Abstract: The present invention relates to processes for loading microsphere polymer particles with crystallisable drug, in the presence of a crystallisation inhibitor whereby crystallisation of the drug is inhibited. The invention is of particular value for loading polymer beads with paclitaxel, ibuprofen and/or dexamethasone. The polymer is suitably an anionic polyvinyl alcohol polymer.
PROCESS FOR LOADING POLYMER PARTICLES WITH DRUG

The present invention relates to processes for loading polymeric beads, to be used as drug delivery media, with drugs. The processes allow loading of drugs susceptible to crystallisation within such media, whereby the burst effect is minimised. In a preferred aspect, the beads are radiopaque.

Embolisation therapy involves the introduction of an agent into the vasculature in order to bring about the deliberate blockage of a particular vessel. This type of therapy is particularly useful for blocking abnormal connections between arteries and veins (such as arteriovenous malformations, or AVMs), and also for occluding vessels that feed certain hypervascularised tumours, in order to starve the abnormal tissue and bring about its necrosis and shrinkage.

The process of embolisation may induce tumour ischemia or necrosis depending upon the extent of the embolisation. The response of the tumour cells to the hypoxic environment can result in an ensuing angiogenesis in which new blood vessels are grown to compensate for the loss of flow to the tumour by the embolisation. It would be desirable therefore to combine embolisation with the administration of agents that could prevent the ensuing angiogenic response. Moreover, it may be desirable to combine this effect with the release of a cytotoxic or other anti-tumoral agent to bring about cell death in those cells that are not killed by the embolisation. There have been many disclosures of polymer bead embolic agents loaded with therapeutic agents, for treatment of solid tumours, such as WO2004/000548, WO2005/087193, PCT/GB2004/003347 and PCT/GB2005/003431.

Oils are commonly used in pharmaceutical formulation technologies and preparations. Soya Bean oil is commonly used in the FDA Inactive ingredients Guide (IV injections, oral capsules and topical preparations).

Lipiodol is iodinated oily X-ray contrast medium wherein poppy-seed oil is iodised to a level of about 40% by weight, it can be used in certain radiological investigations where it is desirable to outline a viscous or other structure with directly instilled radio-opaque material. It is also suitable for introduction into narrow channels and may therefore be used in embolisation procedures. It is commonly used in diagnostic hysterosalpingography (HSG). HSG is radiography (or X-ray) of the uterus and fallopian tubes used for the detection of gynaecological problems, particularly those affecting female fertility.

Lipiodol is also used for lymphography, which is the examination of the lymph nodes and lymphatic vessels, in particular for the prognostic diagnosis of
leukaemia and Hodgkin's and non-Hodgkin's lymphoma. It is also used for detecting
disorders of the salivary glands or ducts.

It is commonly used off-label in combination with chemotherapy i.e.
treatment with a cytotoxic or other anti-tumoural agent, whereby a Lipodolxhemo
emulsion is administered intra arterially in the super-selective treatment of
hepatocellular carcinoma

Ibuprofen (IBU) is a hydrophobic drug and is known to form many types of
crystals. The crystal properties of IBU are known to influence its pharmaceutical
processing (Romero, A J et al., 1991 Pharma Acta Helv 66(2) 34-43). The shape of
IBU crystals depends on the solvent and this can be improved by the choice of a
suitable solvent (Garekam HA, et al., Crystal habit modifications of IBU and their physscornechanical characteristics. Drug Dev Ind Pharm 27(8):803-9, 2001)

We have described the use of microspheres containing IBU to treat uterine
fibroids in W02004/000698.

Other groups have also described use of microspheres for encapsulating
with indomethacin and then encapsulate these with a coacervated mixture of
ethylcellulose and polyisobutylene

Song C X. et at. in Journal of Controlled Release 43(1997) 197-212 prepare
various drug-loaded poly(lactsc-co-glycolfc acid) nanoparticles using an
emulsifscatrøn/solvent evaporation technique.

However, to date the problem of drug-crystalt sation during the encapsulation
process has not been addressed.

Crystal formation on the embolic microspheres (MS) leads to a number of
disadvantages in the manufacturing of this product. Whstie most of the drug is up-
taken inside the MS some drug remains on the surface of the MS These crystals on
the surface lead to an increased burst effect, thus resulting in an immediate
dumpsng of a large dose of drug. The crystals also cause the beads to aggregate
and clump together by hydrophobic interactions, causing them to stick to hubs of the
syringes making them harder to deliver, more likely to be damaged and increasing
the tendency for catheter clogging during delivery

During the sterilisation of iBU-beads by autoclaving at 120°C for 15 minutes,
crystals appear to melt onto the bead surfaces, heatsng above the melting point of
IBU (78°C) leadmg to the formation oily droplets. These droplets are responsible for
a nucleatson process, which leads to re-crystailisation when the vials are opened
and product is exposed to air. The crystals cause the problems indicated above and
lead to catheter and hub Diocckage during use and an increase in the burst effect of the drug.

It has been demonstrated that the physicochemical properties of IBU crystals are affected by the conditions under which the crystallisation occurs, and efforts are being made to produce compositions of IBU with excipients having the desired properties by controlling the process of crystal formation. Crystal alterations were noticed for IBU in the presence of Eudragit R S100 polymer (Kachmanis et al. 1998 Crystallisation conditions and physicochemical properties of IBU- Eudragit S100 spherical crystal agglomerates prepared by solvent-change technique int J Pharm 173,61-74). Rasenack et al. (IBU crystals with optimized properties In! J Pharm 245 (1-2) 9-24, 2002) have used water-soluble additives in an attempt to modify IBU crystals. They suggested that additives can interact with hydrogen bonding formed during the IBU crystallization process leading to a change in the properties of the resulting crystals. Francesco et al. (Polymethacrylates as crystallisation modifiers in monolayer transdermal patches containing IBU E J P B , 60 61-66, 2005) investigated the use of low molecular weight excipients for inhibition of crystallisation of IBU in transdermal systems to maintain efficiency and quality of the patches and prolong the shelf life of the product. They reported that the addition of propylene glycol inhibited IBU crystallisation for up to 50 days and Eudragit E (EUE) and Eudragit RL(EURL) prevented crystallisation for more than 12 months.

The drying conditions or final thermal curing was reported to prevent crystallisation by Campbell et al. in US 4,832,953, a method for preventing the formation of a crystalline hydrate in a dispersion of a liquid in a non-aqueous matrix was described.

The physicochemical properties of IBU can be affected by choosing a suitable polymorphic form, by choosing a suitable crystal habit, by using special crystallisation techniques, and by using a suitable preparation with excipients to modify crystal formation and retard the nucleation process. Lipids have been used as earners for IBU in order to take advantage of the metabolic pathways of lipid biochemistry to allow for a targeted delivery and reduce ulcerogenic^ (Lambert DM, 2000 Eur J Pharm Set 11 Supp! 2: SI 5-27)

According to the first aspect of the present invention there is provided a process in which swellable beads of water-insoluble, oil-insoluble polymer are contacted with a solution of a crystallisable drug in an organic solvent which is capable of penetrating the beads whereby the drug is absorbed α into the beads, characterised in that the solution further contains a crystal modifier which inhibits crystallisation of the drug.
According to a second aspect of the present invention there is provided a composition comprising swellable beads of water-insoluble, oil-insoluble polymer, a crystallisable drug and a crystal modifier which inhibits crystallisation of the drug wherein the drug and crystal modifier are absorbed into the beads and the polymer is crosslinked polyvinyl alcohol.

In the invention the drug which is used is generally one which is susceptible to crystallisation, for instance upon removal of solvent, usually by evaporation, or following sterilisation steps, when migration of absorbed drug to form liquid droplets at temperatures above the melting temperature, may take place forming a metastable phase susceptible to delayed crystallisation.

Crystal forming drugs are generally known to persons skilled in the art. One category of drug to which the invention is of particular value are COX (1 or 2) inhibitors, such as ibuprofen. Another class of drugs which includes such crystal forming drugs, are anti-cancer agents, for instance paclitaxel. Another class of drugs are corticosteroids, for instance having anti-inflammatory properties, one example being dexamethasone.

In the invention the polymer which forms the beads must be water-soluble and oil-insoluble. Although it may be biodegradable, so that drug may be released substantially by erosion of polymer matrix to release drug from the surface, preferably the polymer is substantially biostable (ie non-biodegradable). The polymer is water-swellable. Water-swellable polymer useful in the invention preferably has an equilibrium water content, when swollen in phosphate buffered saline at room temperature, measured by gravimetric analysis in the range of 40 to 99 wt%, preferably 75 to 95%. Such solubility characteristics are generally achieved by utilising cross-linked polymer, in which the cross-links are, for instance, achieved through Van der Waals forces or, more preferably, through electrostatic interactions (attractions between anions and cations) or, most preferably, by covalent crosslinking. The crosslink density should be such as to allow relative movement of the polymer molecules during the swelling step. The beads may therefore be defined as swellable and at the start of the claimed process, the beads must be susceptible to at least a degree of swelling when contacted with swelling solvents. The beads may have been partially swollen before contact with the drug/solvent solution, but preferably are substantially non-swollen at the beginning of the process.

The beads are of a size to be of utility in drug delivery applications. Although very large beads such as having a diameter more than 5 mm may be utilised, the beads preferably have diameter of less than 2 mm preferably up to 1500 μm.
Although the process may be of utility in loading very small beads, for instance having a diameter of less than 10 µm, for instance even as low as 1 µm, such beads are hard to handle in dry form, for instance in the form in which they are swellable. Furthermore the invention is of most benefit for loading beads of utility in embolisation. As such the beads have a diameter in the range 25 to 1500 µm, preferably in the range 50 to 1200 µm, for instance in the range 100 to 1200 µm.

In the invention the term bead is intended to cover particles of all shapes, for instance rod shapes, cubes, irregular and non uniform shapes. However the invention is of most benefit where the beads are spherical, spheroidal or pellet shaped, or disk shaped. In non spherical particles, such as pellets, spheroids or disks, the maximum dimension is preferably no more than three times the minimum diameter, and preferably less than two times the minimum diameter, for instance around 1.5 or less. The size limitations mentioned above are determined by testing a sample of the swellable beads under conditions in which the beads are swollen to equilibrium in phosphate buffered saline at room temperature and the sizes are measured using an optical microscope.

The materials are of particular utility for forming compositions for use in embolisation. The compositions are preferably provided with a particle size specification which defines the spread of diameters. Preferably the beads are graded into calibrated size ranges for accurate embolisation of vessels. The particles preferably have sizes when equilibrated in phosphate buffered saline at room temperature, in the range 100 to 1500 µm, more preferably in the range 100 to 1200 µm. The calibrated ranges may comprise beads having diameters with a bandwidth of about 10 to 300 µm. The size ranges may be for instance 100 to 300 µm, 300 to 500 µm, 500 to 700 µm, 700 to 900 µm and 900 to 1200 µm.

In one embodiment of the method according to the first aspect of the invention, polymers are used which are derived from natural sources, such as albumin, alginate, gelatin, starch, chitosan or collagen, all of which have been used as embolic agents. In a preferred embodiment the polymer is substantially free of naturally occurring polymer or derivatives. It is preferably formed by polymerising ethylenically unsaturated monomers in the presence of di- or higher-functional cross-linking monomers. The ethylenically unsaturated monomers may include an unsaturated (including vinyl) monomer.

Copolymers of hydroxyethyl methacrylate, acrylic acid and cross-linking monomer, such as ethylene glycol dimethacrylate or methylene bisacrylsiloxane as used for etaficon A based contact lenses may be used. Copolymers of N-acrylsoy-
2-amsno-2-hydroxymethyi-propane-1,3-dio! and N,N-b ιsacrylamide may also be used

Other polymers are cross-linking styremc polymers e g with ionic substrt vants, of the type used as separation media or as ion exchange media

Another type of polymer which may be used to form the water-swellable water-i πsoluble matrix = polyvinyl alcohol crosslinked using aldehyde-type crosslinking agents such as glutaraidehyde. For such products, the polyvinyl alcohol (PVA) may be rendered ionic by providing pendant ionic groups by reacting a functional ionic group containing compound with the hydroxy! groups. Examples of suitable functional groups for reactson with the hydroxy! groups are acylating agents, such as carboxylic acids or derivatives thereof, or other acidic groups which may form esters.

The composition according to the second aspect of this invention comprises swellable beads of water-insoluble, oil-insoluble polymer, wherein the polymer = crosslinked polyvinyl alcohol.

The invention is of particular value where the polymer maπx is formed from a polyvinyl alcohol macromer, having more than one ethylenically unsaturated pendant group per molecule, by radical polymerisation of the ethylenic groups. Preferably the PVA macromer is copolyme πsed with ethylencaiy unsaturated monomers for instance including a nonionic and/or ionic monomer including ansonic monomer.

The PVA macromer may be formed, for instance, by providing PVA polymer, of a suitable molecular weight such as in the range 1000 to 500,000 D, preferably 10,000 to 100,000 D, with pendant vinyhc or acrylic groups. Pendant acrylic groups may be provided, for instance, by reacting acryltc or methacrylic acid with PVA to form ester linkages through some of the hydroxy! groups. Other methods for attaching vinyhc groups capable of polymerisation onto polyvinyl alcohol are described in, for instance, US4,978,713 and, preferably, US5,508,317 and 055,583,163. Thus the preferred macromer comprises a backbone of polyvinyl alcohol to whsc is linked, via a cyclic aceta! linkage, an (aik)acrylamfnoalkyi mosety. Example 1 describes the synthesis of an example of such a macromer known by the approved named πellfilcon B. Preferably the PVA macromers have about 2 to 20 pendant ethylene groups per molecule, for instance 5 to 10.

Where PVA macromers are copolyme πsed with ethyjenica üy unsaturated monomers including an ionic monomer, the ionic monomer preferably has the general formula I.
in which $Y^1$ is selected from

$$
\begin{align*}
&\text{GH}_2=\text{C}(\text{R}^{10}J-\text{CH}_2-\text{O}-, \text{CH}_2=\text{C}(\text{R}^{10}J-\text{CH}_2\text{OC(O)}-) - \text{GH}_2=\text{C}(\text{R}^{10}J- \text{G}-, \\
&\text{CH}_2=\text{C}(\text{R}^{10}J\cdot \text{CH}_2\text{OC(O)}\text{N}(\text{R}^{11})-) - \text{R}^{12}\text{OCOCR}^{10}=\text{C}(\text{R}^{10}C\text{O})^{-}, \text{R}^{10}\text{GB}=\text{CHC}(\text{Q})\text{O}^{-}, \\
&\text{R}^{10}\text{GH}=\text{C}(\text{CO}FR^{15})\text{CH}_r\text{C}(\text{Q})\text{Q}^{-}.
\end{align*}
$$

wherein :

- $R^{10}$ is hydrogen or a CrC$_4$ alkyl group;
- $R^{11}$ is hydrogen or a d-C$_4$ alkyl group;
- $R^{12}$ is hydrogen or a Cl$_4$ alkyl group or $BQ^1$ where $B$ and $Q^1$ are as defined below;
- $A^1$ is -O- or -NR$_{11}^-$ ;
- $K^1$ is a group \(-(\text{CH}_2)_r\text{OC(O)}-, \text{O}-(\text{CH}_2)_r\text{QG(Q)G}^-, \text{O}-(\text{CH}_2)_r\text{NR}^{13} \text{C(O)}^-, \text{O}-(\text{CH}_2)_r\text{C}(\text{O})\text{NR}^{13}^-, \text{O}-(\text{CH}_2)_r\text{NR}^{13}\text{C(O)}\text{NR}^{13}^-, \ \text{O}-(\text{CH}_2)_r\text{SO}^{3}^-, \text{or, optionally in combination with B a valence bond and r is from 1 to}
- $B$ is a straight or branched aikanedisy, oxaaalkylene, alkanediylloxalkanediyi, or alkanediyloligo(oxaaikanediyi) chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if $Q^1$ or $Y^1$ contains a terminal carbon atom bonded to $B$ a valence bond; and
- $Q^1$ is an ionic group.

Such a compound including an anionic group $Q^1$ is preferably included.

An anionic group $Q^1$ may be, for instance, a carboxylate, carbonate, suiphonate, sulphate, nitrate, phosphoratate or phosphate group. The monomer may
be polymerised as the free acid or in salt form. Preferably the $pK_a$ of the conjugate acid is less than 5.

A suitable cationic group $Q^1$ is preferably a group $N^+R^{14}_3$, $P^+R^{15}_3$ or $S^+R^{15}_2$ in which the groups $R^{14}$ are the same or different and are each hydrogen, $C_{14}$-alkyl or ary! (preferably phenyl) or two of the groups $R^{14}$ together with the heteroatom to which they are attached from a saturated or unsaturated heterocyclic ring containing from 5 to 7 atoms the groups $R^{15}$ are each $OR^{14}$ or $R^{14}$. Preferably the cationic group is permanently catonic, that is each $R^{14}$ is other than hydrogen. Preferably a cationic group $Q^1$ is $N^+R^{14}_3$ in which each $R^{14}$ is $Cl_4$-alkyl, preferably methy!

A zwit$e$onic group $Q^1$ may have an overall charge, for instance by having a divalent centre of anionic charge and monovalent centre of cationic charge or vice-versa or by having two centres of catonic charge and one centre of anionic charge or vice-versa. Preferably, however, the zwit$e$onic has no overall charge and most preferably has a centre of monovalent catonic charge and a centre of monovalent anionic charge.

Examples of zwit$e$onic groups which may be used as $Q^1$ in the present invention are disclosed in WG-A-GG29481.

Where the ethylenically unsaturated monomer includes zwit$e$onic monomer, for instance, this may increase the hydrophobicity, lubricity, biocompatibility and/or haemocompatibility of the particles. Suitable zwit$e$etonics monomers are described in our earlier publications WG-A-92Q7885, WO-A-9416748, WO-A-9416749 and WO-A-95204G7. Preferably a zwit$e$onic monomer is 2-methacryloyloxy-$2'$-πmethy!ammonium ethyl phosphate inner salt (MPC)

in the monomer of general formula I preferably $Y^1$ is a group $CH_2=CR^{10}COA^1$ in which $R^{10}$ is $H$ or methyl, preferably methyl, and in which $A^1$ is preferably NH. $B$ is preferably an alkanedyl group of 1 to 12, preferably 2 to 6 carbon atoms. Such monomers are acrylic monomers.

There may be included in the ethylenically unsaturated monomer diluent monomer, for instance non-ionic monomer. Such a monomer may be useful to control the $pK_a$ of the acid groups, to control the hydrophilicity or hydrophobicity of the product, to provide hydrophobic regions in the polymer, or merely to act as inert diluent. Examples of non-ionic diluent monomer are, for instance, alkyl (alk) acrylates and (alk) acrylamides, especially such compounds having alkyl groups with 1 to 12 carbon atoms, hydroxy, and di-hydroxy-substituted alkyl (alk) acrylates and -(alk) acrylamides, vinyl lactams, styrene and other aromatic monomers.

In the polymer matrix, the level of arron is preferably $m$ the range 0 1 to 10 meq g$^{-1}$ preferably at least 10 meq g$^{-1}$ Prefered anions are derived from strong...
acids, such as sulphates, sulphonates phosphates, phosphorates and carboxylates

Where PVA macromer is copolymerised with other ethylenically unsaturated monomers, the weight ratio of PVA macromer to other monomer is preferably \( m \) the range of 50:1 to 1:5, more preferably \( m \) the range 20:1 to 1:2 in the ethylenically unsaturated monomer the anionic monomer is preferably present in an amount \( m \) the range 10 to 100 mole\%, preferably at least 25 mole\%

The crosslinked polymer may be formed as such in particulate form, for instance by polymerising in droplets of monomer in a dispersed phase in a continuous immiscible earner. Examples of suitable water-m-oil polymerisations to produce particles having the desired size, when swollen, are known. For instance US4,224,427 describes processes for forming uniform spherical beads (microspheres) of up to 5 mm in diameter, by dispersing water-soluble monomers into a continuous solvent phase, in the presence of suspending agents. Stabilisers and surfactants may be present to provide control over the size of the dispersed phase particles. After polymerisation, the crosslinked microspheres are recovered by known means, and washed and optionally sterilised. Preferably the particles e.g., microspheres, are swollen in an aqueous liquid, and classified according to their size.

In the method according to the first aspect of the present invention, the organic solvent is capable of dissolving the drug and penetrating the beads. In such a preferred embodiment it is selected so as to be capable of dissolving the drug. It is possible that the solvent itself acts as a crystal modifier and should hence be retained in the loaded product, in which case the solvent may be used in an amount less than required for penetrating or loading to equilibrium. However, it is preferred that the solvent is used in excess for ease of handling. After the period of contact during loading of the drug, the beads which may be swollen, and excess solvent may be separated from one another, the solvent, along with unloaded drug and excess crystallisation inhibitor. Suitable separation techniques generally involve SonD-liquid separation techniques such as centrifugation and/or filtration. Generally this is followed by evaporation of further solvent, for instance by subjecting the beads to raised temperature and/or reduced pressure. Where such evaporation techniques are used, the crystal modifier must be sufficiently non-volatile such that it is not removed to a deleterious extent.

In a preferred process, the dried loaded beads following removal of excess organic solvent are contacted with aqueous storage liquor, preferably in an excess such that the beads are penetrated, and preferably are swollen to equilibrium and a
continuous phase of extra-bead liquor is present in which the beads may be or are suspended. Preferably whilst suspended in such aqueous storage liquor, the beads are sterilised by heating the container in which the suspension is contained, for instance to a temperature of at least 90°C, more preferably at least 100°C, preferably for a period of time of at least 5 seconds, more preferably by heating at a temperature of 121°C in an autoclave, for a period of at least 15 minutes.

It may be possible to use as the crystal modifier a material which is immiscible with the organic solvent, whereby a dispersion of crystal modifier in the solvent is used in the loading step. Such a dispersion may be a liquid-in-liquid dispersion, generally an emulsion (i.e. a relatively stable two-phase liquid) or a suspension which is less stable but is maintained as a liquid-in-liquid suspension by physical means such as stirring. Preferably the crystal modifier is a liquid and is substantially miscible with the organic solvent. Since it is preferred that excess solvent is removed by means involving evaporation, the crystal modifier is preferably substantially involatile under the solvent removal conditions. Preferably, the crystal modifier has a boiling point of more than 81°C, more preferably a boiling point of more than 90°C. The material should also be stable under the conditions of sterilisation, where such a step is part of the process, as in the preferred embodiment. The material may also be selected having regard to its density, so that the loaded beads are isobuoyant with the storage and/or delivery medium, so that suspended in their storage solution and/or in the mixture of this suspension with contrast medium prepared immediately before delivery to a patient. In one embodiment, the density of the crystal modifier is slightly higher than that of water, for instance in the range 1.01 to 1.30 g/ml. This is the case, for instance, when Lipiodol is used as the crystal modifier. Alternatively, in a different embodiment, the crystal modifier may be less dense than water. A mixture of two or more ingredients may be used as the crystal modifier.

Examples of non-volatile miscible materials are oils or glycols or glycol ethers. One example of a glycol is glycerol. Examples of oils include soya bean oil (density 0.91-0.92 g/ml), cotton seed oil, almond oil, sunflower oil (density 0.92 g/ml), poppy seed oil and mineral oil (density 0.84-0.87 g/ml).

In a particularly preferred embodiment the crystal modifier has useful properties as an imaging agent, for instance is a radiopaque material, whereby delivery of the composition to a patient may be followed using radiographic techniques. In a highly preferred embodiment of the invention the crystal modifier is an oil based material which is radiopaque, e.g., an iodised oil, such as an iodised fatty acid lower alkyl ester, or mixture, for instance Upiodol or Ethiodol. Lipiodol
consists of iodised poppy seed oil, with some non-iodised oil stabiliser. It contains around 38 to 42% by weight iodine, partly di-iodo partly mono-iodo derivatives.

In the method of this invention the organic solvent is preferably selected from monohydric C-12 aliphatic alcohols and is preferably selected from ethanol and propanol. The solvent should preferably be volatile relative to the crystal modifier. For instance it should preferably have a boiling point of less than 90°C, more preferably less than 80°C, in order to allow removal under mild conditions, e.g., involving evaporation at low temperatures and preferably low pressures.

The invention is suitable for use with a wide variety of drugs. The loading level of drug depends upon the desired dosage and may be selected by a person skilled in the art based on his knowledge of the activity of the drug, the release characteristics from the beads and the indication to be treated. Likewise the concentration of drug in the loading mixture is selected according to the desired level of drug loading. Preferably the concentration of drug in the loading solution is in the range 1 to 1000 mg/ml, preferably in the range 10 to 500 mg/ml. The crystal modifier should be included in the loading solution in an amount such that the end product will have a sufficient level of crystal modifier to modify the crystal formation to the desired degree. This level may be determined by a person skilled in the art by carrying out a series of tests in which different levels of drug and crystal modifier are loaded into the specific type of polymer and subjected to the process steps to which a pharmaceutical composition would be subjected, to determine the minimum level of modifier required to effect the crystallisation of the drug, that is to prevent crystallisation taking place. Suitable levels of crystal modifiers (e.g., crystallisation inhibitors) are in the range 1 to 99% w/w based on the total level of drug in the beads, preferably in the range 5 to 50%.

Suitably the drug-polymer ratio is in the range 10:1 to 1:10, based on dry matter in the beads (i.e., polymer) preferably in the range 2:1 to 1:2.

The method of this invention has been found to be of particular value for producing beads loaded with pacSitaxel (PTX), ibuprofen and dexamethasone (DEX). The drug-oil loaded beads have the advantage of a reduced crystal formation on the bead surface. It is also thought that there is a reduced crystal formation within the beads, which gives a more homogeneous distribution of drug in the beads. PTX-loaded beads may act as anti-tumoural embolic, whereas IBU and Dex-loaded beads may have anti-inflammatory effects as well as potentially anti-tumoral activity by way of their mode of action in COX inhibition. Advantages of lowering crystals formation includes: a reduced burst effect due to drug crystals on Dea α surface, reduced adhesive tendency for the beads to stick to packaging, such
as plastics used for syringes, a reduced probability of self-aggregation in the packaging and hence the catheter and thus improved deliverability and a homogenous loading. An additionally a possibility that the presence of the modifier may enhance the stability and thus the shelf-life of the product. The use of oil-based contrast media (iodinated oils such as lipiodol) as the crystal modifier, may impart an additional benefit in order to allow the visualisation of the beads during delivery, and potentially enabling traceability of the beads after embolisation. Iodised oils possess a greater density than water and their use as crystal modifiers also increases the overall density of the drug-loaded microspheres, such that it is possible to control the suspension properties of the beads when placed in a saline-contrast mixture typically used for the delivery of the device. Lipiodol has a density of 1.280 g/ml at 15°C in the invention is preferred to use oils that are approved by the FDA as inactive ingredients, and these have been found to modify the crystal formation of ibuprofen, paclitaxel and dexamethasone. The effect on reducing aggregation of beads and adhesion to plastics used during handling and delivery is an illustration of the benefit of the invention. Furthermore the visualisation of the beads using radiography, where lipiodol is the crystal modifier, has been shown to be possible and provides a significant combination of useful properties. The use of a high density oil as the crystallisation modifier provided the further benefit that the density of the loaded beads was controlled to be closer to that of the aqueous storage medium, whereby the loaded beads could be mixed with saline and/or other contrast medium, prior to delivery without immediate settlement. In the invention therefore the product beads may be administered in usual techniques used for embolisation, including optionally suspension in additional contrast medium for additional visualisation by radiography.

The following is a brief description of the figures:

Figures 1A and 1C show ibuprofen crystals on beads surface using Comparative Example 1;

Figures 1B and 1D show ibuprofen beads after toading using oils (Lipiodol)- Examplei;

Figure 2 shows the ibuprofen bead size distribution after loading with different concentrations of lipiodol compared to the unloaded control as described in Example 2,

Figure 3A-3E are histograms of the size distributions of ibuprofen loaded beads after hydration using different volumes of water and saline 2mL compared to
the control in 0.9 % saline [w=water, PBS= phosphate buffered saline] - see Example
2;

Figure 4A shows ibuprofen elution profile using 5% and 30% Lipiodoi for the
loading for beads 700-900 µm in Example 2;

Figure 4B shows ibuprofen elution profile using 5% and 30% Lipiodoi for the
loading for beads 500-700 µm in Example 2;

Figure 5 illustrates the compression of ibuprofen loaded beads using 5% and
30% and 70% Lipiodoi compared to unloaded controls and beads loaded without oil
(Example 3);

Figure 6A shows concentrations of ibuprofen eluted in PBS after loading
using different oils (Example 8);

Figure 6B shows the % ibuprofen eluted from beads loaded using different
oils (Example 6);

Figure 7 shows the size distribution of a 500-700 µm beads after loading with
ibuprofen using different oils (Example 6);

Figure 8 shows the % ibuprofen eluted from various beads loaded with
ibuprofen-5% Lipiodoi (Example 7);

Figure 9 shows various beads after 24 hr elution, 9A: Bead Block IBU-5%
Lipiodoi. 9B: Embosphere IBU-5% Lipiodoi. 9C: Contour SE IBU-5% Lipiodoi
(Example 7);

Figure 10 shows paclitaxel loaded Bead Block with Lipiodol (A). Sample 1.
(B). Sample 2 (Example 8);

Figure 11 shows dexamethasone-loaded Bead Block without Lipiodoi (A)
and with 10% Lipiodoi (B) (Example 10);

Figure 12A shows Amberlyst-loaded with ibuprofen-Lipiodol (Example 11);

Figure 12B shows AmberSite-loaded with ibuprofen-Lipiodol (Example 11);

Figure 13 shows the release profile of paclitaxel from Bead Block loaded with
Lipiodol-paclitaxel (Example 9);

Figure 14 shows the localisation of ibuprofen Bead (IBU-BB) and Bead Block
(BB) in the uterus post-embolisation (Example 12); and

Figure 15 shows the level of lymphocytes observed around ibuprofen Bead
(IBU-BB) and Bead Block (BB) at 1 week (Example 12).

The following examples illustrate the invention:

Comparative Example: Preparation of IBU loaded Bead Block (IBU-BB)

IBU-loaded beads were manufactured using the commercial available
product Bead BSock™ beads supplied as a sterile syringes of 2 ml beads with size
range 500-700 µm. The production of such beads is described in WO2004/000548
Example 1 as the "low AMPS" product. Briefly an aqueous mixture of polyvinyl alcohol macromer having acetal-linked ethylenically unsaturated groups and 2-acrylamido-2-methyl-propane sulphonate in a weight ratio of about 12:1 is suspended in a continuous phase of butyi acetate containing cellulose acetate butyrate stabiliser with agitator and is radically polymerised using redox initiation to form beads, which are washed, dyed and sieved into size fractions including the 500-700 µm fraction and 700-900 µm fraction used in subsequent examples. Bead Block was transferred from syringes into glass vials m volumes of 2 ml is per vial! The excess saline was then removed and the beads lyophilised IBU/ethanol solution was prepared to the required final concentration. 1 ml of the solution was then added to the lyophilised beads and left to load for 1 hour (static). The excess loading solution was then removed and the bead sample dried overnight at 45°C in a vacuum oven. To the dried samples, 2 ml water was added to hydrate the beads (Figure 1A) and they were then sterilized by autoclaving at 121°C for 15 minutes (Figure 1C). Figure 1C shows the non-homogenous uptake of ibuprofen by beads (NB- beads with variable degrees of opacities compared to 1D) and some drug crystals in solution after loaded using Comparative Example 1.

Example 1: Preparation of IBU-Lipiodol loaded microspheres (IBU-LBB)

The beads were loaded using the same method as in the comparative example with two exceptions. The loading solution was composed of 33% Lipiodol (L) in IBU/ethanol solution and the bead samples were shaken on a plate shaker set to 150 rpm for 1 hour. Excess loading solution was removed and samples were dried overnight in vacuum oven set to 50°C. Loaded beads were then hydrated in 2 ml water and steam sterilised as in comparative example.

The first microspheres produced using this method (IBU-LBB) were in slurry form, and were blue/white beads to the naked eye. They did not stick to the glass vials and no white crystal formation on the bead surface was apparent.

**Size and Image analysis.** The beads were sized using an optical microscope and visualised using a Colour Video camera. The beads recovered their spherical shape prior to lyophilisation, and were seen to be opaque (white/blue to the naked eye) with a homogenous appearance (Figure 1B and 1D). The size distribution of these microspheres was comparable to the starting beads (Figure 2).

**Elution.** The hydration water was removed and placed in a HPLC vial to determine the drug loss during manufacturing (neat). Each vial (2 ml of beads) was eluted into 200 ml of PBS for 24 hours. At predetermined time points (10, 20, 40, 60 minutes and 2, 4 and 24 hours) 1 ml of solution was removed and placed into HPLC vials to determine drug eluted, degradation and purity. The amount of drug loaded
into the beads was similar to that without adding Lipiodol IBU purity was >99% showing that there was no interference with IBU. Image of the beads after elution showed opaque beads that were similar in appearance to IBU loaded beads (Figure 1D). This suggests that the Lipiodol uptake by the beads contributes to the opaque colour and it does not elute in PBS.

**Deliverability test** The deliverability of the beads was tested as a clinical setting for the feasibility study. The contrast medium was made by making up 10 ml of 50 50 Visspaque 320: Water 9 ml of the mixture was added to the vials. Three injections were earned out for each sample using 3 ml and 2.7Fr Progreat® catheter.

IBU-LBB Beads did not aggregate when vials were opened and dispersed freely in saline. The deliverability test on the 700-900 μm beads demonstrated that they were deliverable from 2.7Fr Progreat microcatheter without problems.

**Example 2:** Effect of hydration media, type and volume using beads loaded with IBU and 5% and 30% Lipiodol concentrations

This example was conducted to examine the degree of water uptake by beads and the effect of the hydration media used. Bead Block of size 700-900 μm was loaded using IBU ethanol solutions containing either 5% or 30% Lipiodol for 1 hour using the same general techniques. Example 1. The excess loading solution was removed and samples were dried overnight in a vacuum oven set at 50°C. Samples were hydrated using either 2 ml water, 3 ml water or 2 ml saline and then steam sterilized at 121°C for 15 minutes.

Size was measured as described in Example 1. Histograms of the size distributions are shown in Figures 3A-3E. There was a statistically significant difference (p<0.0001) between all groups compared to the control beads (prior to iodixanol saturation and loading). No significant difference was found between using 5% Lipiodol 2 ml water and 30% Lipiodol in 2 ml saline (p=0.5158) in both instances, the size ranges were within the acceptance criteria of the size distribution with an overall shift towards the higher beads size (Figure 2).

**Elution** on IBU-5%LBB and IBU-30% LBB on beads 500-700 μm and 700-900 μm

As per Example 2, the hydration water was removed and placed in a HPLC vial to determine the drug loss during manufacturing (neat). Each vial (2 ml of beads) was eluted into 200 ml of PBS for 24 hours. At predetermined time points (10, 20, 40, 80 minutes and 2, 4 and 24 hours), 1 ml of solution was removed and placed into HPLC vials to determine drug eluted. Degradation and purity results demonstrated that for the size 700-900 μm beads there was no difference in elution.
rate between the beads with 5% Lipiodol or those with 30%. Figure 4A shows that for both Lipiodol concentrations, >99% of the total IBU close is eluted in the first 2 hours for beads size 700-900 μm. Similarly for the 500-700 μm range >99% is eluted in the first 2 hours however, there was a small shift to a faster elution with the 30% Lipiodol (Figure 4B).

Example 3: Compression testing of IBU beads containing various Lipiodol concentrations

Bead Block of size 700-900 μm was loaded IBU ethanol solutions containing, 5%, 30%, 50%, 70%, 80%, 90% Lipiodol for 1 hour. The excess loading solution was removed and samples were dried overnight in vacuum oven set at 50°C. Samples were hydrated using 2 ml water and then steam sterilized at 121°C for 15 minutes.

Compression testing of IBU-beads with 5%, 30% and 70% Lipiodol is shown in Figure 5, and demonstrates that IBU-LBB beads at all concentrations of Lipiodol are similar to the comparative product without Lipiodol and were all more compressible than Bead Block when it is hydrated in water. When sahne was used for hydration of 30% Lipiodol IBU-LBB, the compression was higher than unloaded control.

Example 4: Preparation of sunflower oil loaded microspheres

Bead Block was loaded with a 33% Sunflower oil/ethanol solution in place of Lipiodol using the technique described in example 1. The beads did uptake the oil and change colour to white/blue. Oily droplets were visible in the aqueous phase at this concentration. When viewed under microscope they looked similar to the IBU loaded beads (Figure 1D).

Example 5: Loading with different Lipiodol concentrations without drug for fluoroscopic assessment

These samples were prepared using 700-900 μm as described for the IBU/Lipiodol beads above (Example 3) replacing the IBU/Lipiodol solution with Lipiodol/ethanol solutions of the following concentrations: 30%, 50%, 70%, 80%, 90% Lipiodol/ethanol solutions. For the 100% Lipiodol sample these were prepared by adding Lipiodol directly to the beads for 1 hour. Then excess was removed, and then washed once quickly with ethanol. Excess ethanol was removed, dried, hydrated and steam sterilized as described for the IBU/Lipiodol bead. Samples were viewed by fluoroscopy. Beads were visible under X-ray with no clear distinction between the different beads.

Example 6: Loading IBU with different oil excipients
Bead Block of size 500-700 µm were loaded with IBU etbanoi solutions containing: 5% of the following oils: Lipiodoi, soyabean oil, cotton seed oil, mineral oil and almond oil for 1 hour. The excess loading solution was removed and samples were dried 2 hours in vacuum oven set at 50°C. All samples were hydrated using water and then steam sterilized at 121°C for 15 minutes.

All vials looked similar to the naked eye and by image analysis, irrespective of the oil. Elution tests were carried out for all five oils as described in Example 2. The total dose eluted in 24 hours was 25 mg/ml bead ±5mg (Figure, 6A) The results showed a similar elution profile for all oils except cotton seed oil, which appeared to cause a slower rate of elution. All oils eluted 85% in the first hour except for cotton seed oil where only 72% had eluted. Within the first 4 hours, all samples had eluted >99% of the drug (Figure 6B).

The difference in bead size using all oils was not statistically significant relative to each other and to Lipiodol (Figure 7).

Example 7: Loading other commercially available embolic beads

Commercially available embolic beads including: Embosphere (a trisacryl/gelatin microsphere coated with collagen 700-900 µm diameter product), Embogold (300 to 500 µm diameter product), Contour SE (a non-ionic cross-linked polyvinyl alcohol, 500 to 700 µm diameter product) microsphere were loaded with IBU using one loading solution of IBU/ethanol/5% Lipiodol (125 mg/mL). The loading procedure is as described in Example 2.

Visually, beads did not change colour after loading except for Bead Block, which changed to the typical blue/white colour. Embosphere showed high tendency to stick to the glass vial whereas Contour SE showed a great deal of aggregation.

Both stickiness and aggregation are associated with crystals of SBU on the surface of the beads. Images after elution have shown that Embosphere was slightly opaque (Figure 9B) and Embogold was clear red (compared to very opaque Bead Block (Figure 9A)) indicating lower uptake of Lipiodol and hence reduced inhibition for crystal formation. Contour SE was opaque but most beads were in clumps enclosed in oil capsule (Figure 9C). This suggests that the bead opaque colour was due to IBU uptake. The aggregation may have been caused by IBU on the bead surface following the lyophiliisatson stage. The enclosure of Contour SE by Lipiodol was demonstrated by the slow elution of IBU (Figure 8), whereas all other bead types eluted >98% IBU after 2 hours.

Example 8: Paclitaxel B1 (PTX) loading into Lipiodol Bead Block

PTX-loaded beads were prepared using the same method described in Example 2. Bead Block (500-700 µm and 700-900 µm) was first partitioned in 2 mi
into glass vials. The excess saline was then removed, and the beads were lyophilised. PTX-Lipiodol-ethanol solution was prepared to the required final concentration, and subsequently added to the lyophilised beads and left to load for 1 hour on a plate shaker with 150 rpm. The excess loading solution was then removed and the bead sample dried overnight at 45°C in a vacuum oven. To the dried samples, 2 ml water was added to hydrate the beads and they were then steam-sterilized by autoclaving at 121°C for 15 minutes.

The PTX loading content was determined by using DMSO to extract loaded PTX under ultrasonication. The extracted solution was examined by HPLC, and the results are given in Table 1 below.

Table 1: PTX loading efficacy in Lipiodol Bead BSock *

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<tr>
<td>1 (500-700 μm)</td>
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<td>4 (700-900 μm)</td>
<td>48.8</td>
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* Lipoidol is 23 % (v/v) in loading solution

Example 9: Elution of PTX from Lipiodol Bead Block

Sample 3 and 4 from Example 8 were used for the PTX elution test. 1.2 ml of each sample was mixed with 200 ml PBS buffer on a roller mixer under room temperature. At predetermined time interval, 50 or 100 ml solution was removed and 50 or 100 ml fresh PBS was added. The elution profile after HPLC processing is shown in Figure 13.

Example 10: Loading and elution of Dexamethasone (Dex) using Lipiodol

Dex loading solution (5mg/ml) in ethanol was prepared. Using this solution beads were loaded as described in Example 1. As a control, additional beads were loaded with Dex ethanol solution without the use of Lipiodol.

Images showed that samples loaded without the use of Lipiodol did not uptake Dex. Crystals of Dex were present on the beads surface (Figure 11A). Beads loaded using iBU-Lipiodol were opaque and no crystals were apparent on beads surface (Figure 11B).

Example 11: Loading and elution using different beads
Two types of ion-exchange resins (Amberiyst (SIGMA, sulphonic acid based, 1.9 mg/ml exchange capacity) and Amberlite (Sigma, 1RA700 (chloride) quaternary ammonium-group containing styrene-DVB resin having total exchange capacity of 1.4 mg/ml, density 0.7 g/ml)) were loaded with IBU-Upiodol. The loading and elution procedure was as described in Example 1 using a solution containing 100 mg/mL IBU.

Amberiyst uptake was <1 mg/mL bead of IBU (Figure 12B). Amberiyst was loaded with IBU 15 mg/mL (Figure 12A).

Example 12: Use of an Embolisation Bead Containing Sbuprofen and Soya Bean Oil as A Crystallisation Inhibitor in a Sheep Uterine Artery Embolization Model of inflammation

The effect of Ibuprofen loaded Beads was evaluated over a 12-week period post-embolisation of the uterine artery of sheep. The embolisation of blood vessels may result in a variety of side effects which can include pain and inflammation. The objective of this Example was to assess the release and effect of Ibuprofen from ibuprofen loaded Beads containing soya bean oil as the crystallisation inhibitor on the foreign body inflammatory reaction in a sheep uterine artery model. The following were assessed:

- Properties and distribution of beads within the vascular network.
- Effect of ibuprofen / soya bean oil release on the foreign body inflammatory reaction to the embolic beads.
- Level of Ibuprofen present in the bead over time.

Methods:

The test article in this Example was ibuprofen loaded Beads ("Ibuprofen Bead") containing soya bean oil as crystallisation inhibitor as described in Example 6. Samples were tested against a manufacturing control of unloaded Bead Block microspheres that had been processed in a similar way to Ibuprofen Bead. 2 ml of beads were lyophosed as described in Comparative Example 1 and placed in 1 ml of ethanolic containing 10% v/v soya bean oil and 400 mg of ibuprofen. After processing as described in Example 6, the final product contained 125 mg sbuprofen/ml hydrated beads and -10 mg of soya bean oil as determined by extraction and HPLC analysis.

Twenty four non-pregnant hormonally prepared adult Pre-Aipes sheep were divided into 2 groups, unloaded Bead Block (control, BB; 5GG-7GGiim) and Ibuprofen loaded Beads (test group, Ibuprofen Bead, 500-700 µm). Each group was split into 4 time points (24 h, week 1, week 3 and week 12) with 3 animals per time point.
Embolisation was performed using the same sheath catheters and guide wires as used in clinical practice. A 4-Fr vascular sheath was placed in the femoral artery by means of the standard Sefcmger technique under sterile conditions. A 4-Fr pigtail catheter (Opttrtorque Radiform, Terumo) was placed at the level of the iliac bifurcation to perform digital subtraction aortography and to identify the ovarian and uterine arteries. Selective catheterisation of the contralateral internal iliac artery and super selective catheterisation of the uterine artery was performed using a 4-Fr cobra shaped catheter (Radsofocus Angiographic catheter, Terumo). The radiologist then performed the embohsation using the selected embolic agent (Ibuprofen Bead or Bead Block) according to the randomisation sequence.

A volume of 0.5 mL of beads suspended in a 50/50 mixture of Vispaque 270 and saline at a dilution of 1/10, was slowly injected under fluoroscopic control. Embolisation was considered complete when 0.5 mL of beads was delivered into each uterine artery.

The distribution of the beads in the tissue was assessed and gross examination of the organs performed and inflammation was estimated histologically by sems-quanMative classification of lymphocytes by staining and use of videoanalysis post immunohistoiabeling with CD-antibodtes to a variety of inflammatory cells.

Results

Embolisation procedure

Bead delivery was excellent in all animals. Embolisation was successful in all animals. Each animal received a total of 0.5 mL of beads in each uterine artery (total 1 mL).

Bead performance

Localisation of embolised vessels in the different uterine zones was statistically different between the 2 products. Ibuprofen Bead occluded slightly more proximal vessels than Bead Block (p<0.0001, χ²) (Figure 14). In Figure 14 EM stands for endometrium, MM for myometrium, PMM for penmyometr in cm and PX for proximal. The vessel diameter was increased for Ibuprofen Bead (498 μm vs 436 μm, P=0.0001), however there was no difference in the mean number of beads found in embolised vessels.

More vessel necrosis was observed with Ibuprofen Bead than Bead Block at 24 hours (25.8% vs 4.9%) and 1 week (32.8% vs 4.3%) post-embolisation, however at 3 weeks and 3 months no necrosis was found for either group.

Inflammatory response

Minor differences in numbers of neutrophils and eosinophils were observed for Bead Block and Ibuprofen Bead at certain time points. There were statistically
less giant cells for Sbuprofen Bead than Bead Block at 1 week (p = 0.01). At 24 hours few lymphocytes were observed in both groups, and levels were not significantly different. At 1 week the number of lymphocytes was significantly lower around Ibuprofen Bead compared to Bead Block (Figure 15). At 3 weeks and 3 months the number of lymphocytes with Ibuprofen Bead increased, but was not significantly different from Bead Block.

In some of the histological slides there were signs of resorption of both BB and Ibuprofen Bead products, with some apparent phagocytosis, increased presence of giant cells and continued presence of CD4 and CD8. This is not unexpected given previous Song-term observations with PVA embolisation agents.

The reduction in inflammatory response was confirmed by reduced levels of CD172a-positive cells in the Ibuprofen Bead group at week 1. Further, the addition of a crystallisation inhibitor did not result in infiltration of CD5 positive T-cells or CD21 B-cells, indicating no adverse reaction to the optimised formulation of Ibuprofen Bead. The other CD markers did not show any difference between the two groups. The study did confirm, however, that there was no "rebound effect" at 3 months, with CD172, CD3 and MHC-II all remaining low, and no signs of hypersensitivity with absence of CD21-r or eosinophilic cells.

Areas of specific staining with the anti-Ibuprofen antibody were identified as those with a "reticule" pattern. High levels of staining were observed at 24 hours post-embohsation. Ibuprofen was still detectable at week 1, but at much lower levels. No Ibuprofen was detected in the beads at 3 week and 3 months post-embolisation.

Conclusions

This Example confirms that emboisation with Ibuprofen Bead can reduce the foreign body inflammatory response to the embolic beads. Ibuprofen can be detected in the beads up to one week post-embolisation but not at 3 weeks or beyond. Further, the reduction in the inflammatory response at 1 week does not result in any adverse rebound-effect on the inflammatory response at 3 weeks and 3 months post-embohsation. There was no obvious versus effect of the inclusion of the soya bean oil crystallisation inhibitor.
CLAIMS

1. A process in which swellable beads of water-insoluble, oil-insoluble polymer are contacted with a solution of a crystallisable drug in an organic solvent which is capable of penetrating the beads whereby drug is absorbed into the beads, characterised in that the solution further contains a crystal modifier which inhibits crystallisation of the drug.

2. A process according to claim 1, in which excess solvent is removed from the beads to produce dried loaded beads, preferably by steps including bead/liquid separation and evaporation or sublimation of the solvent, more preferably by evaporation at raised temperature and/or reduced pressure.

3. A process according to claim 2, in which the loaded loaded beads are contacted with excess aqueous storage liquor to swell them to equilibrium and are then sterilised by heating preferably at a temperature of at least 99°C for a period of at least 5 seconds, more preferably by heating at a temperature of 121°C in an autoclave, for at least 15 minutes.

4. A process according to any preceding claim, wherein the crystal modifier has a boiling point of more than 81°C, preferably more than 90°C

5. A process according to any preceding claim, in which the crystal modifier is miscible with the organic solvent and is preferably an oil or glycol.

6. A process according to claim 5, in which the oil is selected from soya bean oil, poppy seed oil, sunflower oil and mineral oil.

7. A process according to claim 6, in which the oil is iodinated

8. A process according to any preceding claim, in which the organic solvent is a volatile solvent, preferably having a boiling point of less than 90°C, more preferably less than 80°C

9. A process according to claim 8, in which the solvent is selected from monohydric C1-Ci aliphatic alcohols preferably ethanol or propanol

10. A process according to any preceding claim, in which the concentration of drug in the solution is in the range 1 to 1000 mg/ml, preferably in the range 10 to 500 mg/ml.

11. A process according to any preceding claim, in which the concentration of crystal modifier in the solution is in the range 1 to 99% w/w base α on drug preferably 5 to 50%

12. A process according to any preceding claim, in which the loading efficiency of drug is in the range 1 to 100% base α on the total drug contacted with Deads and the amount of drug loaded in the beads preferably at least 5%, more preferably at least 10%
13. A process according to any preceding claim, in which the weight ratio of drug to polymer in the loading step is in the range 10:1 to 1:10, preferably 2:1 to 1:2.

14. A process according to any preceding claim, in which the polymer is anionically charged, preferably in which the anionic groups are selected from sulphonate, phosphonate and carboxylate, more preferably sulphonate groups.

15. A process according to any preceding claim, in which the polymer is crosslinked polyvinyl alcohol, preferably formed by copolymerising ethylenically unsaturated polyvinyl alcohol macromer with ethylenically unsaturated polyvinyl alcohol macromer with ethylenically unsaturated comonomer.

16. A process according to any preceding claim, in which the swellable beads are substantially spherical in shape.

17. A process according to any preceding claim, in which at the start of the process the beads have sizes such that, when swollen to equilibrium in phosphate buffered saline at 20°C, the average diameter is in the range 50 to 1500 μm, preferably in the range 100 to 1200 μm.

18. A process according to claim 17, in which the beads have sizes such that, when swollen to equilibrium in phosphate buffered saline at 20°C, 90% by weight of the beads have diameters within a range which is no more than 300 μm wide.

19. A process according to any preceding claim, in which the drug is selected from chemotherapeutics and antiinflammatories, steroids and analgesics.

20. A process according to claim 19, in which the drug is selected from pacitaxel, ibuprofen and dexamethasone.

21. A composition comprising swellable beads of water-insoluble, oil-insoluble polymer, a crystallisable drug and a crystal modifier which inhibits crystallisation of the drug wherein the drug and crystal modifier are absorbed into the beads and the polymer is crosslinked polyvinyl alcohol.

22. A composition according to claim 21, wherein the crystal modifier has a boiling point of more than 81°C, preferably more than 90°C.

23. A composition according to claim 21 or 22, in which the crystal modifier is an oil or glycol.

24. A composition according to claim 23, wherein the oil is selected from soya bean oil, poppy seed oil, sunflower oil and mineral oil.

25. A composition according to claim 24, wherein the oil is iodinated.

26. A composition according to any of claims 21-25, in which the crosslinked polyvinyl alcohol polymer is formed by copolymerising ethylenically unsaturated polyvinyl alcohol macromer with ethylenically unsaturated comonomer.
27. A composition according to any of claims 21-26, in which the polymer is anionically charged.

28. A composition according to claim 27, wherein the polymer comprises sulfonate anionic groups.

29. A composition according to claim 27, wherein the polymer comprises phosphonate anionic groups.

30. A composition according to claim 27, wherein the polymer comprises carboxylate anionic groups.

31. A composition according to any of claims 21-30, in which the swellable beads are substantially spherical in shape.

32. A composition according to any of claims 21-31, which is sterile and further comprises excess aqueous storage liquor with which the beads are in contact, wherein the beads are swelled to equilibrium.

33. A composition according to claim 32, wherein the aqueous storage liquor is phosphate buffered saline and the beads have sizes such that, when swollen to equilibrium, the average diameter is in the range 50-1500 µm, preferably in the range 100 to 1200 µm.

34. A composition according to claim 33, in which 90% by weight of the beads within a range which is no more than 300 µm wide.

35. A composition according to any of claims 21-34, wherein the drug is selected from chemotherapeutics and antiinflammatories, steroids and analgesics.

36. A composition according to claim 35, in which the drug is selected from paclitaxel, ibuprofen and dexamethasone.

37. A composition according to any of claims 21-36, wherein the drug:polymer ratio is in the range 10:1 to 1:10, preferably in the range 2:1 to 1:2.

38. A composition according to any of claims 21-37, wherein the crystal modifier is present in the range 1 to 99% w/w based on the total level of the drug in the beads, preferably in the range 5 to 50%.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search 15 May 2007

Date of mailing of the international search report 25/05/2007

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer
Giró, Annelisa
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