200 N.

The breaking strength of conventional round pharmaceutical dosage forms/particles may be estimated according to the following empirical formula: Breaking Strength [in N]=10xDiameter Of The Pharmaceutical dosage form/Particle [in mm]. Thus, according to said empirical formula, a round pharmaceutical dosage form/particle having a breaking strength of at least 300 N would require a diameter of at least 30 mm). Such a particle, however, could not be swallowed, let alone a pharmaceutical dosage form containing a plurality of such particles. The above empirical formula preferably does not apply to the particles according to the invention, which are not conventional but rather special.

Further, the actual mean chewing force is 220 N (cf., e.g., P. A. Proeschel et al., *J Dent Res*, 2002, 81(7), 464-468). This means that conventional particles having a breaking strength well below 200 N may be crushed upon spontaneous chewing, whereas the particles according to the invention may preferably not.

Still further, when applying a gravitational acceleration of 9.81 m/s^2 , 300 N correspond to a gravitational force of more

than 30 kg, i.e. the particles according to the invention can preferably withstand a weight of more than 30 kg without being pulverized.

Methods for measuring the breaking strength of a pharmaceutical dosage form are known to the skilled artisan. Suitable devices are commercially available.

For example, the breaking strength (resistance to crushing) can be measured in accordance with the Eur. Ph. 5.0, 2.9.8 or 6.0, 2.09.08 "Resistance to Crushing of Pharmaceutical dosage forms". The test is intended to determine, under defined conditions, the resistance to crushing of pharmaceutical dosage forms and particles, respectively, measured by the force needed to disrupt them by crushing. The apparatus consists of 2 jaws facing each other, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the pharmaceutical dosage form and particle, respectively. The apparatus is calibrated using a system with a precision of 1 Newton. The pharmaceutical dosage form and particle, respectively, is placed between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the pharmaceutical dosage form and particle, respectively, is oriented in the same way with respect to the direction of application of the force (and the direction of extension in which the breaking strength is to be measured). The measurement is carried out on 10 pharmaceutical dosage forms and particles, respectively, taking care that all fragments have been removed before each determination. The result is expressed as the mean, minimum and maximum values of the forces measured, all expressed in Newton.

A similar description of the breaking strength (breaking force) can be found in the USP. The breaking strength can alternatively be measured in accordance with the method described therein where it is stated that the breaking strength is the force required to cause a pharmaceutical dosage form and particle, respectively, to fail (i.e., break) in a specific plane. The pharmaceutical dosage forms and particles, respectively, are generally placed between two platens, one of which moves to apply sufficient force to the pharmaceutical dosage form and particle, respectively, to cause fracture. For conventional, round (circular cross-section) pharmaceutical dosage forms and particles, respectively, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in the plane. The breaking force of pharmaceutical dosage forms and particles, respectively, is commonly called hardness in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term hardness refers to the resistance of a surface to penetration or indentation by a small probe. The term crushing strength is also frequently used to describe the resistance of pharmaceutical dosage forms and particle, respectively, to the application of a compressive load. Although this term describes the true nature of the test more accurately than does hardness, it implies that pharmaceutical dosage forms and particles, respectively, are actually crushed during the test, which is often not the case.

Alternatively, the breaking strength (resistance to crushing) can be measured in accordance with WO 2008/107149, which can be regarded as a modification of the method described in the Eur. Ph. The apparatus used for the measurement is preferably a "Zwick Z 2.5" materials tester, $F_{max}=2.5 \text{ kN}$ with a maximum draw of 1150 mm, which should be set up with one column and one spindle, a clearance behind of 100 mm and a test speed adjustable

between 0.1 and 800 mm/min together with testControl software. A skilled person knows how to properly adjust the test speed, e.g. to 10 mm/min, 20 mm/min, or 40 mm/min, for example. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, F_{max} 1 kN, diameter=8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force F_{max} =1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

When using the testControl software (testXpert V10.11), the following exemplified settings and parameters have revealed to be useful: LE-position: clamping length 150 mm. LE-speed: 500 mm/min, clamping length after pre-travel: 195 mm, pre-travel speed: 500 mm/min, no pre-force control—pre-force: pre-force 1N, pre-force speed 10 mm/min—sample data: no sample form, measuring length traverse distance 10 mm, no input required prior to testing—testing/end of test; test speed: position-controlled 10 mm/min, delay speed shift: 1, force shut down threshold 50% F_{max} , no force threshold for break-tests, no max length variation, upper force limit: 600N—expansion compensation: no correction of measuring length—actions after testing: LE to be set after test, no unload of sample—TRS: data memory: TRS distance interval until break 1 TRS time interval 0.1 s, TRS force interval 1N—machine; traverse distance controller: upper soft end 358 mm, lower soft end 192 mm—lower test space. Parallel arrangement of the upper plate and the ambos should be ensured—these parts must not touch during or after testing. After testing, a small gap (e.g. 0.1 or 0.2 mm) should still be present between the two brackets in intimated contact with the tested particle, representing the remaining thickness of the deformed particle.

In a preferred embodiment, the particle is regarded as being broken if it is fractured into at least two separate pieces of comparable morphology. Separated matter having a morphology different from that of the deformed particle, e.g. dust, is not considered as pieces qualifying for the definition of breaking.

The particles according to the invention preferably exhibit mechanical strength over a wide temperature range, in addition to the breaking strength (resistance to crushing) optionally also sufficient hardness, yield strength, fatigue strength, impact resistance, impact elasticity, tensile strength, compressive strength and/or modulus of elasticity, optionally also at low temperatures (e.g. below -24°C ., below -40°C . or possibly even in liquid nitrogen), for it to be virtually impossible to pulverize by spontaneous chewing, grinding in a mortar, pounding, etc. Thus, preferably, the comparatively high breaking strength of the particle according to the invention is maintained even at low or very low temperatures, e.g., when the pharmaceutical dosage form is initially chilled to increase its brittleness, for example to temperatures below -25°C ., below -40°C . or even in liquid nitrogen.

The particle according to the invention is characterized by a certain degree of breaking strength. This does not mean that the particle must also exhibit a certain degree of hardness. Hardness and breaking strength are different physical properties. Therefore, the tamper-resistance of the pharmaceutical dosage form does not necessarily depend on the hardness of the particles. For instance, due to its breaking strength, impact strength, elasticity modulus and tensile

strength, respectively, the particles can preferably be deformed, e.g. plastically, when exerting an external force, for example using a hammer, but cannot be pulverized, i.e., crumbled into a high number of fragments. In other words, the particles according to the invention are characterized by a certain degree of breaking strength, but not necessarily also by a certain degree of form stability.

Therefore, in the meaning of the specification, a particle that is deformed when being exposed to a force in a particular direction of extension but that does not break (plastic deformation or plastic flow) is preferably to be regarded as having the desired breaking strength in said direction of extension.

Preferred particles present in the pharmaceutical dosage forms according to the invention are those having a suitable tensile strength as determined by a test method currently accepted in the art. Further preferred particles are those having a Youngs Modulus as determined by a test method of the art. Still further preferred particles are those having an acceptable elongation at break.

Irrespective of whether the particles according to the invention have an increased breaking strength or nor, the particles according to the invention preferably exhibit a certain degree of deformability. The particles contained in the pharmaceutical dosage form according to the invention preferably have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above.

This mechanical property, i.e. the deformability of the individual particles, is illustrated in FIGS. 1 and 2.

FIG. 1 schematically illustrates the measurement and the corresponding force-displacement-diagram. In particular, FIG. 1A shows the initial situation at the beginning of the measurement. The sample particle (2) is placed between upper jaw (1a) and lower jaw (1b) which each are in intimate contact with the surface of the particle (2). The initial displacement d_0 between upper jaw (1a) and lower jaw (1b) corresponds to the extension of the particle orthogonal to the surfaces of upper jaw (1a) and lower jaw (1b). At this time, no force is exerted at all and thus, no graph is displayed in the force-displacement-diagram below. When the measurement is commenced, the upper jaw is moved in direction of lower jaw (1b), preferably at a constant speed. FIG. 1B shows a situation where due to the movement of upper jaw (1a) towards lower jaw (1b) a force is exerted on particle (2). Because of its deformability, the particle (2) is flattened without being fractured. The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (1a) and lower jaw (1b) by distance x_1 , i.e. at a displacement of $d_1=d_0-x_1$, a force F_1 is measured. FIG. 1C shows a situation where due to the continuous movement of upper jaw (1a) towards lower jaw (1b), the force that is exerted on particle (2) causes further deformation, although the particle (2) does not fracture. The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (1a) and lower jaw (1b) by distance x_2 , i.e. at a displacement of $d_2=d_0-x_2$, a force F_2 is measured. Under these circumstances, the particle (2) has not been broken (fractured) and a substantially steady increase of the force in the force-displacement-diagram is measured.

In contrast, FIG. 2 schematically illustrates the measurement and the corresponding force-displacement-diagram of a conventional comparative particle not having the degree of deformability as the particles according to the invention. FIG. 2A shows the initial situation at the beginning of the

measurement. The comparative sample particle (2) is placed between upper jaw (1a) and lower jaw (1b) which each are in intimate contact with the surface of the comparative particle (2). The initial displacement d_0 between upper jaw (1a) and lower jaw (1b) corresponds to the extension of the comparative particle orthogonal to the surfaces of upper jaw (1a) and lower jaw (1b). At this time, no force is exerted at all and thus, no graph is displayed in the force-displacement-diagram below. When the measurement is commenced, the upper jaw is moved in direction of lower jaw (1b), preferably at a constant speed. FIG. 2B shows a situation where due to the movement of upper jaw (1a) towards lower jaw (1b) a force is exerted on comparative particle (2). Because of some deformability, the comparative particle (2) is slightly flattened without being fractured. The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (1a) and lower jaw (1b) by distance x_1 , i.e. at a displacement of $d_1 = d_0 - x_1$, a force F_1 is measured. FIG. 2C shows a situation where due to the continuous movement of upper jaw (1a) towards lower jaw (1b), the force that is exerted on particle (2) causes sudden fracture of the comparative particle (2). The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (1a) and lower jaw (1b) by distance x_2 , i.e. at a displacement of $d_2 = d_0 - x_2$, a force F_2 is measured that suddenly drops when the particle fractures. Under these circumstances, the particle (2) has been broken (fractured) and no steady increase of the force in the force-displacement-diagram is measured. The sudden drop (decrease) of the force can easily be recognized and does not need to be quantified for the measurement. The steady increase in the force-displacement-diagram ends at displacement $d_2 = d_0 - x_2$ when the particle breaks.

In a preferred embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), preferably at least until the displacement d of upper jaw (1a) and lower jaw (1b) has been reduced to a value of 90% of the original displacement d_0 (i.e. $d = 0.9 \cdot d_0$), preferably to a displacement d of 80% of the original displacement d_0 , more preferably to a displacement d of 70% of the original displacement d_0 , still more preferably to a displacement d of 60% of the original displacement d_0 , yet more preferably to a displacement d of 50% of the original displacement d_0 , even more preferably to a displacement d of 40% of the original displacement d_0 , most preferably to a displacement d of 30% of the original displacement d_0 , and in particular to a displacement d of 20% of the original displacement d_0 , or to a displacement d of 15% of the original displacement d_0 , to a displacement d of 10% of the original displacement d_0 , or to a displacement d of 5% of the original displacement d_0 .

In another preferred embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), preferably at least until the displacement d of upper jaw (1a) and lower jaw (1b) has been reduced to 0.80 mm or 0.75 mm, preferably 0.70 mm or 0.65 mm, more preferably 0.60 mm or 0.55 mm, still more

preferably 0.50 mm or 0.45 mm, yet more preferably 0.40 mm or 0.35 mm, even more preferably 0.30 mm or 0.25 mm, most preferably 0.20 mm or 0.15 mm and in particular 0.10 or 0.05 mm.

In still another preferred embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), at least until the displacement d of upper jaw (1a) and lower jaw (1b) has been reduced to 50% of the original displacement d_0 (i.e. $d = d_0/2$), whereas the force measured at said displacement ($d = d_0/2$) is at least 25 N or at least 50 N, preferably at least 75 N or at least 100 N, still more preferably at least 150 N or at least 200 N, yet more preferably at least 250 N or at least 300 N, even more preferably at least 350 N or at least 400 N, most preferably at least 450 N or at least 500 N, and in particular at least 625 N, or at least 750 N, or at least 875 N, or at least 1000 N, or at least 1250 N, or at least 1500 N.

In another preferred embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), at least until the displacement d of upper jaw (1a) and lower jaw (1b) has been reduced by at least 0.1 mm, more preferably at least 0.2 mm, still more preferably at least 0.3 mm, yet more preferably at least 0.4 mm, even more preferably at least 0.5 mm, most preferably at least 0.6 mm, and in particular at least 0.7 mm, whereas the force measured at said displacement is within the range of from 5.0 N to 250 N, more preferably from 7.5 N to 225 N, still more preferably from 10 N to 200 N, yet more preferably from 15 N to 175 N, even more preferably from 20 N to 150 N, most preferably from 25 N to 125 N, and in particular from 30 N to 100 N.

In yet another embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (1a) and lower jaw (1b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (1a) and lower jaw (1b) is at most 90% of the original displacement d_0 (i.e. $d \leq 0.9 \cdot d_0$), preferably at most 80% of the original displacement d_0 (i.e. $d \leq 0.8 \cdot d_0$), more preferably at most 70% of the original displacement d_0 (i.e. $d \leq 0.7 \cdot d_0$), still more preferably at most 60% of the original displacement d_0 (i.e. $d \leq 0.6 \cdot d_0$), yet more preferably at most 50% of the original displacement d_0 (i.e. $d \leq 0.5 \cdot d_0$), even more preferably at most 40% of the original displacement d_0 (i.e. $d \leq 0.4 \cdot d_0$), most preferably at most 30% of the original displacement d_0 (i.e. $d \leq 0.3 \cdot d_0$), and in particular at most 20% of the original displacement d_0 (i.e. $d \leq 0.2 \cdot d_0$), or at most 15% of the original displacement d_0 (i.e. $d \leq 0.15 \cdot d_0$), at most 10% of the original displacement d_0 (i.e. $d \leq 0.1 \cdot d_0$), or at most 5% of the original displacement d_0 (i.e. $d \leq 0.05 \cdot d_0$).

Preferably, the particles contained in the pharmaceutical dosage form according to the invention have a deformability

such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (1a) and lower jaw (1b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (1a) and lower jaw (1b) is at most 0.80 mm or at most 0.75 mm, preferably at most 0.70 mm or at most 0.65 mm, more preferably at most 0.60 mm or at most 0.55 mm, still more preferably at most 0.50 mm or at most 0.45 mm, yet more preferably at most 0.40 mm or at most 0.35 mm, even more preferably at most 0.30 mm or at most 0.25 mm, most preferably at most 0.20 mm or at most 0.15 mm and in particular at most 0.10 or at most 0.05 mm.

In another embodiment, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (1a) and lower jaw (1b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (1a) and lower jaw (1b) is at least 5% of the original displacement d_0 (i.e. $d \geq 0.05 \cdot d_0$), preferably at least 10% of the original displacement d_0 (i.e. $d \geq 0.1 \cdot d_0$), more preferably at least 15% of the original displacement d_0 (i.e. $d \geq 0.15 \cdot d_0$), still more preferably at least 20% of the original displacement d_0 (i.e. $d \geq 0.2 \cdot d_0$), yet more preferably at least 30% of the original displacement d_0 (i.e. $d \geq 0.3 \cdot d_0$), even more preferably at least 40% of the original displacement d_0 (i.e. $d \geq 0.4 \cdot d_0$), most preferably at least 50% of the original displacement d_0 (i.e. $d \geq 0.5 \cdot d_0$), and in particular at least 60% of the original displacement d_0 (i.e. $d \geq 0.6 \cdot d_0$), or at least 70% of the original displacement d_0 (i.e. $d \geq 0.7 \cdot d_0$), at least 80% of the original displacement d_0 (i.e. $d \geq 0.8 \cdot d_0$), or at least 90% of the original displacement d_0 (i.e. $d \geq 0.9 \cdot d_0$).

Preferably, the particles contained in the pharmaceutical dosage form according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (1a) and lower jaw (1b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (1a) and lower jaw (1b) is at least 0.05 mm or at least 0.10 mm, preferably at least 0.15 mm or at least 0.20 mm, more preferably at least 0.25 mm or at least 0.30 mm, still more preferably at least 0.35 mm or at least 0.40 mm, yet more preferably at least 0.45 mm or at least 0.50 mm, even more preferably at least 0.55 mm or

at least 0.60 mm, most preferably at least 0.65 mm or at least 0.70 mm and in particular at least 0.75 or at least 0.80 mm.

The pharmaceutical dosage form according to the invention provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur. Preferably, the pharmaceutical dosage form according to the invention provides an release profile such that under in vitro conditions in 600 ml 0.1 M HCl (pH 1) at 75 rpm after 30 min (USP apparatus II) at least 90 wt.-% of the pharmacologically active ingredient that was originally contained in the dosage form have been released.

The term "immediate release" as applied to pharmaceutical dosage forms is understood by persons skilled in the art which has structural implications for the respective pharmaceutical dosage forms. The term is defined, for example, in the current issue of the US Pharmacopoeia (USP), General Chapter 1092, "THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION", heading "STUDY DESIGN", "Time Points". For immediate-release dosage forms, the duration of the procedure is typically 30 to 60 minutes; in most cases, a single time point specification is adequate for Pharmacopeia purposes. Industrial and regulatory concepts of product comparability and performance may require additional time points, which may also be required for product registration or approval. A sufficient number of time points should be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the Biopharmaceutics Classification System referred to in several FDA Guidances, highly soluble, highly permeable drugs formulated with rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release 85% or more of the active drug substance within 15 minutes. For these types of products a one-point test will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products typically show a gradual increase reaching 85% to 100% at 30 to 45 minutes. Thus, dissolution time points in the range of 15, 20, 30, 45, and 60 minutes are usual for most immediate-release products.

Preferably, under physiological conditions the pharmaceutical dosage form according to the invention has released after 30 minutes at least 70%, more preferably at least 75%, still more preferably at least 80%, yet more preferably at least 82%, most preferably at least 84% and in particular at least 86% of the pharmacologically active compound originally contained in the pharmaceutical dosage form.

Preferably, under physiological conditions the pharmaceutical dosage form according to the invention has released after 10 minutes at least 70%, more preferably at least 73%, still more preferably at least 76%, yet more preferably at least 78%, most preferably at least 80% and in particular at least 82% of the pharmacologically active compound originally contained in the pharmaceutical dosage form.

Further preferred release profiles B¹ to B¹⁰ are summarized in the table here below [all data in wt.-% of released pharmacologically active compound]:

time	B ¹	B ²	B ³	B ⁴	B ⁵	B ⁶	B ⁷	B ⁸	B ⁹	B ¹⁰
10 min	≥30	≥35	≥40	≥45	≥50	≥60	≥70	≥80	≥80	≥80
20 min	≥50	≥55	≥60	≥65	≥70	≥75	≥80	≥85	≥90	≥95
30 min	≥55	≥60	≥65	≥70	≥75	≥85	≥90	≥95	≥95	≥95
40 min	≥60	≥65	≥70	≥80	≥85	≥90	≥95	≥95	≥95	≥95
50 min	≥65	≥70	≥80	≥85	≥88	≥92	≥95	≥95	≥95	≥95
60 min	≥75	≥80	≥85	≥90	≥92	≥94	≥95	≥95	≥95	≥95

Preferably, the release profile, the drug and the pharmaceutical excipients of the pharmaceutical dosage form according to the invention are stable upon storage, preferably upon storage at elevated temperature, e.g. 40° C., for 3 months in sealed containers.

In connection with the release profile “stable” means that when comparing the initial release profile with the release profile after storage, at any given time point the release profiles deviate from one another by not more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

In connection with the drug and the pharmaceutical excipients “stable” means that the pharmaceutical dosage forms satisfy the requirements of EMEA concerning shelf-life of pharmaceutical products.

Suitable in vitro conditions are known to the skilled artisan. In this regard it can be referred to, e.g., the Eur. Ph. Preferably, the release profile is measured under the following conditions: Paddle apparatus equipped without sinker, 50 rpm, 37±5° C., 900 mL simulated intestinal fluid pH 6.8 (phosphate buffer) or pH 4.5. In a preferred embodiment, the rotational speed of the paddle is increased to 75 rpm.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration once daily. In another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration twice daily. In still another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration thrice daily. In yet another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration more frequently than thrice daily, for example 4 times daily, 5 times daily, 6 times daily, 7 times daily or 8 times daily.

For the purpose of the specification, “twice daily” means equal or nearly equal time intervals, i.e., every 12 hours, or different time intervals, e.g., 8 and 16 hours or 10 and 14 hours, between the individual administrations.

For the purpose of the specification, “thrice daily” means equal or nearly equal time intervals, i.e., every 8 hours, or different time intervals, e.g., 6, 6 and 12 hours; or 7, 7 and 10 hours, between the individual administrations.

Preferably, the pharmaceutical dosage form according to the invention has under in vitro conditions a disintegration time measured in accordance with Ph. Eur. of at most 5 minutes, more preferably at most 4 minutes, still more preferably at most 3 minutes, yet more preferably at most 2.5 minutes, most preferably at most 2 minutes and in particular at most 1.5 minutes.

It has been surprisingly found that oral dosage forms can be designed that provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

Tamper-resistance and drug release antagonize each other. While smaller particles should typically show a faster release of the pharmacologically active compound, tamper-resistance requires some minimal size of the particles in order to effectively prevent abuse, e.g. i.v. administration. The larger the particles are the less they are suitable for being abused nasally. The smaller the particles are the faster gel formation occurs. Thus, drug release on the one hand and tamper-resistance on the other hand can be optimized by finding the best compromise.

In a preferred embodiment of the pharmaceutical dosage form according to the invention, the particles are hot melt-extruded. Thus, the particles according to the invention are preferably prepared by melt-extrusion, although also other methods of thermoforming may be used in order to manufacture the particles according to the invention such as press-molding at elevated temperature or heating of particles that were manufactured by conventional compression in a first step and then heated above the softening temperature of the polyalkylene oxide in the particles in a second step to form hard pharmaceutical dosage forms. In this regards, thermoforming means the forming, or molding of a mass after the application of heat. In a preferred embodiment, the particles are thermoformed by hot-melt extrusion.

In a preferred embodiment, the particles are prepared by hot melt-extrusion, preferably by means of a twin-screw-extruder. Melt extrusion preferably provides a melt-extruded strand that is preferably cut into monoliths, which are then optionally compressed and formed into particles. Preferably, compression is achieved by means of a die and a punch, preferably from a monolithic mass obtained by melt extrusion. If obtained via melt extrusion, the compressing step is preferably carried out with a monolithic mass exhibiting ambient temperature, that is, a temperature in the range from 20 to 25° C. The strands obtained by way of extrusion can either be subjected to the compression step as such or can be cut prior to the compression step. This cutting can be performed by usual techniques, for example using rotating knives or compressed air, at elevated temperature, e.g. when the extruded stand is still warm due to hot-melt extrusion, or at ambient temperature, i.e. after the extruded strand has been allowed to cool down. When the extruded strand is still warm, singulation of the extruded strand into extruded particles is preferably performed by cutting the extruded strand immediately after it has exited the extrusion die. It is possible to subject the extruded strands to the compression step or to the cutting step when still warm, that is more or less immediately after the extrusion step. The extrusion is preferably carried out by means of a twin-screw extruder.

The particles of the pharmaceutical dosage form according to the invention may be produced by different processes, the particularly preferred of which are explained in greater detail below. Several suitable processes have already been described in the prior art. In this regard it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, and WO 2006/082099.

In general, the process for the production of the particles according to the invention preferably comprises the following steps:

- (a) mixing all ingredients;
- (b) optionally pre-forming the mixture obtained from step (a), preferably by applying heat and/or force to the mixture obtained from step (a), the quantity of heat supplied preferably not being sufficient to heat the polyalkylene oxide up to its softening point;
- (c) hardening the mixture by applying heat and force, it being possible to supply the heat during and/or before the application of force and the quantity of heat supplied being sufficient to heat the polyalkylene oxide at least up to its softening point; and thereafter allowing the material to cool and removing the force
- (d) optionally singulating the hardened mixture; and
- (e) optionally providing a film coating.

Heat may be supplied directly, e.g. by contact or by means of hot gas such as hot air, or with the assistance of ultra-

sound; or is indirectly supplied by friction and/or shear. Force may be applied and/or the particles may be shaped for example by direct tableting or with the assistance of a suitable extruder, particularly by means of a screw extruder equipped with one or two screws (single-screw-extruder and twin-screw-extruder, respectively) or by means of a planetary gear extruder.

The final shape of the particles may either be provided during the hardening of the mixture by applying heat and force (step (c)) or in a subsequent step (step (e)). In both cases, the mixture of all components is preferably in the plastified state, i.e. preferably, shaping is performed at a temperature at least above the softening point of the polyalkylene oxide. However, extrusion at lower temperatures, e.g. ambient temperature, is also possible and may be preferred.

In a preferred embodiment, the mixture of ingredients is heated and subsequently compressed under conditions (time, temperature and pressure) sufficient in order to achieve the desired mechanical properties, e.g. in terms of breaking strength and the like. This technique may be achieved e.g. by means of a tableting tool which is either heated and/or which is filled with the heated mixture that is subsequently compressed without further supply of heat or with simultaneous additional supply of heat.

In another preferred embodiment, the mixture of ingredients is heated and simultaneously compressed under conditions (time, temperature and pressure) sufficient in order to achieve the desired mechanical properties, e.g. in terms of breaking strength and the like. This technique may be achieved e.g. by means of an extruder with one or more heating zones, wherein the mixture is heated and simultaneously subjected to extrusion forces finally resulting in a compression of the heated mixture.

In still another embodiment, the mixture of ingredients is compressed under ambient conditions at sufficient pressure and subsequently heated (cured) under conditions (time, temperature) sufficient in order to achieve the desired mechanical properties, e.g. in terms of breaking strength and the like. This technique may be achieved e.g. by means of a curing oven in which the compressed articles are cured for a sufficient time at a sufficient temperature, preferably without exerting any further pressure. Such process is further described e.g. in US 2009/0081290.

A particularly preferred process for the manufacture of the particles according to the invention involves hot-melt extrusion. In this process, the particles according to the invention are produced by thermoforming with the assistance of an extruder, preferably without there being any observable consequent discoloration of the extrudate.

This process is characterized in that

- a) all components are mixed,
- b) the resultant mixture is heated in the extruder at least up to the softening point of the polyalkylene oxide and extruded through the outlet orifice of the extruder by application of force,
- c) the still plastic extrudate is singulated and formed into the particles or
- d) the cooled and optionally reheated singulated extrudate is formed into the particles.

Mixing of the components according to process step a) may also proceed in the extruder.

The components may also be mixed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The, preferably molten, mixture which has been heated in the extruder at least up to the softening point of polyalkylene oxide is extruded from the extruder through a die with at least one bore, preferably a multitude of bores.

The process according to the invention requires the use of suitable extruders, preferably screw extruders. Screw extruders which are equipped with two screws (twin-screw-extruders) are particularly preferred.

Preferably, extrusion is performed in the absence of water, i.e., no water is added. However, traces of water (e.g., caused by atmospheric humidity) may be present.

The extruder preferably comprises at least two temperature zones, with heating of the mixture at least up to the softening point of the polyalkylene oxide proceeding in the first zone, which is downstream from a feed zone and optionally mixing zone. The throughput of the mixture is preferably from 1.0 kg to 15 kg/hour. In a preferred embodiment, the throughput is from 0.5 kg/hour to 3.5 kg/hour. In another preferred embodiment, the throughput is from 4 to 15 kg/hour.

In a preferred embodiment, the die head pressure is within the range of from 25 to 200 bar. The die head pressure can be adjusted inter alia by die geometry, temperature profile, extrusion speed, number of bores in the dies, screw configuration, first feeding steps in the extruder, and the like.

The die geometry or the geometry of the bores is freely selectable. The die or the bores may accordingly exhibit a round, oblong or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 2 mm, preferably of 0.5 mm to 0.9 mm. Preferably, the die or the bores have a round cross-section. The casing of the extruder used according to the invention may be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is so arranged that the mixture to be extruded exhibits at least an average temperature (product temperature) corresponding to the softening temperature of the polyalkylene oxide and does not rise above a temperature at which the pharmacologically active compound to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180° C., preferably below 150° C., but at least to the softening temperature of polyalkylene oxide. Typical extrusion temperatures are 120° C. and 150° C.

In a preferred embodiment, the extruder torque is within the range of from 30 to 95%. Extruder torque can be adjusted inter alia by die geometry, temperature profile, extrusion speed, number of bores in the dies, screw configuration, first feeding steps in the extruder, and the like.

After extrusion of the molten mixture and optional cooling of the extruded strand or extruded strands, the extrudates are preferably singulated. This singulation may preferably be performed by cutting up the extrudates by means of revolving or rotating knives, wires, blades or with the assistance of laser cutters.

Preferably, intermediate or final storage of the optionally singulated extrudate or the final shape of the particles according to the invention is performed under oxygen-free atmosphere which may be achieved, e.g., by means of oxygen-scavengers.

The singulated extrudate may be press-formed into particles in order to impart the final shape to the particles.

The application of force in the extruder onto the at least plasticized mixture is adjusted by controlling the rotational speed of the conveying device in the extruder and the geometry thereof and by dimensioning the outlet orifice in such a manner that the pressure necessary for extruding the plasticized mixture is built up in the extruder, preferably

immediately prior to extrusion. The extrusion parameters which, for each particular composition, are necessary to give rise to a pharmaceutical dosage form with desired mechanical properties, may be established by simple preliminary testing.

For example but not limiting, extrusion may be performed by means of a twin-screw-extruder type ZSE 18 or ZSE27 (Leistritz, Nürnberg, Germany), screw diameters of 18 or 27 mm. Screws having eccentric or blunt ends may be used. A heatable die with a round bore or with a multitude of bores each having a diameter of 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 mm may be used. For a twin-screw-extruder type ZSE 18, the extrusion parameters may be adjusted e.g. to the following values: rotational speed of the screws: 120 Upm; delivery rate 2 kg/h for a ZSE 18 or 5 kg/h, 10 kg/h, or even 20 kg/h and more for a ZSE27; product temperature: in front of die 125° C. and behind die 135° C.; and jacket temperature: 110° C. The throughput can generally be increased by increasing the number of dies at the extruder outlet.

Preferably, extrusion is performed by means of twin-screw-extruders or planetary-gear-extruders, twin-screw extruders (co-rotating or contra-rotating) being particularly preferred.

The particles according to the invention are preferably produced by thermoforming with the assistance of an extruder without any observable consequent discoloration of the extrudates. The particles may be produced e.g. by means of a Micro Pelletizer (Leistritz, Nürnberg, Germany).

The process for the preparation of the particles according to the invention is preferably performed continuously. Preferably, the process involves the extrusion of a homogeneous mixture of all components. It is particularly advantageous if the thus obtained intermediate, e.g. the strand obtained by extrusion, exhibits uniform properties. Particularly desirable are uniform density, uniform distribution of the active compound, uniform mechanical properties, uniform porosity, uniform appearance of the surface, etc. Only under these circumstances the uniformity of the pharmacological properties, such as the stability of the release profile, may be ensured and the amount of rejects can be kept low.

Preferably, the particles according to the invention can be regarded as "extruded pellets". The term "extruded pellets" has structural implications which are understood by persons skilled in the art. A person skilled in the art knows that pelletized dosage forms can be prepared by a number of techniques, including:

- drug layering on nonpareil sugar or microcrystalline cellulose beads,
- spray drying,
- spray congealing,
- rotogranulation,
- hot-melt extrusion,
- spheronization of low melting materials, or
- extrusion-spheronization of a wet mass.

Accordingly, "extruded pellets" can be obtained either by hot-melt extrusion or by extrusion-spheronization.

"Extruded pellets" can be distinguished from other types of pellets, as extruded pellets typically have a different shape. The shape of the extruded pellets is typically more cut-rod-like than perfectly globated round.

"Extruded pellets" can be distinguished from other types of pellets because they are structurally different. For example, drug layering on nonpareils yields multilayered pellets having a core, whereas extrusion typically yields a monolithic mass comprising a homogeneous mixture of all ingredients. Similarly, spray drying and spray congealing

typically yield spheres, whereas extrusion typically yields cylindrical extrudates which can be subsequently spheronized.

The structural differences between "extruded pellets" and "agglomerated pellets" are significant because they may affect the release of active substances from the pellets and consequently result in different pharmacological profiles. Therefore, a person skilled in the pharmaceutical formulation art would not consider "extruded pellets" to be equivalent to "agglomerated pellets".

The pharmaceutical dosage forms according to the invention may be prepared by any conventional method. Preferably, however, the pharmaceutical dosage forms are prepared by compression. Thus, particles as hereinbefore defined are preferably mixed, e.g. blended and/or granulated (e.g. wet granulated), with matrix material and the resulting mix (e.g. blend or granulate) is then compressed, preferably in moulds, to form pharmaceutical dosage forms. It is also envisaged that the particles herein described may be incorporated into a matrix using other processes, such as by melt granulation (e.g. using fatty alcohols and/or water-soluble waxes and/or water-insoluble waxes) or high shear granulation, followed by compression.

When the pharmaceutical dosage forms according to the invention are manufactured by means of an eccentric press, the compression force is preferably within the range of from 5 to 15 kN. When the pharmaceutical dosage forms according to the invention are manufactured by means of a rotating press, the compression force is preferably within the range of from 5 to 40 kN, in certain embodiments >25 kN, in other embodiments 13 kN.

The pharmaceutical dosage forms according to the invention may optionally comprise a coating, e.g. a cosmetic coating. The coating is preferably applied after formation of the pharmaceutical dosage form. The coating may be applied prior to or after the curing process. Preferred coatings are Opadry® coatings available from Colorcon. Other preferred coating are Opaglos® coatings, also commercially available from Colorcon.

The pharmaceutical dosage form according to the invention is characterized by excellent storage stability. Preferably, after storage for 6 months, 3 months, 2 months, or 4 weeks at 40° C. and 75% rel. humidity, the content of pharmacologically active compound amounts to at least 98.0%, more preferably at least 98.5%, still more preferably at least 99.0%, yet more preferably at least 99.2%, most preferably at least 99.4% and in particular at least 99.6%, of its original content before storage. Suitable methods for measuring the content of the pharmacologically active compound in the pharmaceutical dosage form are known to the skilled artisan. In this regard it is referred to the Eur. Ph. or the USP, especially to reversed phase HPLC analysis. Preferably, the pharmaceutical dosage form is stored in closed, preferably sealed containers.

The particles and pharmaceutical dosage forms according to the invention may be used in medicine, e.g. as an analgesic. The particles and pharmaceutical dosage forms are therefore particularly suitable for the treatment or management of pain. In such pharmaceutical dosage forms, the pharmacologically active compound is preferably an analgesic.

A further aspect according to the invention relates to the pharmaceutical dosage form as described above for use in the treatment of pain.

A further aspect according to the invention relates to the use of a pharmaceutical dosage form as described above for

avoiding or hindering the abuse of the pharmacologically active compound contained therein.

A further aspect according to the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the unintentional overdose of the pharmacologically active compound contained therein.

In this regard, the invention also relates to the use of a pharmacologically active compound as described above and/or a polyalkylene oxide as described above for the

tion. Accordingly, it is more significant to evaluate tamper resistance of the extrudates instead of the overall dosage forms.

EXAMPLE 1—OXYCODONE

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded under the following extrusion conditions:

per dosis	1-1 mg/wt.-%	1-2 mg/wt.-%	1-3 mg/wt.-%	1-4 mg/wt.-%	1-5 mg/wt.-%
Oxycodone HCl	10.00/5.56	10.00/5.56	10.00/5.56	10.00/5.56	10.00/5.56
Citric acid	1.44/0.80	1.44/0.80	1.44/0.80	1.44/0.80	1.44/0.80
Macrogol 6000	25.20/14.00	25.20/14.00	25.20/14.00	25.20/14.00	25.20/14.00
α -Tocopherol	0.36/0.20	0.36/0.20	0.36/0.20	0.36/0.20	0.36/0.20
Xanthan Gum Type 602	9.00/5.00	9.00/5.00	9.00/5.00	9.00/5.00	9.00/5.00
Polyethylene oxide 7 Mio.	98.00/54.44	98.00/54.44	98.00/54.44	98.00/54.44	95.22/52.20
Sodium bicarbonate	—	—	—	—	2.78/1.54
Sodium starch glycolate	36.00/20.00	—	—	—	—
Croscarmellose sodium	—	36.00/20.00	—	—	—
Starch 1500	—	—	36.00/20.00	—	—
Maize starch	—	—	—	36.00/20.00	—
Carbomer Carbopol 71G	—	—	—	—	36.00/20.00
Σ	180.00/100.00	180.00/100.00	180.00/100.00	180.00/100.00	180.00/100.00
Speed screw [rpm]	100	100	100	100	120
Feed rate [g/min]	16.66	16.66	16.66	16.66	16.66
Melt pressure [bar]	119	141	136	135	116
melt temperature discharge [° C.]	140	143	142	143	145

manufacture of the pharmaceutical dosage form according to the invention for the prophylaxis and/or the treatment of a disorder, thereby preventing an overdose of the pharmacologically active compound, particularly due to comminution of the pharmaceutical dosage form by mechanical action.

The following examples further illustrate the invention but are not to be construed as limiting its scope.

General Operation Procedures

Powder mixtures of various ingredients were manufactured by weighing (10 kg balance), sieving (1.0 mm hand sieve) and blending. The thus obtained powder mixtures were then hot-melt extruded (twin-screw extruder, Leistritz ZSE 18, blunt ends of kneading elements, and extrusion diameter of 8×0.8 mm). The extrudates were pelletized (LMP) and then analyzed.

In vitro dissolution was tested in accordance with USP (apparatus II), in 600 ml 0.1 M HCl (pH 1) at 75 rpm (n=3).

Resistance against solvent extraction was tested by dispensing particles in 5 ml of boiling water. After boiling for 5 minutes the liquid was drawn up into a syringe (needle 21G equipped with a cigarette filter), and the amount of the pharmacologically active ingredient contained in the liquid within the syringe was determined via HPLC.

The test was performed on the extrudates as such but not on capsules or tablets containing such extrudates, as this test more relevant with respect to drug abuse. The other constituents of dosage forms (e.g. capsules or tablets) typically make it even more difficult for the abuser to tamper with the dosage form, e.g. by blocking the filters of syringes and the like. Thus, in the course of tampering, abusers frequently initially separate the drug containing subunits of dosage forms (here extrudates) from the remainder of the dosage forms in order to facilitate subsequent abuse, e.g. by extrac-

The in vitro dissolution test revealed the following release profiles:

	Dissolution Oxycodone %				
	1-1	1-2	1-3	1-4	1-5
after 5 min	70	74	66	78	58
after 15 min	88	91	88	94	83
after 30 min	94	94	95	100	92
after 60 min	96	96	97	102	96

The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	1-1	1-2	1-3	1-4	1-5
1	0.00*	1.34	0.00*	22.40	0.00*
2	0.00*	3.07	20.20	30.32	0.00*
3	0.00*	1.26	6.03	18.67	0.00*
mean [%]	0.00*	1.89	8.74	28.80	0.00*
SD [%]	0.00*	1.02	10.37	5.95	0.00*

*not tested, sample too jelly and could not be drawn into syringe

It becomes clear from the above experimental data that as far as tamper-resistant dosage forms providing immediate release are concerned, the tested disintegrants provide different performance. Under the given experimental conditions, cellulose derivatives (e.g. croscarmellose sodium) provided the best performance, followed by starch derivatives (e.g. sodium starch glycolate) and gas releasing substances (here sodium bicarbonate), followed by pregelatinized starch (e.g. starch 1500) and standard starch (e.g. native maize starch).

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EXAMPLE 2—HYDROCODONE

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded under the following extrusion conditions:

per dosis	2-1 mg/wt.-%	2-2 mg/wt.-%
Hydrocodone bitartrate	10.00/5.56	10.00/5.56
Citric acid	1.44/0.80	1.44/0.80
Macrogol 6000	25.20/14.00	25.20/14.00
α -Tocopherol	0.36/0.20	0.36/0.20
Xanthan Gum Type 602	9.00/5.00	9.00/5.00
Polyethylene oxide 7 Mio.	98.00/54.44	98.00/54.44
Carboxymethyl starch	36.00/20.00	—
Croscarmellose sodium	—	36.00/20.00
Σ	180.00/100.00	180.00/100.00
Speed screw [rpm]	100	100
Feed rate [g/min]	16.66	16.66
Melt pressure [bar]	132	157
melt temperature discharge [° C.]	143	143

The in vitro dissolution test revealed the following release profiles:

	Dissolution Hydrocodone %	
	2-1	2-2
after 5 min	73	81
after 15 min	87	98
after 30 min	92	102
after 60 min	94	104

The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	2-1	2-2
1	8.79	0.00*
2	4.75	1.09
3	2.78	1.70
mean [%]	5.44	0.93
SD [%]	3.06	0.86

*not tested, sample too jelly and could not be drawn into syringe

EXAMPLE 3—HYDROMORPHONE

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded under the following extrusion conditions:

per dosis	3-1 mg/wt.-%	3-2 mg/wt.-%
Hydromorphone HCl	8.00/5.33	8.00/5.33
Citric acid	1.20/0.80	1.20/0.80
Macrogol 6000	15.00/10.00	15.00/10.00
α -Tocopherol	0.30/0.20	0.30/0.20
Xanthan Gum Type 602	7.50/5.00	7.50/5.00

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-continued

per dosis	3-1 mg/wt.-%	3-2 mg/wt.-%
Polyethylene oxide 7 Mio.	88.00/58.67	88.00/58.67
Carboxymethyl starch	30.00/20.00	—
Croscarmellose sodium	—	36.00/20.00
Σ	150.00/100.00	150.00/100.00
Speed screw [rpm]	100	100
Feed rate [g/min]	16.66	16.66
Melt pressure [bar]	94	159
melt temperature discharge [° C.]	146	145

The in vitro dissolution test revealed the following release profiles:

	Dissolution Hydromorphone %	
	3-1	3-2
after 5 min	51	43
after 15 min	81	78
after 30 min	91	91
after 60 min	93	94

The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	3-1	3-2
1	22.89	12.25
2	18.18	4.47
3	0.00*	3.10
mean [%]	13.69	6.61
SD [%]	12.09	4.94

*not tested, sample too jelly and could not be drawn into syringe

EXAMPLE 4—MORPHINE

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded under the following extrusion conditions:

per dosis	4-1 mg/wt.-%	4-2 mg/wt.-%
Morphine sulfate•5 H ₂ O	10.00/5.56	10.00/5.56
Citric acid	1.44/0.80	1.44/0.80
Macrogol 6000	25.20/14.00	25.20/14.00
α -Tocopherol	0.36/0.20	0.36/0.20
Xanthan Gum Type 602	9.00/5.00	9.00/5.00
Polyethylene oxide 7 Mio.	98.00/54.44	98.00/54.44
Carboxymethyl starch	36.00/20.00	—
Croscarmellose sodium	—	36.00/20.00
Σ	180.00/100.00	180.00/100.00
Speed screw [rpm]	100	*
Feed rate [g/min]	16.66	
Melt pressure [bar]	181	
melt temperature discharge [° C.]	143	

* could not be extruded under the given conditions; stronger equipment or higher temperatures needed

The in vitro dissolution test revealed the following release profile:

Dissolution Morphine sulfate % 4-1	
after 5 min	58
after 15 min	83
after 30 min	90
after 60 min	91

The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	4-1
1	0.00*
2	0.00*
3	0.00*
mean [%]	0.00*
SD [%]	0.00*

*not tested, sample too jelly and could not be drawn into syringe

EXAMPLE 5—AMPHETAMINE SULFATE

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded under the following extrusion conditions:

per dosis	5-1 mg/wt.-%	5-2 mg/wt.-%	5-3 mg/wt.-%	5-4 mg/wt.-%
Amphetamine sulfate	30.00/12.00	30.00/12.00	30.00/12.00	30.00/12.00
Citric acid	2.00/0.80	2.00/0.80	—	—
PEG 6000	35.00/14.00	35.00/14.00	32.60/13.00	32.60/13.00
α-Tocopherol	0.50/0.20	0.50/0.20	0.50/0.20	0.50/0.20
Xanthan Gum Type 602	—	12.50/5.00	—	—
Polyethylene oxide 7 Mio.	182.50/73.00	120.00/48.00	136.90/54.70	136.90/54.70
Sodium hydrogen carbonate	—	—	—	—
Croscarmellose sodium	—	50/20.00	50.00/20.00	—
Starch 1500	—	—	—	—
Carboxymethyl starch	—	—	—	50.00/20.00
PVP-CL	—	—	—	—
Σ	250.00/100.00	250.00/100.00	250.0/100.00	250.0/100.00
Speed screw [rpm]	100	100	100	100
Extruder Load [%]	75.00	75.00	75.00	75.00
Melt pressure [bar]	1	1	1	1
melt temperature discharge [° C.]	145	145	145	145

per dosis	5-5 mg/wt.-%	5-6 mg/wt.-%	5-7 mg/wt.-%
Amphetamine sulfate	30.00/12.00	30.00/12.00	30.00/12.00
Citric acid	—	—	—
PEG 6000	32.60/13.00	32.60/13.00	32.60/13.04
α-Tocopherol	0.50/0.20	0.50/0.20	0.50/0.20
Xanthan Gum Type 602	—	—	—
Polyethylene oxide 7 Mio.	136.90/54.70	136.90/54.70	136.90/54.76
Sodium hydrogen carbonate	—	50.00/20.00	—
Croscarmellose sodium	—	—	—
Starch 1500	50.00/20.00	—	—
Carboxymethyl starch	—	—	—
PVP-CL	—	—	50.00/20.00
Σ	250.0/100.00	250.0/100.00	250.00/100.00
Speed screw [rpm]	100	100	100
Extruder Load [%]	75.00	75.00	75.00
Melt pressure [bar]	1	1	1
melt temperature discharge [° C.]	145	145	145

The in vitro dissolution test revealed the following release profiles:

Dissolution Amphetamine sulfate %	5-1	5-2	5-3	5-4	5-5	5-6	5-7
after 5 min	67	61	51	48	62	45	63
after 15 min	90	90	85	81	83	70	87
after 30 min	96	97	94	93	94	80	93
after 60 min	98	99	97	97	98	84	96

The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	5-1	5-2	5-3	5-4	5-5	5-6	5-7
1	38.41	32.54	6.11	11.31	4.57	8.23	44.80
2	28.83	33.63	11.43	8.18	0.00*	8.61	51.17
3	23.67	12.16	14.56	5.20	0.00*	12.77	50.96
mean [%]	30.30	26.11	10.70	8.23	0.00*	9.87	48.98
SD [%]	7.48	12.09	4.27	3.06	0.00*	2.52	3.62

*not tested, sample too jelly and could not be drawn into syringe

It becomes clear from the above experimental data that as far as tamper-resistant dosage forms providing immediate release are concerned, the tested disintegrants provide an improved resistance against solvent extraction. Croscarmel-

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lose sodium (5-2, 5-3), carboxymethyl starch (5-4), starch 1500 (5-5) and sodium hydrogen carbonate provided the best results, whereas PVP-CL (5-7) did not show an advantage over the comparative composition (5-1).

EXAMPLE 6—GELLING AGENT AND DISINTEGRANT

The influence of the presence and absence of gelling agent as well as the influence of the presence and absence of disintegrant was investigated in analogy to Examples 1 to 5. The following compositions A to F were each prepared for Oxycodone, Hydrocodone, Morphine sulfate and Hydromorphone, respectively:

	6-A		6-B		6-C		6-D		6-E		6-F	
Substance	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%
API ¹	10.00	5.56	10.00	5.56	10.00	5.56	10.00	5.56	10.00	5.56	10.00	5.56
Citric acid	1.44	0.80	1.44	0.80	1.44	0.80	1.44	0.80	1.44	0.80	1.44	0.80
PEG	25.20	14.00	25.20	14.00	25.20	14.00	25.20	14.00	25.20	14.00	25.20	14.00
α -Toc.	0.36	0.20	0.36	0.20	0.36	0.20	0.36	0.20	0.36	0.20	0.36	0.20
PEO	143.0	79.44	107.0	59.44	107.0	59.44	134.0	74.44	98.00	54.44	98.00	54.44
Carbopol	—	—	36.00	20.00	27.00	15.00	—	—	—	—	—	—
Xanthan	—	—	—	—	9.00	5.00	9.00	5.00	9.00	5.00	9.00	5.00
Carb.MS	—	—	—	—	—	—	—	—	36.00	20.00	—	—
CrosCS	—	—	—	—	—	—	—	—	—	—	36.00	20.00
Σ	180	100	180	100	180	100	180	100	180	100	180	100

¹The compositions A to F containing Hydromorphone as API were modified in that they contained 8.00 mg Hydromorphone only. The difference of 2.00 mg was replaced by the corresponding amount of PEO

API = pharmacologically active ingredient;

PEG = Polyethylene glycol 6000;

α -Toc. = α -Tocopherole;

PEO = polyethylene oxide 7 Mio;

Carbopol = Carbopol 71G;

Xanthan = Xanthan gum;

Carb. MS = Carboxy methyl starch;

CrosCS = Croscarmellose sodium

In vitro release as well as resistance against solvent extraction were determined in accordance with the invention. The results for the different pharmacologically active ingredients are shown in the table here below:

	Oxycodone		Hydrocodone		Morphine sulfate		Hydromorphone	
Formulation	extract.	diss.	extract.	diss.	extract.	diss.	extract.	diss.
6-A	50%	73%	40%	87%	34%	87%	49%	84%
6-B	40%	90%	0%	91%	9%	83%	29%	87%
6-C	28%	90%	0%	95%	3%	82%	26%	89%
6-D	12%	91%	32%	75%	14%	88%	33%	91%
6-E	0%	94%	5%	92%	0%	90%	14%	91%
6-F	2%	94%	1%	103%	—	—	7%	91%

extract. = extracted in solvent;

diss = dissolution after 30 minutes

It becomes clear from the above comparative data that the disintegrants in inventive formulations E and F in accordance with the present invention provide best performance with respect to immediate drug release and resistance against solvent extraction for all tested pharmacologically active ingredients, whereas the comparative formulations A, B, C and D only provided partial effects for some of the tested pharmacologically active ingredients.

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EXAMPLE 7—QUANTITY OF DISINTEGRANT PART I

The influence of the content of disintegrant was investigated in analogy to Examples 1 to 6. Compositions 7-1 to 7-3 were prepared and in vitro dissolution as well as resistance against solvent extraction were determined.

Substance	7-1		7-2		7-3	
per dose	mg	wt.-%	mg	wt.-%	mg	wt.-%
Oxycodone HCl	10.00	5.56	10.00	5.56	10.00	5.56
Citric acid	1.44	0.80	1.44	0.80	1.44	0.80

-continued

Substance	7-1		7-2		7-3	
per dose	mg	wt.-%	mg	wt.-%	mg	wt.-%
PEG 6000	27.51	15.28	25.20	14.00	27.51	15.28
α -Tocopherol	0.36	0.20	0.36	0.20	0.36	0.20
Xanthan Gum Type 602	9.00	5.00	9.00	5.00	9.00	5.00

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-continued

Substance	7-1		7-2		7-3	
per dose	mg	wt.-%	mg	wt.-%	mg	wt.-%
PEO 7 Mio.	104.69	58.16	98.00	54.44	91.31	50.73
Sodium starch glycolate	27.00	15.00	36.00	20.00	45.00	25.00
	180.00	100.00	180.00	100.00	180.00	100.00
Dissolution (n = 3):						
0	0.00		0.00		0.00	
5	64.46		69.73		62.04	
15	78.42		87.57		81.83	
30	91.24		94.44		91.76	
60	94.82		96.49		95.12	
extraction without milling:						
mean [%]	10.10		0.00*		16.37	
SD [%]	4.67		0.00*		12.67	

*not tested, sample too jelly and could not be drawn into syringe

It becomes clear from the above comparative data that under the given conditions the best results could be achieved at a content of 20 wt.-% disintegrant (here sodium starch glycolate).

EXAMPLE 8—QUANTITY OF DISINTEGRANT PART II

The influence of the content of disintegrant was investigated in analogy to Examples 1 to 7. Compositions 8-1 to 8-4 were prepared and in vitro dissolution as well as resistance against solvent extraction were determined.

per dose	8-1		8-2		8-3		8-4	
	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%
Amphetamine sulfate	30.00	13.95	30.00	16.67	30.00	13.95	30.00	16.67
PEG 6000	27.20	12.65	21.85	12.14	27.20	12.65	21.85	12.14
α-Tocopherol	0.43	0.20	0.36	0.20	0.43	0.20	0.36	0.20
Polyethylene oxide 7 Mio.	114.37	53.20	91.79	50.99	114.37	53.20	91.79	50.99
Croscarmellose sodium	43.00	20.00	36.00	20.00				
Starch 1500					43.00	20.00	36.00	20.00
Σ	215.00	100.00	180.00	100.00	215.00	100.00	180.00	100.00
Speed screw [rpm]	100		100		100		100	
Extruder Load [%]	75.00		75.00		75.00		75.00	
Melt pressure [bar]	1		1		1		1	
melt temperature	145		145		145		145	
discharge [° C.]								

The in vitro dissolution test revealed the following release profiles:

Dissolution Amphetamine sulfate %				
	8-1	8-2	8-3	8-4
after 5 min	60	74	75	78
after 15 min	91	94	82	81
after 30 min	97	99	84	87
after 60 min	97	99	85	88

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The test for tamper-resistance provided the following results (where all tested pellets remained intact after the breaking strength tester had reached its upper force limit):

test battery	8-1	8-2	8-3	8-4
1	7.92	17.51	0.00*	6.42
2	7.74	12.79	0.00*	3.66
3	8.49	16.85	0.00*	1.83
mean [%]	8.05	15.72	0.00*	3.97
SD [%]	0.39	2.56	0.00*	2.31

*not tested, sample too jelly and could not be drawn into syringe

It becomes clear from the above comparative data that under the given conditions lower contents of disintegrant provide an improved resistance against solvent extraction.

EXAMPLE 9—TABLETS CONTAINING PELLETS 8-1 AND 8-4

Tablets containing pellets 8-1 and 8-4 were prepared:

per tablet [mg]	per tablet [mg]	Excipients	[%]	Form
215.00	30.00	Amfetamine Sulfate	30.71	Pellets
	114.37	Polyethylenoxid 7 Mio.		
	27.20	Macrogol 6000		
	0.43	Alpha-Tocopherol		
	43.00	Croscarmellose Sodium		
485.00		Microcrystalline Cellulose	69.29	Powder Mix

-continued

per tablet [mg]	per tablet [mg]	Excipients	[%]	Form
		Crospovidone		
		Magnesiumstearate		
		Ph. Eur.		
700.0	700.0	—	100.00	—
180	30.00	Amfetamine Sulfate	25.71	Pellets
	91.79	Polyethylenoxid 7 Mio.		
	21.85	Macrogol 6000		
	0.36	Alpha-Tocopherol		
	36.0	Starch 1500		

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-continued

per tablet	per tablet			
[mg]	[mg]	Excipients	[%]	Form
520.00		Microcrystalline Cellulose	74.29	Powder Mix
		Crospovidone		
		Magnesiumstearate		
		Ph. Eur.		
700.0	700.0	—	100.00	—

The test for tamper-resistance of pulverized pellets and pulverized tablets provided the following results:

test battery	Tablet containing pellets 8-1	Tablet containing pellets 8-4
1	2.27	0.00*
2	2.48	0.00*
3	0.00*	0.00*
mean [%]	0.00*	0.00*
SD [%]	0.00*	0.00*

*not tested, sample too jelly and could not be drawn into syringe

It becomes clear from the above comparative data that under the given conditions tablets containing pellets provide an improved resistance against solvent extraction compared to pellets alone.

EXAMPLE 10—OXYCODONE PELLETS AND TABLETS CONTAINING OXYCODONE PELLETS

Powder mixtures of the following ingredients were manufactured and subsequently hot-melt extruded:

per dosis	10-1 mg/wt.-%
Oxycodone HCl	30.00/12.00
Citric acid	1.25/0.50
α-Tocopherol	0.50/0.20
Polyethylene oxide 7 Mio.	133.25/53.30
Macrogol 6000	35.00/14.00
Carbopol 71G	50.00/20.00
Σ	250.00/100.00

Tablets containing oxycodone pellets were prepared:

	per tablet	
Excipients	[mg]/	[wt.-%]
Oxycodone pellets	250.00	50.00
Avicel PH101/PVP-CL	250.00	50.00
Aerosil 200		
Mg stearate		
Σ	500.00	100.00

The test for tamper-resistance of intact tablets and intact pellets provided the following results:

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test battery	Oxycodone pellets	Tablet containing oxycodone pellets
1	47.10	30.90
2	46.82	27.97
3	39.68	27.23
mean [%]	44.53	28.70

It becomes clear from the above comparative data that under the given conditions tablets containing pellets provide an improved resistance against solvent extraction compared to pellets alone.

EXAMPLE 11—AMPHETAMINE PELLETS AND CAPSULES CONTAINING AMPHETAMINE PELLETS

a) Capsules containing pellets 8-1 and 8-4 were prepared.

Phase [mg]	Component	Amount per capsule [mg]	Amount [%]
20 Pellets 215.00	Amphetamine sulfate	30.00	54.43
	Polyethylene oxide 7000000	114.37	
	Macrogol 6000	27.20	
	Alpha Tocopherol	0.43	
25 Powder blend 180.00	Croscarmellose sodium (Vivasol ®)	43.00	
	Mannitol (Partek M200 ®)	180.00	45.57
	Colloidal silicon dioxide		
30 Pellets 180.00	Sum	395.00 mg	100.00
	Amphetamine sulfate	30.00	50.00
	Polyethylene oxide 7000000	91.79	
	Macrogol 6000	21.85	
	Alpha Tocopherol	0.36	
	Pre-gelatinized maize starch (Starch 1500)	36.00	
35 Powder blend 180.00	Mannitol (Partek M200 ®)	180.00	50.00
	Colloidal silicon dioxide		
40 Sum		360.00 mg	100.00

The mixtures were filled in capsules of size 0.

b) Pellets 8-4 were coated with a protective coating (Opadry clear) by means of a fluid-bed granulation process and the thus coated pellets were filled in capsules without additional constituents.

Phase [mg]	Component	Amount per capsule [mg]	Amount [%]
50 Pellets 193.90	Amphetamine sulfate	30.00	100.00
	Polyethylene oxide 7000000	91.79	
	Macrogol 6000	21.85	
	Alpha Tocopherol	0.36	
	Pre-gelatinized maize starch (Starch 1500)	36.00	
55 Opadry II clear		13.90	
Sum		193.90 mg	100.00

The coated pellets were filled in capsules of size 0.

The in vitro release profiles of all three capsules is shown in FIG. 4.

The invention claimed is:

1. A tamper-resistant pharmaceutical dosage form comprising a multitude of particles which comprise a pharmacologically active compound, a polyalkylene oxide, and a disintegrant;

wherein the pharmacologically active compound is a stimulant selected from the group consisting of phenylethylamine derivatives;

wherein the pharmacologically active compound is dispersed in a matrix comprising the polyalkylene oxide and the disintegrant;

wherein the disintegrant is selected from the group consisting of croscarmellose sodium, partially pre-gelatinized starch, carboxymethyl starch, and mixtures thereof;

wherein the content of the disintegrant is 15 ± 5.5 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles;

wherein the content of the polyalkylene oxide is at least 25 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles;

wherein the dosage form provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur;

wherein the particles exhibit an increased resistance against solvent extraction compared to comparison particles that are otherwise identical to said particles except the comparison particles lack any content of any disintegrant; and

wherein the increased resistance against solvent extraction is determined by (a) dispensing the particles or the comparison particles in 5 ml of boiling water to form a liquid, (b) after five minutes drawing the liquid up into a syringe needle 21G equipped with a cigarette filter, and (c) determining the amount of the pharmacologically active ingredient in the liquid in the syringe by high performance liquid chromatography, wherein the increased resistance against solvent extraction compared to the comparison particles is proven by a lower amount of the pharmacologically active ingredient in the syringe in the case of the particles compared to the amount of the pharmacologically active ingredient in the syringe in the case of the comparison particles.

2. The pharmaceutical dosage form according to claim 1, wherein the stimulant is selected from the group consisting of methylphenidate, dexamethylphenidate, and the physiologically acceptable salts thereof.

3. The pharmaceutical dosage form according to claim 1, wherein the stimulant is selected from the group consisting of pseudoephedrine, and the physiologically acceptable salts thereof.

4. The pharmaceutical dosage form according to claim 1, which has a breaking strength of at least 300 N.

5. The pharmaceutical dosage form according to claim 1, which exhibits resistance against solvent extraction such that when

- (i) dispensing the pharmaceutical dosage form that is either intact or has been manually comminuted by means of two spoons in 5 ml of purified water,
- (ii) heating the liquid up to its boiling point,
- (iii) boiling the liquid in a covered vessel for 5 min without the addition of further purified water,
- (iv) drawing up the hot liquid into a syringe, and

- (v) determining the amount of the pharmacologically active compound contained in the liquid within the syringe,

the liquid part of the formulation that can be separated from the remainder by means of the syringe is not more than 10 wt.-% of the pharmacologically active compound originally contained in the dosage form.

6. The pharmaceutical dosage form according to claim 1, wherein the disintegrant is partially pregelatinized starch.

7. The pharmaceutical dosage form according to claim 1, wherein the disintegrant is sodium carboxymethyl starch.

8. The pharmaceutical dosage form according to claim 1, wherein the disintegrant is croscarmellose sodium.

9. The pharmaceutical dosage form according to claim 1, wherein the content of the disintegrant is at least 10 wt.-%, based on the total weight of the particles.

10. The pharmaceutical dosage form according to claim 1, wherein the polyalkylene oxide has a weight average molecular weight of at least 500,000 g/mol.

11. The pharmaceutical dosage form according to claim 1, which provides a release profile such that under in vitro conditions in 600 ml 0.1 M HCl (pH 1) at 75 rpm after 30 min at least 90 wt.-% of the pharmacologically active ingredient that was originally contained in the dosage form have been released.

12. The pharmaceutical dosage form according to claim 1, which additionally comprises a gelling agent.

13. The pharmaceutical dosage form according to claim 12, wherein the gelling agent is a polysaccharide; or the content of the gelling agent is at least 1.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

14. The pharmaceutical dosage form according to claim 1, wherein the stimulant is selected from the group consisting of amphetamine, dexamphetamine, methylenedioxymethamphetamine, lisdexamphetamine, methamphetamine, and the physiologically acceptable salts thereof.

15. The pharmaceutical dosage form according to claim 1, wherein the content of the pharmacologically active compound is at least 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form and/or based on the total weight of the particles.

16. The pharmaceutical dosage form according to claim 1, wherein the particles are hot melt-extruded.

17. The pharmaceutical dosage form according to claim 1, wherein the particles are film coated.

18. The pharmaceutical dosage form according to claim 1, which is a tablet or capsule.

19. The pharmaceutical dosage form according to claim 1, wherein the content of the polyalkylene oxide is at least 40 wt.-%, based on the total weight of the particles.

20. The pharmaceutical dosage form according to claim 1, wherein all of the polyalkylene oxide that is contained in the pharmaceutical dosage form is contained in the particles.

21. The pharmaceutical dosage form according to claim 1, wherein the stimulant is the only active ingredient in the pharmaceutical dosage form.