

POROUS HYDROXYAPATITE PARTICLES AS CARRIERS FOR DRUG SUBSTANCES

Field of the invention

- 5 The present invention is related to a new oral pharmaceutical dosage form comprising porous inorganic particles incorporated with considerable amounts of greasy, oily or sticky (greasy/oily/sticky) substances where the new dosage form is characterised by being dry and easy to handle and having fast release properties.

10 Background of the invention.

- In many thereapeutic areas the need for incorporating absorption enhancers (e.g. glycerol esters for increased absorption of heparin or heparin fragments or derivatives as described in WO 95/00152 to Pharmacia), solubilizing agents (like polyethoxylated hydrogenated
15 castor oils for felodipine as disclosed in EP 0249587 to AB Hässle), suspending agents (e.g. soybean oil or fractionated coconut oil for 1,2,4- benzotriazine oxide as disclosed in US patent 5,597,582 to Sanofi), or the like into the dosage forms for drug delivery has arisen.

- 20 Incorporation of larger amounts of greasy, oily or sticky substances into pharmaceutical dosage forms have since long been known to cause technical problems. One of the problems has been to get pharmaceutically acceptable dry materials that are easy to handle and use as such or to use in later processing steps.

- 25 Earlier ways to circumvent the problem include filling the greasy/oily/sticky substances as such into soft gelatin capsules, as for instance described in US 5589455 (Han Mi Pharm) where a concentrate for soft gelatin capsule filling comprising a cyclosporin and an oil component (improving bioavailability) is disclosed.

Many researchers have during the years described the advantage of using many small pellets (multiple unit) as a dosage form, with respect to their behaviour in vivo, i.e. especially with respect to their gastric emptying properties, see for instance Bogentoft et al, J. Clin. Pharmacol. 1978, 14, 351-5.

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Another way to circumvent the problem, in line with the above findings, is to use microencapsulation. This method is, however, expensive as it includes many steps and is also often associated with big scaling-up troubles. The method has been described e.g by Luzzi in J.Pharm.Sci, 1970, 59, (10), 1367-76 .

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Prior Art

WO 94/23703 (Kabi Pharmacia AB) discloses the manufacture of porous cellulose matrices and a multiple unit preparation containing a bioactive substance comprising porous cellulose matrice particles. However, this reference neither pertains to the problem of handling greasy, oily or sticky substances nor does it pertain to inorganic matrices.

EP 294 206 (Unilever NV) discloses porous spheroidal silica having certain characteristics having up to 50 % by weight of the SiO₂ of included material such for example therapeutic agents. However, this reference neither pertains to the problem of handling greasy, oily or sticky substances nor does it show any achievement of fast release properties.

Description of the invention

It has now been found that a drug delivery system for oral administration in solid dry form of greasy, oily or sticky substance(s) and pharmaceutically active substance(s) or pharmaceutically active substance(s) which itself/themselves is/are greasy, oily or sticky characterized by having porous inorganic particles of small size incorporated with considerable amounts of greasy, oily or sticky substances and having fast release characteristics can overcome the drawbacks associated with previous techniques.

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Thus, the present invention provides a new dosage form principle for incorporation of greasy, oily or sticky materials into particles of small size, thus enabling a possibility to make multiple unit systems thereof. To achieve this, it has been found that highly porous
5 inorganic particles are beneficial to use.

One characteristic of the present invention is the small size of the porous particles. The size is between 5 to 150 μm , preferably 20 to 100 μm .

10 Another characteristic of the present invention is the considerable amount of the greasy, oily or sticky substance. By considerable amount in this specification is meant 15% w/w to 40 % w/w, preferably 20 % w/w to 40% w/w, most preferably 30% w/w to 40% w/w.

The greasy, oily or sticky substances incorporated may be, but are not restricted to,
15 pharmaceutically active substances, such as almokalant or vitamin A; pharmaceutically active substances which are themselves not greasy, oily or sticky but which together with a greasy, oily or sticky substance is especially suitable to be incorporated into the formulation are such as felodipine, melagatran, or inogatran; absorption enhancers which are greasy, oily or sticky and selected among mono-, di- or triglycerides or mixtures
20 thereof, such as Akoline[®] MCM, Invitor 308, Invitor 742, Invitor 928, Invitor 988, glycerol de caprylate[®]; solubilizers, such as semi-solid or liquid non-ionic surface active agents, for example such containing polyethyleneglycols as esters or ethers, and which are chosen from polyethoxylated fatty acids, hydroxylated fatty acids and fatty alcohols and especially chosen from the group polyethoxylated castor oil, polyoxyethylenated
25 hydrogenated castor oils (Cremophors), polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil and are known under the trade names such as Cremophor[®], Myrj, Polyoxol 40 stearate, Emerest 2675, Lipal 395 and HCO 50.

The drug delivery system according to the invention is also characterized by having fast release characteristics when they with an in vitro dissolution test release not less than 60 % (preferably 70% w/w) of pharmaceutically active substance and greasy/oily/sticky substances, or drug when the drug is the greasy, oily or sticky substance, within 30 minutes or shorter.

For the greasy, oily or sticky substances the dissolution rate is determined using USP apparatus No. 2 (paddle), operated at 100 rpm. The dissolution medium has a temperature of 37 °C. Further there is a demand on the amount and art of dissolution medium, that it enables for the whole dose to be tested a non-retarded homogenous distribution of liberated greasy , oily or sticky substance within the medium.

For the specific greasy, oily or sticky substances shown in the examples, the medium disclosed in each example is the appropriate one.

For the drug substances the dissolution rate is determined using USP apparatus No. 2 (paddle), operated at 100 rpm. The dissolution medium has a temperature of 37 °C. Further there is a demand on the amount and art of dissolution medium, that it enables for the whole dose to be tested, a non-retarded homogenous distribution of liberated drug within the medium (sink conditions).

For the specific drugs shown in the examples, the medium disclosed in each example is the appropriate one.

It should be noted that for the one and same formulation different dissolution media might be chosen depending on the properties of the substances to be tested, if there are a greasy, oily or sticky substance and a pharmaceutically active substance present in the formulation, depending on which one of these that are to be tested.

Inorganic porous particle material used in the invention is ceramic hydroxyapatite.

The ceramic hydroxyapatite is characterized by having a range particle diameter size between 5 - 150 μm , preferably between 20 - 80 μm , a nominal pore diameter between 5 - 100 μm , preferably 50-100 μm and a surface area between 40- 50 m^2/g . Ceramic
5 hydroxyapatite is commercially available from e.g. BIO-RAD Laboratories under trade name Macro-Prep[®].

Loading of porous particles

10 The incorporation of the greasy, oily or sticky materials into the particles may be accomplished by conventional known methods. One is to dissolve the oil in suitable solvent and then mix with the porous particle material and dry. Alternatively the oil can be mixed directly with the porous particle materials. Another way is to use phase separation from a solution containing particles by addition of a non-solvent.

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The porosity of the particles is 50-70 % (v/v), preferably 62 % (v/v).

When used in a drug delivery system the loaded porous particles may be used as such or filled into capsules, compressed to tablets or coated by ways well known in the art.

20 The filling into capsules, compressing to tablets or coating should be performed in a manner that the fast release characteristics are not substantially changed. If fast release in the small intestine is desired, the loaded porous particles could be enteric coated.

Working examples**Example 1 - Hydroxyapatite particles containing felodipine and 19.5 % Cremophor[®] RH 40.**

5 The greasy/oily substance Cremophor[®] RH40 (312 mg) was melted at approx. 30°C and used to dissolve felodipine (88 mg) in. The solution was poured on 1200 mg of hydroxyapatite particles having an average diameter of 80 µm (Macro Prep[®] Ceramic Hydroxyapatite; BIO-RAD Laboratories), under gentle manual mixing and mixing was continued until homogeneity.

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The obtained particles were analyzed with regard to dissolution of felodipine using USP dissolution apparatus No. 2 (paddle), operated at 100 rpm. The dissolution medium used, having a temperature of 37 C, was phosphate buffer pH 6.5 containing 0.4 per cent of cetyltrimethylammonium bromide. The amount of felodipine released was determined by

15 UV-spectrometry.

After 30 minutes the amount of felodipine dissolved was 84 % (as average, n=2) of the found content.

20 Example 2 - Hydroxyapatite particles containing melagatran and 37 % Akoline[®]

The greasy/oily substance Akoline[®] (779 mg) was melted at approx. 30°C and used to dissolve melagatran (21 mg) in. The solution was poured on hydroxyapatite particles (1200 mg) having an average particle diameter of 80 µm (Macro Prep[®] Ceramic Hydroxyapatite; BIO-RAD Laboratories), under gentle mixing and mixing was continued until

25 homogeneity.

The obtained particles were analyzed with regard to dissolution of Akoline[®] MCM and melagatran using a USP dissolution apparatus No. 2 (paddle), operated at 100 rpm. The dissolution medium used, having a temperature of 37°C, was phosphate buffer pH 6.8 with

30 additions of 2 mM lecithin and 5 mM taurocholate to make the sample uptake

homogenous. The sample components were separated by liquid chromatography. The amount of Akoline released was determined using a light scattering detector and the amount of melagatran released was determined by UV-spectrometry.

- 5 After 20 minutes the amount of Akoline[®] MCM dissolved was 71 % (as average, n=2) of the found content. The amount of melagatran dissolved after 20 minutes was 94 % (as average, n=2) of the found content.

Example 3 - Hydroxyapatite particles containing 33.3 % almokalant

- 10 The oily/sticky substance almokalant (0.6 g, room temperatured) was poured on hydroxyapatite (1200 mg) particles having an average diameter of 80 μm (Macro Prep[®] Ceramic Hydroxyapatite; BIO-RAD Laboratories), under gentle manual mixing and mixing was continued until homogeneity.
- 15 The obtained particles were analyzed with regard to dissolution of almokalant using USP dissolution apparatus No.2 (paddle), operated at 100 rpm. The dissolution medium, used having a temperature of 37 C, was phosphate buffer pH 6.8. The amount of almokalant released was determined by UV- spectrometry.
- 20 After 30 minutes the amount of almokalant dissolved was 100 % (as average, n=2) of the found content.

Example 4 - Hydroxyapatite particles containing 17.4 % almokalant

- The oily/sticky substance almokalant (0.35 g, room temperatured) was poured on
- 25 hydroxyapatite (1.7 g) particles having an average diameter of 80 μm (Macro Prep[®] Ceramic Hydroxyapatite; BIO-RAD Laboratories), under gentle manual mixing and mixing was continued until homogeneity.

- The obtained particles were analyzed with regard to dissolution of almokalant using USP
- 30 dissolution apparatus No.2 (paddle), operated at 100 rpm. The dissolution medium, used

having a temperature of 37 C, was phosphate buffer pH 6.8. The amount of almokalant released was determined by UV- spectrometry.

After 30 minutes the amount of almokalant dissolved was 80 % (as average, n=2) of the found content.

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Example 5

Particles obtained in example 1 were filled into hard gelatine capsules of size 3. Each capsule was filled with 190 mg of felodipine/hydroxyapatite particles.



CLAIMS

1. A dry, solid drug delivery composition which comprises:
 - 5 (i) at least one greasy, oily or sticky substance and at least one pharmaceutically active substance, or
 - (ii) at least one greasy, oily or sticky pharmaceutically active substance,
- 10 characterized in that the composition is in form of a plurality of porous inorganic particles composed of ceramic hydroxyapatite having a diameter of from 5 to 150 μm , said composition having fast release characteristics and incorporating from 15 wt% to 40 wt% of the component (i) or (ii).
- 15 2. A drug delivery system according to claim 2 wherein the ceramic hydroxyapatite has a diameter size of 20 - 80 μm .
3. A drug delivery system according to any of the preceeding claims wherein the pharmaceutically active substance has a molecular weight less than 1000 dalton.
- 20 4. A drug delivery system according to any of the preceeding claims wherein the pharmaceutically active substance is a thrombin inhibiting peptide drug.
5. A drug delivery system according to any of the preceeding claims wherein the
- 25 pharmaceutically active substance is melagatran.
6. A drug delivery system according to claims 1 - 3 wherein the pharmaceutically active substance is felodipine.



7. A drug delivery system according to claims 1 - 3 wherein the pharmaceutically active substance is almokalant.

8. A process for the preparation of a dry, solid drug delivery composition which
s comprises:

(i) at least one greasy, oily or sticky substance and at least one pharmaceutically active substance, or

10 (ii) at least one greasy, oily or sticky pharmaceutically active substance,

characterized by the mixing of from 15 wt % to 40 wt % of the component (i) or (ii) and a plurality of porous inorganic particles composed of ceramic hydroxyapatite having a diameter of from 5 to 150 μm .

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9. Use of a plurality of porous inorganic particles composed of ceramic hydroxyapatite having a diameter of from 5 to 150 μm , incorporated with from 15 wt % to 40 wt % of a component

20 (i) at least one greasy, oily or sticky substance and at least one pharmaceutically active substance, or

(ii) at least one greasy, oily or sticky pharmaceutically active substance

in the preparation of a dry, solid drug delivery composition having fast release

25 characteristics.

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

200002486-9 IPOs



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/16, 31/275, 31/44, 38/55	A1	(11) International Publication Number: WO 99/27912 (43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/SE98/02089 ✓ (22) International Filing Date: 19 November 1998 (19.11.98) ✓ (30) Priority Data: ① 9704400-2 ✓ 28 November 1997 (28.11.97) ✓ SE ✓ (71) Applicant (for all designated States except US): ① ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (73) Inventors/Applicants (for US only): ① KARLSSON, Christer ✓ [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE) LUND- BERG, Per, Johan ✓ [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE) SROSIŃSKI, Adam ✓ [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE) SÖDERBOM, Malin ✓ [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. IPD. 1 appl ⁿ (change name, see 18/306) (Take note of symbols) 4 Invs. (Take note of symbol in 4th inventor)	
(54) Title: POROUS HYDROXYAPATITE PARTICLES AS CARRIERS FOR DRUG SUBSTANCES ✓ (57) Abstract A drug delivery system for oral administration in solid dry form of a greasy/oily/sticky substance and a pharmaceutically active substance of a pharmaceutically active substance which itself is greasy/oily/sticky characterized by having a plurality of porous inorganic particles of small size incorporated with considerable mounts of greasy/oily/sticky substances and having fast release characteristics and a process for the preparation of such porous inorganic particles containing greasy/oily/sticky substances. IPC = A61K 9/16, A61K 31/275, A61K 31/44 A61K 38/55 IPER 21/6/99		