AU9221664

(12) PATENT ABRIDGMENT (11) Document No. AU-B-21664/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 659192

(54) Title
PROCESS FOR PREPARING DRUG SUBSTANCES IN BEADLET FORM

International Patent Classification(s)
(51)[5] **B01J 002/14** **B01J 002/16**

(21) Application No. : **21664/92** (22) Application Date : **30.06.92**

(87) PCT Publication Number : **WO93/00991**

(30) Priority Data

(31) Number	(32) Date	(33) Country
9114374	**03.07.91**	**GB UNITED KINGDOM**

(43) Publication Date : **11.02.93**

(44) Publication Date of Accepted Application : **11.05.95**

(71) Applicant(s)
SMITHKLINE BEECHAM PLC

(72) Inventor(s)
JOHN KENNETH HUGHES; MAIRI MCNAIR

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
US 4895733
US 4740390
WO 90/12643

(57) Claim

1. A process for the preparation of drug substances in beadlet form comprising:
forming a fluidised bed of particles of inert core material within ~~the~~ a processing chamber of a coater-granulator apparatus by passing a gaseous current between a rotating disc and ~~the~~ an inner wall of the processing chamber; and forming beadlets by layering a drug onto the particles of the core material by spray-coating with a solution of the drug; characterised in that during beadlet formation, the spray-coated particles are (i) transferred to a drying zone surrounding the processing chamber, (ii) carried through the drying zone by a gaseous current, and (iii) returned to the processing chamber; the recirculation process being continued until beadlets having the desired drug load are formed.

17. A drug beadlet ~~obtainable~~ obtained by a process as defined in any one of claims 1 to 16.

OPI DATE 11/02/93 APPLN. ID 21664/92
AOJP DATE 08/04/93 PCT NUMBER PCT/GB92/01185

AU9221664

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : B01J 2/14, 2/16	A1	(11) International Publication Number: WO 93/00991
		(43) International Publication Date: 21 January 1993 (21.01.93)

(21) International Application Number: PCT/GB92/01185

(22) International Filing Date: 30 June 1992 (30.06.92)

(30) Priority data:
9114374.3 3 July 1991 (03.07.91) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : HUGHES, John, Kenneth [GB/GB]; SmithKline Beecham Health Care, Westfield Street, St Helens, Merseyside, Lancashire WA10 1QL (GB). McNAIR, Mairi [GB/GB]; SmithKline Beecham Consumer Brands, St George's Avenue, Weybridge, Surrey KT13 0DE (GB).

(74) Agent: WHITE, Susan, Mary; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

659192

(54) Title: PROCESS FOR PREPARING DRUG SUBSTANCES IN BEADLET FORM

(57) Abstract

Drug substances in beadlet form are prepared with high bulk density spray-coating onto inert core particles, using coater-granulator apparatus, comprising: forming a fluidised bed of particles of inert core material within the processing chamber of a coater-granulator apparatus by passing a gaseous current between the rotating disc and the inner wall of the processing chamber; and forming beadlets by layering a drug onto the particles of the core material by spray-coating with a solution of the drug; characterised in that during beadlet formation, the spray-coated particles are (i) transferred to a drying zone surrounding the processing chamber, (ii) carried through the drying zone by a gaseous current, and (iii) returned to the processing chamber; the recirculation process being continued until beadlets having the desired drug load are formed.

PROCESS FOR PREPARING DRUG SUBSTANCES IN BEADLET FORM

The present invention relates to a process for the manufacture of drug substances in the form of substantially spherical pellets (beadlets) having a high drug content and to products obtainable thereby.

The many advantages associated with the manufacture of drug substances in the form of solid, substantially spherical pellets or beadlets include, inter alia, ease of handling, the provision of a convenient substrate for subsequent coating in order, for example, to achieve taste-masking and/or sustained release properties, and the ability to combine two or more actives in a single dosage presentation. When ingested into the body, the additional potential benefits of pelleted products include maximisation of drug absorption and the avoidance of dose dumping.

Known methods for the manufacture of drugs in pelletised form include extrusion spheronisation from wet granulations and pan-coating techniques. For applications requiring a highly reproducible, free-flowing, high density, high potency, substantially spherical product, such methods have proved inadequate.

Uniform, substantially spherical particles can be obtained by the layering of drug from solution onto non-pareil seeds or granules using a centrifugal, fluidised bed, coater-granulator, known as a rotogranulator. Such apparatus comprises a rotation apparatus consisting of a variable speed, rotating disc (rotor) within a stationary cylinder (stator), with a slit between the stator and the rotor through which a fluidising air current is forced.

It has been found that beadlets prepared by this method do not meet the bulk density requirements of certain drug presentations. For example, in capsule dosage forms, the available volume has been found insufficient to accommodate the desired drug load. This problem is exacerbated when, for example, beadlets to be contained in compact capsules or formulated as tablets are prepared from drug substances having an inherently low density, when a significant proportion of binder is present in the beadlets, and for combination drug presentations in beadlet form.

The non-steroidal anti-inflammatory agent (NSAID) ibuprofen is typical of a compound for which formulation difficulties have been encountered. It is available as a crystalline powder (mp 75-77°C) which is only slightly soluble in water but readily soluble in solvents such as acetone and ethanol, and is inherently a low density material. Beadlets formed using standard rotating disc (spheroniser)/fluidised bed tray-dried techniques were found unsatisfactory; the bulk density of beadlets thus prepared was insufficient to achieve a target capsule (size 0) fill-weight in excess of 400mg. Moreover, the relatively low melting point of ibuprofen imposes limitations on the temperature of the air current for the fluidised bed and for drying the beadlets, once formed. The initially-formed beadlets incorporate a significant amount of solvent such that an extended post-preparation drying phase is required to ensure complete solvent removal.

The problem which the present invention sets out to solve is the provision of drug substances in beadlet form which have an increased bulk density when compared with beadlets made available by existing rotating disc (spheroniser)/fluidised bed techniques. This problem is solved according to the present invention which furthermore confers additional advantages with respect to overall processing time.

Accordingly, the present invention provides a process for the preparation of drug substances in beadlet form comprising:

forming a fluidised bed of particles of inert core material within ~~the~~ a processing chamber of a coater-granulator apparatus by passing a gaseous current between a rotating disc and ~~the~~ an inner wall of the processing chamber; and forming beadlets by layering a drug onto the particles of the core material by spray-coating with a solution of the drug; characterised in that during beadlet formation, the spray-coated particles are (i) transferred to a drying zone surrounding the processing chamber, (ii) carried through the drying zone by a gaseous current, and (iii) returned to the processing chamber; the recirculation process being continued until beadlets having the desired drug load are formed.

Coater-granulator apparatus suitable for carrying out the process of the present invention are commercially available or may be constructed by modification of standard fluidised bed granulators. In a preferred

apparatus, an annular ring gap in the wall of the processing chamber is provided through which spray-coated particles are transferred to the drying zone. The physical characteristics of the rotor and stator are suitably designed to achieve optimum granulation and coating of beadlets, and a free-flowing, substantially spherical product in accordance with apparatus known in the art. A tangentially aligned, adjustable spray-rate, spray-coating system is preferred. A gaseous current required to form a particulate fluidised bed and transfer spray - coated beadlets within the coater-granulator during beadlet formation may comprise any suitable drying gas and is preferably an air current. The variable operating parameters for the coater-granulator apparatus are selected to optimise beadlet formation for a chosen drug substance. Key, variable operating parameters include rotor speed, atomising gas pressure, annular gap gas pressure, air volume, solution spray-rate and spray-gun nozzle diameter, slit width for the fluidised bed and inlet and outlet air temperatures.

An advantageous feature of the process of the invention is that an extended post-preparation drying phase is not required. By a suitable choice of operating temperatures, solvent evaporation takes place as beadlets are formed, during transport of the newly-drug-coated beadlets through the drying zone surrounding the processing chamber and during the subsequent recirculation. The process of the invention thus gives rise to a non-porous beadlet in which drug is bound to the core particle in uniform, dense layers. Interstices created in drug layers, when solvent evaporates during post-preparation drying according to known coater-granulator techniques, are not present in beadlets of the present invention. The beadlets obtainable by the process of the invention are structurally novel and accordingly form part of the invention.

The process of the present invention is amenable to the preparation of beadlets from both hydrophilic and lipophilic drug substances. Drugs particularly suited to processing in beadlet form according to the invention include ibuprofen, pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan and diphenhydramine including pharmaceutically acceptable salts thereof, for example ibuprofen, pseudoephedrine HCl, phenylpropanolamine HCl, chlorpheniramine maleate, dextromethorphan HBr and diphenhydramine HCl.

Solutions of drug substances for spray-coating onto inert core particles may be prepared from one or more solvents. Suitable solvents or solvent mixtures are those which both dissolve the selected drug substance and which are sufficiently volatile to evaporate at the operating temperature of the coater-granulator apparatus. Preferred solvents include acetone, water or aliphatic alcohols, for example lower alkyl aliphatic alcohols such as ethanol, or mixtures thereof.

Beadlets prepared according to the invention may comprise a single drug substance or mixtures of two or more substances. Different drugs may be layered sequentially onto core particles, or alternatively, where a single solvent system is compatible with two or more drugs, drug combinations may be deposited in a single layer.

The concentration of drug in the spray-coating solution will be selected according to known coating procedures and will of course be determined to some extent by drug solubility in the chosen solvent system. Good results are generally obtained using a drug concentration in the range 20-60% w/w, preferably 25-45% w/w. For example, ibuprofen beadlets are suitably prepared from ethanol solution, preferably at a concentration of approximately 40% w/w. Water-soluble materials such as phenylpropanolamine HCl and pseudoephedrine HCl are conveniently formed into beadlets from aqueous solution at concentrations in the range 25-40% w/w.

Conventional binder materials, routinely used in wet-granulation techniques, may be incorporated into beadlets by mixing with drug in the coating solution. Suitable binder materials include gelatin, starch, polyvinylpyrrolidone (PVP), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose. Since it is a primary object of the present invention to maximise beadlet drug load, the amount of binder incorporated is preferably small, for example no more than 1.0% w/w and preferably less than 1.0% w/w of the coating solution.

Preferred core materials for use in the invention include commercially available non-pareil seeds with mesh size in the range 20-40#, for example

in the ranges 20-25#, 25-30#, 30-35#, and 35-40#.

The size and bulk density of beadlets formed by coater-granulator techniques is influenced by the diameter of the core particles. Smaller core particles, for example 35-40# non-pareils, produce a more compact beadlet than larger core particles, for example 20-25# non-pareils. It has been shown by scanning electron photomicroscopy that beadlets formed from larger core particles have a more porous structure than beadlets formed from small particles. Bulk densities required for high drug loads in accordance with the present invention are therefore promoted by use of smaller core particles. (I. Ghebre-Sellassie et al.; Drug Devel.& Ind. Pharmacy, 11(8), 1523-1541, 1985.)

Experiments with certain drugs, for example ibuprofen, have however shown that there is a tendency for beadlets formed by layering of drug onto small diameter non-pareils (eg 35-40#) to cling together (clump) and float during dissolution testing.

It is a particular feature of the present invention that beadlets can be prepared from small diameter non-pareil seeds without the disadvantages of clumping and floating. This is achieved by reducing the quantity of binder material below the generally accepted level and preferably excluding it altogether.

Beadlets formed in the absence of binder material thus constitute part of the present invention.

Beadlets having a theoretical drug load in excess of 85%w/w and an actual fill weight in excess of 450mg, for example 480 to 490mg per size 0 capsule are obtainable according to the invention. Good quality, substantially spherical, free flowing beadlets having a smooth surface are produced when the spray-coating rate is carefully controlled, the best results being observed when spray-rate is increased throughout the coating process. Short drying times for example from 1 to 10 minutes after spray-coating is terminated are all that is generally required.

In a further aspect the present invention extends to the film-coating of beadlets formed by the process hereinbefore described, for example to

provide a protective coating for taste-masking purposes or to provide controlled and/or sustained release of the active drug substance after dosing.

Coating operations may be performed using any suitable coating equipment known in the art. Coating may be carried out as a separate operation to that of preparing the drug beadlets *per se* using any suitable equipment. Alternatively beadlet preparation and coating may be carried out in a single operation, the coating step forming an extension of the beadlet forming process, using equipment of the type hereinbefore described.

Suitable film-coating materials include natural and synthetic polymer materials and polymer mixtures such as cellulose and acrylate based polymers, including commercially available materials. Examples of commercially available coating materials include those made available under the trade names Eudragit and Aquacoat. Coating is suitably carried out by spray-coating from a polymer emulsion or colloidal dispersion, for example from an aqueous colloidal dispersion of a polymer material.

The following Examples illustrate the process of the invention and beadlets obtainable thereby. The coater-granulator apparatus used for the preparation of beadlets as described in the Examples is an Aeromatic Roto-Processor (Multi-Processor MPI) made available by Niro Atomiser. The Roto-Processor was operated using the spinning disk, fluidised bed and drying zone transference functions in combination. Throughout all processing operations spray-gun diameter was set at 0.8mm, atomisation air pressure at 2.0 bar, and annular air gap pressure at 0.5 bar.

Example 1

Preparation of Ibuprofen Beadlets Using 20-25# Non-Pareil Seeds

Rotating Disc Speed	: 200 rpm
Air Volume	: 5.0
Inlet Temperature	: 60°C
Outlet Temperature	: 40°C (dropping to 38°C)

2kg of non-pareils (20-25#) were placed in the bowl of the rotoprocessor. A 40% solution of ibuprofen in industrial methylated spirit (IMS), containing 0.8% polyvinylpyrrolidone (PVP) was sprayed onto the non-pareils at a rate of 104g/min..

Ibuprofen beadlets with a fill weight of 508mg per size 0 capsule were obtained. 89.6% by weight of beadlets were shown by sieve analysis to have a diameter in the range 1000-1680um.

Example 2

Preparation of Ibuprofen Beadlets Using 35-40# Non-Pareil Seeds

1.5kg of 35-40# non-pareils were placed in the bowl of the rotoprocessor. Ibuprofen solution as described in Example 1 was sprayed onto the non-pareils in three separate coating operations. The spray-rate was increased during each coating operation.

1st Coat :	Rotating disc speed	: 200rpm
	Air vol.	: 5.0

Amount of solution sprayed on in g.	Inlet air temp.°C	Outlet air temp.°C	Spray rate g/min
0	50	43	40
700	50	43	44
1000	50	43	51
1300	50	42	55
1800	55	43	55

2100	55	44	60
2400	55	44	62
2700	55	43	68
3800	55	42	68
5900	55	41	68

Spraying was stopped when the theoretical drug load had reached 62.5% w/w (6.25kg of solution applied). A drying time of 5 minutes then followed, with the outlet temperature being raised to 47°C. Sieve analysis showed that 99.5% of beadlets had a diameter in the range 500-1000um.
Yield of product = 4.062kg
Fill weight per size 0 capsule = 503mg

2nd Coat :	Rotating disc speed	: 433rpm
	Inlet air temp.	: 55° C
	Air vol.	: 5.0-7.5

1.5kg of beadlets obtained from the 1st coating operation were coated with a further 6.25kg of ibuprofen solution.

Amount of solution sprayed on in g.	Outlet air temp.°C	Spray rate g/min
0	45	32
200	46	47
400	45	58
1000	44	65
2000	43	65
4000	43	65
6000	42	65
6100	41	65
6200	41	65

The outlet temperature was raised to 49°C during a drying time of 5mins. 94% by weight of the beadlets obtained had a diameter in the range 1000-2000um.

Theoretical drug load	= 85.9%
Yield of product	= 4.052kg
Fill weight per size 0 capsule	= 449mg

3rd Coat : Rotating disc speed : 433rpm
Inlet air temp. : 55° C
Air vol. : 5.0-8.0

1.5kg of ibuprofen beadlets obtained from the 2nd coating operation were coated with a further 6.25kg of ibuprofen solution.

Amount of solution sprayed on in g.	Outlet air temp.°C	Spray temp. g/min
0	43	32
300	45	54
600	46	69
1000	45	73
2800	45	73
3500	45	73
3800	45	73
4000	45	73
4050	45	73
4200	48	73
5000	46	73
6000	46	73

Beadlets were dried for 3 mins., whilst raising the outlet temperature to 49°C. 99.0% by weight of beadlets had a diameter in the range 1000-2000um.

Theoretical drug load = 94.7%
Yield of product = 4.038kg
Fill weight per size 0 capsule = 403mg

Example 3

Preparation of Ibuprofen Beadlets Using 35-40# Non-Pareil Seeds in the Absence of Binder Material.

The process of Example 2 was repeated using a 40% w/w solution of ibuprofen in IMS but omitting the binder material. Three coating

operations were carried out, each separate run using 6.25kg of ibuprofen solution. In the first run, a 1st ibuprofen layer was applied to the non-pareils. In the 2nd and 3rd runs, a second ibuprofen layer was applied to batches of the single-coat beadlets, under different operating conditions.

1st Coat: Rotating disc speed : 433rpm
Air vol. : 4.0-6.5

Time in mins.	Inlet air temp.°C	Outlet air temp.°C	Spray Rate g/min
0	55	43	32
6	55	41	40
12	55	41	50
19	55	39	61
23	60	38	61
37	60	38	66
74	60	40	66
103	60	41	66

Drying Time = 5mins.
Theoretical drug load = 62.5%

2nd Coat (a) : Rotating disc speed : 433rpm
Air vol. : 4.0-10.5

Time in mins.	Inlet air temp.°C	Outlet air temp.°C	Spray Rate g/min
0	60	44	39
5	60	44	48
9	60	43	58
13	60	43	66
33	60	40	66
87	60	33	68
115	60	34	68
125	60	32	68
130	60	30	68
150	60	32	68

Spraying was complete after 150mins. Spraying was interupted after 20mins (10 mins) and after 34 mins. (45 mins).Beadlets were dried for 5 mins.

Theoretical drug load = 85.9% w/w
Actual drug load = 84.1%w/w
Fill weight per size 0 capsule = 487mg

2nd Coat (b) : Rotating disc speed : 433rpm
Air vol. : 3.0-4.7

Time in mins.	Inlet air temp.°C	Outlet air temp.°C	Spray Rate g/min
0	60	40	57
5	60	37	68
9	60	34	72
15	65	30	72
52	65	31	73
60	65	32	70
156	65	32	56
166	65	37	57
176	65	38	73

Beadlets were dried for 5 mins.

Theoretical drug load = 85.9% w/w
Actual drug load = 85.4% w/w
Fill weight per size 0 capsule = 485mg

96.06% by weight of beadlets were shown by sieve analysis to have a diameter in the range 710-1000um.

Example 4

Preparation of Phenylpropanolamine Beadlets using 20-25# Non-Pareil Seeds

1.5kg of non-pareil seeds (20-25#) were placed in the bowl of the rotoprocessor. 8.33kg of PPA HCl solution (27% w/w in filtered tap water) with no binder present was sprayed onto the seeds. The spray rate was increased during processing.

Rotating disc speed	: 433 rpm
Inlet Temperature	: 60°C
Air vol.	: 4.7-5.3

Time in mins.	Outlet air temp.°C	Spray Rate g/min
0	50	11
8	54	8.5
19	59	11
23	52	26
34	52	36
55	48	40
68	46	45
84	45	49
102	44	52
114	43	54
270	41	56

Spraying was complete after 295 mins. The beadlets were allowed to dry for 5 mins.

Theoretical drug load	= 60% w/w
Actual drug load	= 59.1% w/w
Fill weight per size 0 capsule	= 498mg

Example 5

Preparation of Pseudoephedrine HCl Beadlets Using 30-35# Non-Pareil Seeds

1.5kg of non-pareil seeds were placed in the bowl of the rotoprocessor. 6.583kg of pseudoephedrine HCl solution (38% w/w in filtered tap water) with no binder present was sprayed onto the seeds. Spray rate was increased as processing progressed.

Rotating disc speed	: 433 rpm
Inlet Temperature	: 60°C
Air vol.	: 4.5-6.0

Time in mins	Outlet air temp.°C	Spray Rate g/min
0	47	9
10	52	13
20	51	20
22	50	25
30	47	27
35	46	28
40	47	31
50	46	32
55	46	36
80	44	38
90	42	43
110	39	44
130	40	46
140	39	49
160	37	52

Spraying was complete after 175 mins.

Theoretical drug load	= 62.5% w/w
Actual drug load	= 60.7% w/w
Fill weight per size 0 capsule	= 504mg

Example 6

Preparation of Pseudoephedrine HCl Sustained Release Beadlets

Pseudoephedrine HCl beadlets prepared by the method of Example 5 were coated with sustained release polymers to provide a sustained release of pseudoephedrine HCl after oral dosing.

Raw Material	% w/w
Aquacoat	40.70
Citroflex 2	2.80
Quinoline Yellow	0.12
Deionised Water	56.38
Total Suspenion	100.00

Method

A suspension of Aquacoat plasticized with Citroflex was sprayed onto the pseudoephedrine beadlets (62.5% drug) using a bottom spray technique. The coat was sprayed onto the beadlets to give 4% slow coat plus 30% top coat (% w/w of the total beads). Slow coat was sprayed onto the beadlets slowly to seal water soluble drug into the beadlets and prevent dissolution into the coat.

Figure 1 shows the dissolution profile of the coated beads in comparison to the beadlets of Example 5. A BP dissolution apparatus with paddles and 1 litre of distilled water per dissolution cell was used.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Claims

1. A process for the preparation of drug substances in beadlet form comprising:
forming a fluidised bed of particles of inert core material within ~~the~~ a processing chamber of a coater-granulator apparatus by passing a gaseous current between a rotating disc and ~~the~~ an inner wall of the processing chamber; and forming beadlets by layering a drug onto the particles of the core material by spray-coating with a solution of the drug; characterised in that during beadlet formation, the spray-coated particles are (i) transferred to a drying zone surrounding the processing chamber, (ii) carried through the drying zone by a gaseous current, and (iii) returned to the processing chamber; the recirculation process being continued until beadlets having the desired drug load are formed.

2. A process as claimed in Claim 1 wherein spray-coated particles are transferred to the drying zone surrounding the processing chamber through an annular ring gap in the wall of the processing chamber.

3. A process as claimed in claim 1 or claim 2 in which the coater-granulator apparatus is provided with a tangentially aligned, adjustable spray-rate, spray-coating system.

4. A process as claimed in any one of claims 1 to 3 in which the drug substance is selected from one or more of ibuprofen, pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan and diphenhydramine or pharmaceutically acceptable salts thereof.

5. A process as claimed in any one of claims 1 to 4 wherein drug is spray-coated onto core particles from a solution comprising a lower alkyl aliphatic alcohol, acetone or water, or mixtures thereof.

6. A process as claimed in any one of claims 1 to 5 wherein at least two drug substances are layered sequentially onto core particles.

7. A process as claimed in any one of claims 1 to 5 wherein at least two drug substances are deposited onto core particles as a single layer.

8. A process as claimed in any one of claims 1 to 7 wherein the concentration of drug in the spray-coating solution is in the range 20 to 60% w/w.

9. A process as claimed in any one of claims 1 to 8 wherein the particles of inert core material are non-pareil seeds with mesh size in the range 20-40#.

10. A process as claimed in any one of claims 1 to 9 in which the spray-coating solution further comprises a binder material.

11. A process as claimed in claim 10 wherein the binder material is selected from gelatin, starch, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxymethylpropylcellulose and carboxymethylcellulose and mixtures thereof.

12. A process as claimed in claim 10 or 11 wherein the spray-coating solution comprises less than 1.0% of binder material.

13. A process as claimed in any one of claims 1 to 9 wherein binder material is not present in the spray-coating solution.

14. A process as claimed in any one of claims 1 to 13 comprising a further process step in which beadlets are film-coated.

15. A process as claimed in claim 14 in which the film-coating comprises an acrylate or cellulose based polymer.

16. A process as claimed in any one of claims 1 to 15 providing a drug beadlet with a fill weight per size 0 capsule in excess of 450 mg.

17. A drug beadlet, ~~obtainable~~ obtained by a process as defined in any one of claims 1 to 16.

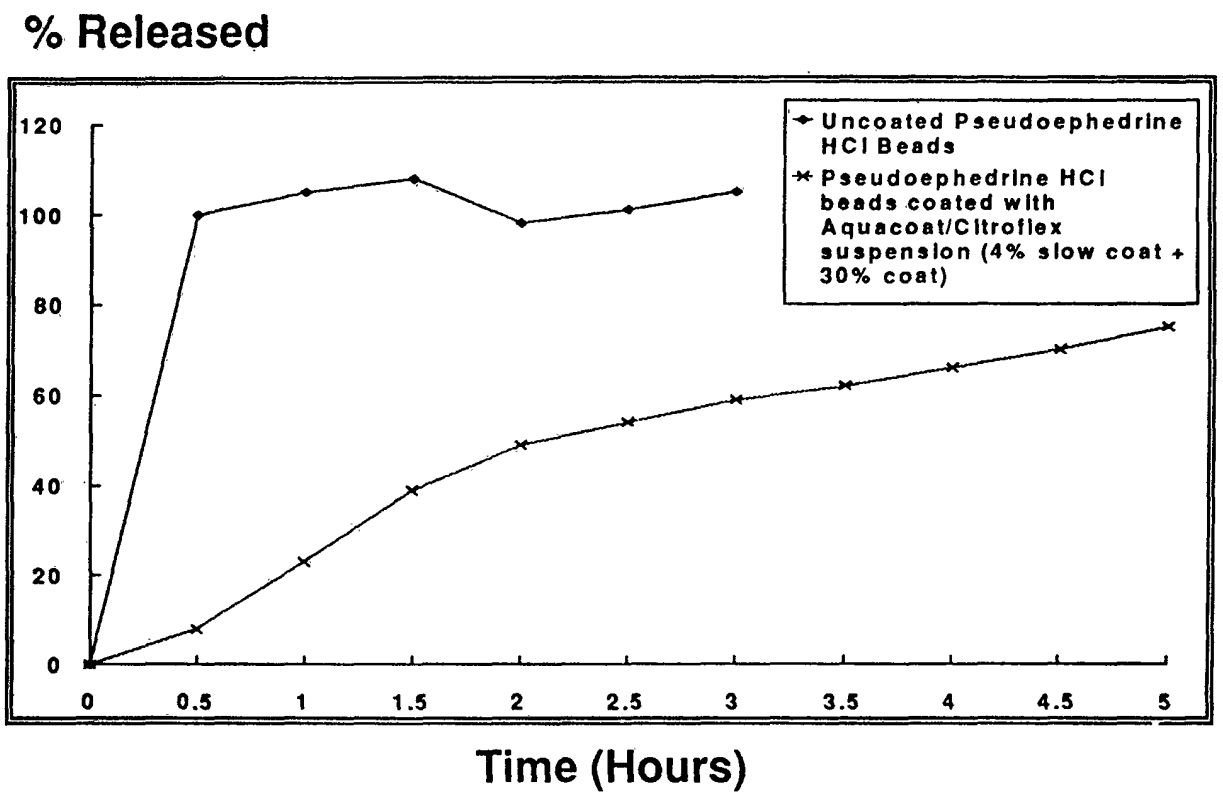
18. A drug beadlet as claimed in claim 17 which comprises ibuprofen.

19. Processes for the preparation of drug substances in beadlet form or drug beadlets obtained by said processes, substantially as hereinbefore described with reference to the Examples and/or drawing.

DATED this 1st day of March, 1995
SmithKline Beecham plc
By Its Patent Attorneys
DAVIES COLLISON CAVE

Figure 1

RELEASE PROFILE OF COATED AND UN-COATED PSEUDOEPHEDRINE HCl BEADS



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01185

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 B01J2/14; B01J2/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	B01J ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 228 633 (AEROMATIC AG) 15 July 1987 see column 2, line 9 - column 5, line 29; figure 1	1-3
A	EP,A,0 361 874 (TAKEDA CHEMICAL INDUSTRIES LTD.) 4 April 1990 see page 2, line 44 - page 4, line 19	1,4,5,7, 9-11,12, 13,17,18
A	US,A,3 408 746 (REYNOLDS ET AL.) 5 November 1968 see column 2, line 60 - column 3, line 37; figure 1	1

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 SEPTEMBER 1992	11. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	CUBAS ALCARAZ J.L.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201185 SA 61475

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/09/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0228633	15-07-87	CH-A- 666828	31-08-88
		JP-C- 1606840	13-06-91
		JP-B- 2034652	06-08-90
		JP-A- 62160125	16-07-87
		US-A- 4740390	26-04-88
EP-A-0361874	04-04-90	AU-A- 4233289	05-04-90
		JP-A- 2174931	06-07-90
US-A-3408746		BE-A- 712115	13-09-68
		DE-A- 1642818	19-05-71
		FR-A- 1573059	04-07-69
		GB-A- 1228241	15-04-71
		NL-A- 6803497	16-09-68
		SE-B- 354969	02-04-73
WO-A-8801904	24-03-88	EP-A,B 0282514	21-09-88
		JP-T- 1500807	23-03-89
		US-A- 4895733	23-01-90