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(54) **Title:** MANUFACTURE OF A PHARMACEUTICAL PRODUCT

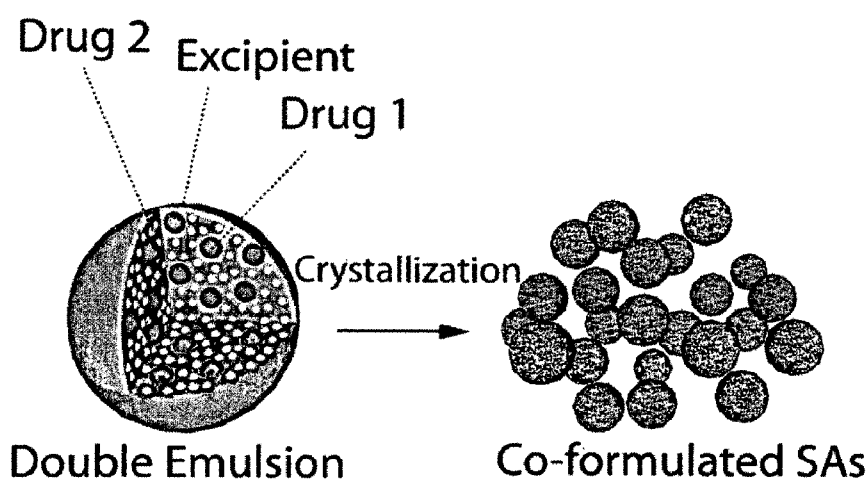


Figure 1

(57) **Abstract:** The invention concerns an emulsion-based method for the manufacture of a crystallized spherical agglomerate and/or a pharmaceutical product; and crystallized spherical agglomerate and/or a pharmaceutical product manufactured thereby.

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Manufacture of a Pharmaceutical Product

Field of the Invention

The invention concerns an emulsion-based method for the manufacture of a crystalized
5 spherical agglomerate and/or a pharmaceutical product; and crystalized spherical
agglomerate and/or a pharmaceutical product manufactured thereby.

Background of the Invention

Pharmaceutical formulation processes, in which active pharmaceutical ingredients
10 (APIs) are blended with additives and excipients, are crucial downstream operations
that dictate the final pharmacokinetic attributes of the product. Presently, most APIs are
produced in crystalline form and their formulation typically involves energy intensive
downstream operations such as comminution, milling, sieving, blending and granulation,
before tableting into the final product.

15 These steps are necessitated by poorly controlled primary crystallization processes
which typically yield large crystals of irregular size and shape. The differently shaped
crystals have different physical properties, such as plasto-elasticity and compaction
behaviour, which affects the afore downstream operations.

Indeed, particle size is extremely important in the pharmaceutical industry. The size,
20 and hence the surface area of an API in particle form, can be related to the physical,
chemical and pharmacologic properties of the drug containing same. Clinically, the
particle size of an API can affect its release from dosage forms that are administered
orally, parenterally, rectally and topically. The successful formulation of
pharmaceuticals; both their physical stability and pharmacologic response also depends
25 on the particle size achieved in the final product.

An alternative manufacturing technique - emulsion-based crystallization - has shown
great potential by producing monodispersed, spherical agglomerates (SAs) which
possess superior micromeritic properties (such as powder packability and flowability),
improved chemical stability and bioavailability, and most importantly, the feasibility of
30 direct compression into tablets.

Furthermore, multiple emulsions (such as double, triple, quadruple, etc. emulsions)
which have been known since 1925 offer the potential benefits of multiple liquid
domains of different natures (hydrophobic and hydrophilic) and thus flexibility in the

choice of ingredients to be formulated are compatible with the mentioned technique. However, one of the main problems associated with the use of multiple emulsions to date is their inherent instability. Multiple emulsions are complex systems as the drops of the dispersed phase themselves contain even smaller dispersed droplets.

5

Some of the possible instabilities of these systems include: multiple oil drops may coalesce with other oil drops, one or more internal aqueous droplets may be expelled from within an oil droplet in a water/oil/water system, the internal droplets may coalesce before being expelled from within the droplet containing them, and water may pass
10 through the oil phase by diffusion resulting in the gradual shrinkage of the internal droplet.

It is therefore considered that that multiple emulsions whilst having many potential uses are complex and inherently unstable systems.

15

The invention described herein involves the use of emulsions in a one-step formulation followed by crystallization to form SAs. Our invention circumvents several drawbacks in conventional processing, such as wide size distribution in batch crystallization, de-mixing in blending and challenges in the formulation of hydrophobic and hydrophilic
20 APIs and excipients thereby offering the potential for continuous, sustainable pharmaceutical crystallization coupled with advanced formulations.

Statements of the Invention

According to a first aspect of the invention there is provided a method for the manufacture of a pharmaceutical product comprising:

25

- i) dispersing a first pharmacologically active ingredient in a first fluid;
- ii) dispersing an excipient in a second fluid;
- iii) mixing said first and second fluids with a third carrier fluid to form a multiple emulsion; and
- iv) collecting the emulsion on a heated surface and allowing the emulsion to
30 crystalize to form spherical agglomerates.

Preferably, the invention is worked using more than one pharmacologically active ingredient and the method comprises:

- i) dispersing a first pharmacologically active ingredient in a first fluid;

- ii) dispersing a second pharmacologically active ingredient and an excipient in a second fluid
- iii) mixing said first and second fluids with a third carrier fluid to form a multiple emulsion; and
- 5 iv) collecting the emulsion on a heated surface and allowing the emulsion to crystallize to form spherical agglomerates.

The invention can involve the co-formulation of a hydrophobic and hydrophilic drugs in the presence of an excipient. The methods of the invention circumvent several energy
10 intensive downstream processes in traditional manufacturing, thereby offering the potential of continuous, sustainable pharmaceutical crystallization coupled with advanced drug formulations which can be used to achieve a multitude of drug delivery objectives.

In a preferred embodiment of the invention said pharmacologically active ingredient is
15 either hydrophobic or hydrophilic.

In a preferred embodiment of the invention said hydrophobic pharmacologically active ingredient is dispersed in a compatible fluid such as a non-aqueous first fluid.

20 In a preferred embodiment of the invention said hydrophilic pharmacologically active ingredient is dispersed in a compatible fluid such as an aqueous first fluid.

In a further preferred embodiment of the invention said excipient is dispersed in a compatible fluid such as an aqueous or non-aqueous second fluid.

25 In yet a further preferred embodiment of the invention said hydrophobic pharmacologically active ingredient and excipient is dispersed in a compatible fluid such as a non-aqueous second fluid.

30 In yet another preferred embodiment of the invention said hydrophilic pharmacologically active ingredient and excipient is dispersed in a compatible fluid such as an aqueous second fluid.

Those skilled in the art will appreciate that the emulsion of the invention may therefore
35 be either a water/oil/water emulsion or an oil/water/oil emulsion.

In yet further preferred embodiments of the invention the method may involve the use of a fourth, fifth, etc. fluid in each of which there is dispersed a further hydrophobic/hydrophilic pharmacologically active ingredient and, optionally, an excipient. In this embodiment of the invention a complex multiple emulsion is formed prior to crystallization on a heated surface.

In yet a further preferred embodiment of the invention said mixing is undertaken by passing the said fluids through a mixing device such as a channel, ideally, a micro channel and so ideally involves the use of a microfluidic device. More preferably still, each fluid is introduced into the microfluidic device via a different channel each one of which converges at a mixing point where the said channels are brought together.

More preferably, the rate of flow of said fluids through said channels is controlled or regulated in accordance with the desired formulation of the pharmacologically active ingredient(s). Thus, in addition to controlling the amount of pharmacologically active ingredient in its compatible fluid one can also control the flow of each fluid through said mixing device thus helping to refine the nature of the formulation.

We have discovered the microfluidic method enables formulations that are nearly impossible to achieve using conventional crystallization methods.

Using the method of the invention we have produced monodispersed microparticles containing crystals of a hydrophobic API embedded within an excipient ('DE' i.e. Drug/Excipient formulation), which in turn may also contain a hydrophilic API ('D²E' Drug/Drug/Excipient formulation). Whilst the invention has been worked as described, it can be worked using various combinations of hydrophobic/hydrophilic/excipient. For example, monodispersed microparticles containing crystals of a hydrophilic API embedded within an excipient ('DE' formulation), which in turn may also contain a hydrophobic API ('D²E' formulation) can be produced.

More specifically, using the method of the invention we have produced monodispersed microparticles containing crystals of a hydrophobic model API (5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, termed ROY) embedded within a hydrophilic excipient (sucrose) matrix ('DE' formulation), which in turn may also contain a hydrophilic model API (glycine) ('D²E' formulation).

Further, using the method of the invention we have produced monodispersed microparticles or SAs in the order of 100-300µm and typically 200µm.

- 5 Furthermore, our method also involves controlling the polymorphic selection of the crystallized spherical agglomerate (SA) via the kinetics of two simultaneous processes occurring within the evaporating emulsion drops containing API-excipient mixtures – (i) liquid-liquid phase separation, which compartmentalizes the API while also providing sites for heterogeneous polymorphic nucleation and (ii) increasing supersaturation of
10 both the API and excipient rich phases, eventually leading to solidification of the excipient, which further facilitates nucleation and crystallization of the API.

We have demonstrated our method using two model hydrophobic APIs – 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (also known as 'ROY', due to the
15 characteristic color of its polymorphs) and carbamazepine (CBZ), formulated with ethyl cellulose (EC) as excipient. ROY and CBZ both exhibit conformational polymorphism, with ten and four known polymorphs respectively. In our method, an API-excipient solution in the solvent, dichloromethane (DCM) is used to form oil-in-water (OW) emulsions with an aqueous solution of polyvinyl alcohol (PVA) serving as the continuous
20 phase, in a micro-capillary emulsion generator. This is followed by thin-film evaporation. Remarkably, we are able to control the polymorphic selection by varying solvent evaporation rate, which is simply tuned by the film thickness; fast (film thickness ~0.5 mm, the thinnest we can achieve without breaking the emulsions) and slow (film thickness ~2 mm) lead to completely specific and different polymorphic outcomes for
25 both model APIs - yellow (YT04) and orange (OP) for ROY, and form II and form III for CBZ respectively. Our method thus paves the way for simultaneous, bottom-up crystallization and formulation processes coupled with unprecedented polymorphic selection through process driven kinetics. We envision it to form the basis of simple, robust and sustainable process platforms for continuous pharmaceutical drug particle
30 manufacturing.

Accordingly, in a further embodiment the method in part iv) involves collecting the emulsion on a heated surface at a selected film thickness and allowing the emulsion to crystallize to form spherical agglomerates.

Most preferably said film thickness is selected having regard to the desired emulsion droplet size to be produced and so is subject to routine determination by those skilled in the art, however, as exemplified herein a film size between 0.5 - 2mm is used to work the invention.

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According to a second aspect of the invention there is provided a crystalized spherical agglomerate (SA) manufactured according to the method of the invention comprising at least one pharmacologically active ingredient (API) and an excipient or carrier.

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According to a third aspect of the invention there is provided a crystalized spherical agglomerate (SA) comprising at least one pharmacologically active ingredient (API) and an excipient or carrier.

15

Additionally, or alternatively, said crystalized spherical agglomerate (SA) comprises at least one further pharmacologically active ingredient (API).

In a preferred embodiment of the invention said spherical agglomerate (SA) comprises particles in the order of 100-300µm and typically 200µm.

20

According to a further aspect of the invention there is provided a pharmaceutical comprising the said crystalized spherical agglomerate (SA).

25

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprises", or variations such as "comprises" or "comprising" is used in an inclusive sense i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

30

All references, including any patent or patent application, cited in this specification are hereby incorporated by reference. No admission is made that any reference constitutes prior art. Further, no admission is made that any of the prior art constitutes part of the common general knowledge in the art.

35

Preferred features of each aspect of the invention may be as described in connection with any of the other aspects.

Other features of the present invention will become apparent from the following examples. Generally speaking, the invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including the accompanying claims and drawings). Thus, features, integers, characteristics, compounds or chemical
5 moieties described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith.

Moreover, unless stated otherwise, any feature disclosed herein may be replaced by an
10 alternative feature serving the same or a similar purpose.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as
15 singularity, unless the context requires otherwise.

Throughout the description and claims of this specification agarose is denoted as AG and heparin as HEP.

20 An embodiment of the present invention will now be described by way of example only with particular reference to the following wherein:

Figure 1 shows a schematic descriptive of the technique for co-formulation and crystallization of hydrophobic and hydrophilic API using double emulsions. Drug 1
25 (Red/dark grey) represents a hydrophobic API while Drug 2 (Yellow/light grey) represents a hydrophilic API, dispersed in a matrix comprising of an excipient (Pink/ mid grey).

Figure 2 shows the apparatus and equipment required for working the invention. The
30 components are marked with numbers: 1) double emulsion generation apparatus; 2) heated surface; 3) stereo microscope; 4(a)-(c) syringe pumps; 5) light source.

Figure 3 shows a schematic of emulsion generation apparatus depicting generation of $O_1/W/O_2$ (Red/Blue/Yellow) double emulsion drops with multiple (n' -in-1) inner O_1 droplets (Red Spheres) using capillary microfluidics, followed by evaporative

crystallization of the droplets to form SAs. Temporal progress of crystallization is represented as an increase in opacity of the W phase due to the presence of excipient.

Figure 4. Stereomicroscopic images depicting; (a) controlled generation of O1/W/O2 double emulsion drops, (b), (c), (d) & (e) time lapse images of double emulsion droplet break-up, (f) collected double emulsions of the 'n'-in-1 droplet morphology on a PDMS coated glass slide. All scale bars represent 300 μm .

Figure 5 shows stereomicroscopic images depicting (a) collected double emulsions of the 'n'-in-1 droplet morphology, (b)-(c) monodispersed 'DE' and 'D²E' SAs, respectively, which are the end products of crystallization.

Figure 6. Schematic representation of the crystallization process and micrographs of 'DE' (Left Column) and 'D²E' (Right Column) formulations showing: initial shrinkage and generation of supersaturation prior to the formation of a sucrose shell at the onset of crystallization. Thereafter, either translucent SAs of the DE formulation or fully opaque SAs of the D²E formulation are obtained. All scale bars represent 100 μm .

Figure 7. shows representative FESEM images, XRD characterization of spherical agglomerates from 'DE' and 'D²E' experiments. (a) SA of excipient (sucrose) and hydrophobic API (ROY) displaying a uniform and smooth surface, (b) SA of hydrophilic API (glycine), sucrose and ROY exhibiting a rough surface with crystals packed together with sucrose, (c) Close-up of faceted crystals located on the surface of the 'D²E' SAs, (d) XRD pattern of the 'DE' SAs showing peaks corresponding to the yellow prism and red plate polymorph of ROY, (e) XRD pattern of the 'D²E' SAs showing peaks corresponding to the yellow prism and red plate polymorph of ROY and γ -glycine.

Figure 8. shows DSC profiles from (a) 'D²E' and (b) 'DE' experiments - characteristic peaks are found in the vicinity of 109°C (ROY), 180°C - 192°C (Sucrose) and 250°C (Glycine) respectively.

Figure 9. (a), (c) Optical and (b), (d) FESEM images of microparticles containing ROY and ethyl cellulose (EC) for the 'thin' (0.5 mm) and 'thick' (2 mm) film scenarios respectively. The drug-excipient loading ratio is 4:1 (320 mg of ROY: 80 mg of EC) for both cases. (e) Differential scanning calorimetry (DSC) profiles for the particles with

exotherms at 106.9 °C and 112.7 °C corresponding to the yellow needle (YT04) and orange plate (OP) polymorphs of ROY respectively.

Figure 10. Representative FESEM images of ROY-EC microparticles from thin and thick film experiments: (a), (b) YT04 particles displaying a compact, cellular structure with an EC scaffold harboring polycrystalline ROY domains, and (c), (d) Orange plate (OP) ROY particles displaying plate like crystals on the surface and within 'the domains' surrounded by a porous EC scaffold.

Figure 11. (a) – (e) Time lapse stereomicroscopic images of emulsion drops subjected to evaporative crystallization under the thin film (0.5 mm) condition. Images were taken at intervals of 10 minutes each. (f) A phenomenological schematic capturing the various stages in the microparticle formation process, including solvent evaporation/shrinkage, liquid-liquid phase separation, EC scaffold formation and crystallization. All scale bars represent 100 µm.

Figure 12. Optical [(a), (b)] and FESEM [(c), (d)] images of pure ROY (400 mg/mL) microparticles: a mixture of yellow, orange and brown colored particles indicate poor polymorphic selectivity; (e) Differential scanning calorimetry (DSC) profiles indicating concomitant polymorphism of YT04 and OP polymorphs of ROY for both thin (0.5 mm) and thick film (2 mm) conditions.

Figure 13. Time-lapse stereomicroscopic images of ROY-DCM emulsion drops subjected to evaporative crystallization under the thin film (0.5 mm) condition. Droplet shrinkage followed by oiling out of ROY from DCM and subsequent crystallization was observed. All scale bars represent 100 µm.

Figure 14. Optical and FESEM images of CBZ-EC microparticles from thin and thick film experiments: (a),(b),(d),(e) monodisperse population of particles with a smooth surface morphology and (c),(f) broken cross section of particle displaying needle shaped crystals embedded in the porous excipient matrix. (g) XRD patterns corresponding to form II and form III polymorphs of CBZ obtained for the thin and thick film cases respectively. (h) Differential scanning calorimetry (DSC) profiles for thin film and thick film cases: characteristic exotherms for form II and form III polymorphs of CBZ are found at 188 °C and 192 °C respectively.

Experimental section

Materials

Materials. Glycine (>99%), dodecane (>99%), Span-80, trichloro- (1H,1H,2H,2H-perfluorooctyl)-silane (97%), (3-aminopropyl)triethoxysilane (97%), ammonium lauryl sulphate solution (ALS, 30% in water), n-hexane (HPLC grade, 95%) and mineral oil (light) were purchased from Sigma-Aldrich (Singapore) and used as received. Sodium dodecyl sulphate (SDS, 85%) was purchased from Merck (Germany). 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile(ROY) was purchased from Nanjing Chemlin Chemical Industry Co. Ltd, China. Ethyl acetate (99.9%) was purchased from Fischer scientific (Singapore). Ultrapure water (18.3 MΩ) obtained using a Millipore Milli-Q purification system was used to prepare aqueous glycine solutions. Harvard PHD 22/2000 series syringe pump was used for regulated flow at μL scales. Square and cylindrical glass capillaries of ID 1mm and 0.7mm respectively were purchased from Arte glass associates Co., Ltd. Japan. Poly(vinyl) alcohol (PVA) (M.W. - 67,000), dichloromethane (DCM) (99.5%), ethyl cellulose (EC) (viscosity 10 cP) and carbamazepine (CBZ) were purchased from Sigma-Aldrich (Singapore) and used as received.

Methods

A photograph of the apparatus for working the invention is shown in Figure 2. The setup consists of an emulsion generation apparatus, syringe pumps (Harvard PHD 22/2000 series), stereo microscope and heated surface has been assembled to demonstrate the capabilities of the invention.

The emulsion generation apparatus is an assembly of three glass capillaries – two round and a square capillary– as presented by Weitz and co-workers. [4] A schematic of the apparatus depicting generation of $\text{O}_1/\text{W}/\text{O}_2$ double emulsions is shown in Figure 3.

The axisymmetric coaxial glass capillary flow-focusing device was assembled using a square and two round capillaries. Round capillary 1 (C1) (colored red in Figure 3) serves as the inlet for the inner fluid whilst round capillary 2 (C2) (colored yellow in Figure 3) serves as the collection tube for the double emulsions. The round glass capillary collection nozzle (colored yellow in Figure 3) and the square glass capillary are silanized to alter their wetting properties, specifically, for hydrophobicity and hydrophilicity, respectively. The square capillary was silanized with (3-aminopropyl)triethoxysilane (97%) and C2 was silanized with trichloro-(1H,1H,2H,2H-

perfluorooctyl)-silane for hydrophilic and hydrophobic wetting properties respectively, to aid in double emulsion generation. 10 μ L of either silane was used per glass capillary and silanization was carried out for a minimum of 8 hours in a vacuum chamber at a pressure of 0.08 MPa.

5

A total of 3 fluids (outer O_2 , middle W and inner O_1) are infused into the emulsion generating device via the round glass dispensing nozzle (colored red in Figure 3) and through the coaxial regions to form oil-in-water-in-oil (O_1 /W/ O_2) double emulsions. The O_1 and W phases carry the hydrophobic and hydrophilic APIs respectively while the O_2 phase serves as the continuous phase. The excipient, usually hydrophilic in nature, resides in the W phase.

10

The inner-most oil phase (O_1) was prepared by mixing 1 parts ROY (30 mg/mL) in ethyl acetate solution with 5 parts dodecane containing 0.3% (w/w) surfactant, Span 80. Middle aqueous phase (W) was prepared by dissolving 1g of sucrose, 100mg of glycine and 100mg of surfactant (SDS) in 5 mL ultra pure water for the D2E formulation. Light mineral oil with 0.5% (w/w) of surfactant (Span80), was used as the continuous phase (O_2).

15

In the specific embodiment of the invention described herein, O_2 and W phases were infused from the two ends of the square capillary through the outer coaxial region while O_1 phase was infused through C1 using syringe pumps (Harvard PHD 22/2000 series). However the skilled man will appreciate that the various phases can be infused through the apparatus in different manners.

20

The flow rates of these phases can be tuned to adjust the size of each of the liquid domains (i.e. O_1 and W phase) and thus achieve the desired loading of each API. The typical operating flow rates follow a decreasing trend in the order of O_2 , W and O_1 respectively. Specifically, the flow rates of 40 μ L/min, 7 μ L/min and 1.8 μ L/min were used for the O_2 , W and O_1 phases respectively.

25

All the three fluids were hydrodynamically flow focused through the nozzle of C2 resulting in the formation of the double emulsion drops. Approximately 1 mL of the double emulsion was collected on a glass slide spun coated with a thin layer of polydimethylsiloxane (PDMS) and subsequently heated to a temperature of 80-100°C, typically 90°C on a hot plate (Thermo Scientific CIMAREC) for evaporative

30

crystallization resulting in the formation of the formulated spherical agglomerates (SAs) of ~200 µm. High-speed real time imaging of the droplet breakup and stable emulsions collected on the glass slide was performed with high speed digital cameras (Basler pl640 or Miro Phantom EX2) mounted onto a stereomicroscope (Leica MZ16). A Leica
5 CLS 150 XE light source was used.

For the purpose of exemplification, we prepared two types of formulations with the flow setup. We formulated a hydrophobic API (Drug) in a hydrophilic excipient (E) matrix (DE formulation) in our first exemplification and formulated a hydrophobic API (Drug) in a
10 hydrophilic matrix (E) containing excipient and a hydrophilic API (D²E formulation) in the D²E exemplification.

In each exemplification, we carried out high-speed imaging with high speed digital cameras mounted on a stereomicroscope to document the operation of the emulsion
15 generating device. The SAs of each formulation were characterized by using microscopic image analysis, field emission scanning electron microscopy (FE-SEM), powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). For the size distribution studies we used an inverted microscope (Nikon Eclipse Ti) operated in bright field mode. The inbuilt software (NIS Elements 3.22.0) was used to measure the
20 diameters of the agglomerates (circle by three points method) and to estimate the average diameters and standard deviations based on measurements of at least 100 SAs.

A field emission scanning electron microscope (JEOL JSM-6700F) at 5 kV accelerating
25 voltage was used to acquire further structural information on the SAs. All samples were prepared on conventional SEM stubs with carbon tape and were coated with ~10 nm of platinum by sputter coating. An XRD diffractometer (LabX XRD-6000, Shimadzu) with characteristic Cu radiation was used for polymorphic characterization. The X-ray diffractometer was operated at 40 kV, 30 mA and at a scanning rate of 2°/min over the
30 range of 10-40°, using the Cu radiation wavelength of 1.54 Å. The DSC thermograms were obtained using a Mettler Toledo DSC 882 apparatus. Around 5 or 10 mg of sample was crimped in a sealed aluminium pan and heated at 5°C/ min in the range of room temperature to 225 °C or 280°C using an empty sealed pan as reference. Dry nitrogen was used as purge gas and the N2 flow rate was 50 µL/min. GC analysis was carried
35 out on a Shimadzu GC 2010 Plus apparatus equipped with an auto injector (AOC-20i), flame-ionization detector and a separation column (30m, i.d. 0.25 mm). Around 10 mg of

sample was crushed and added to 1mL of hexane and loaded into the GC. The system was run for 8 minutes from 50 to 250 °C for a helium gas purge flow of 3 mL/min.

We observed droplet generation in the microfluidic device using high speed imaging. A uniform stream of double emulsions with multiple inner droplets (n-in-1) (Figure 4a) is observed while operating in the jetting regime where droplet formation occurs downstream of the circular orifice of the collection tube. Jetting is a result of dominant viscous effects over inertial effects and interfacial forces; the viscosity of the outer O² phase is ~30 times that of the middle W phase. The system operates at a low Reynolds number, as is characteristic of most microfluidic flow scenarios. The transition from the dripping to jetting regime is described by a Capillary number $Ca = \frac{\mu V}{\gamma} \sim 1$, where μ is the viscosity of the O² phase, V is a mean velocity of the inner W phase and γ is the interfacial tension between the O² and W phases. The size of the middle and the inner phase droplets can be tuned by varying the flow rates of the respective fluids. The volumetric flow rates of the O₂, W and O₁ phases were set to 40, 7 and 1.8 $\mu\text{L}/\text{min}$ respectively. At these flow conditions, the frequency of droplet generation is 5 droplets per second (Figures 4b to 4e).

Analysis using high speed imaging reveals double emulsions of a mean diameter of 382 μm (Figures 4f & 5a) with a standard deviation of 2%. A count of the number of inner O₁ droplets within these double emulsions gives ' n ' = 85 $\pm$ 8 droplets. The diameter of the inner O₁ droplets is ~25 μm . By calculating the total volume of the O₁ droplets and the volume of the W phase, we estimate that ~45% of the droplet volume is occupied by the O₁ phase. A typical SA of the drug-drug-excipient ('D²E') formulation contains 1.3 μg of sucrose, 0.13 μg of glycine and 0.03 μg of ROY, yielding a loading ratio of 40:4:1 (Sucrose/Glycine/ROY). Similarly, SAs of the drug-excipient ('DE') formulation yield a loading ratio of 40:1 (Sucrose/ROY).

The presence of the O¹ and W phases allows for hydrophobic and hydrophilic APIs to be formulated as a single entity; a challenging task in contemporary pharmaceutical processing. The loading ratio of the APIs can also be monitored and controlled accurately. The concentration of the API in the O¹ or W phase can be regulated to increase or decrease the drug loading while the droplet morphology remains fixed. Alternatively, the loading can also be adjusted by altering the number of O¹ droplets or by varying the overall diameter of the double emulsion droplet.

We were able to fabricate monodispersed SAs of both drug-excipient ('DE') and drug-drug-excipient ('D²E') types with tunable particle sizes in the 100-300 μm diameter range. Under the specific flow conditions mentioned earlier in the description, the mean particle size of the 'DE' (Figure 5b) and 'D²E' (Figure 5c) SAs were $\sim 200 \mu\text{m}$ diameter with a standard deviation of $<5\%$. This approach to monodisperse particulate formulations potentially circumvents several drawbacks in conventional processing, such as wide size distribution in batch crystallization, de-mixing in blending and challenges in the co-formulation of hydrophobic and hydrophilic APIs and excipients.

We observed several stages in the process of crystallization. Firstly, the double emulsion droplets shrank to $\sim 60\%$ of their original droplet diameter. Thereafter, a hard and brittle shell was observed to form at the W/O² interface, encapsulating the inner droplets (Figure 6a and 6b). Stereomicroscopic images obtained during the course of crystallization show the formation of a sucrose shell while the O¹ droplets are still present. Encapsulation is crucial in ensuring entrapment of the hydrophobic API in the event of coalescence of O¹ droplets with the O² phase. An increase in opacity of the encapsulated emulsions followed. The 'D²E' SAs appeared opaque due to the presence of glycine while those of the 'DE' SAs appeared translucent (Figure 6c and 6d).

Electron microscopy revealed that the surface of the 'DE' SAs was smooth while that of the 'D²E' SAs was coarse (Figure 7a and 7b). The smooth texture of the 'DE' SAs is expected as it is typical of formulations containing sucrose. On closer observation (Figure 7c), crystal facets of $\sim 2 \mu\text{m}$ were observed to populate the surface of the 'D²E' SAs; these facets can be attributed to the presence of hydrophilic API in the excipient matrix.

XRD reveals the presence of γ -glycine and the red and yellow polymorphs of ROY respectively, as indicated in Figure 7d and 7e; the observed characteristic peak for ROY at 15.6° , 18.2° and 23.8° , which are the major peaks in bulk ROY, provides strong validation for its presence within the SAs. XRD characterization revealed that the yellow prism (Y) polymorph was the major component. Interestingly, we obtained γ -glycine in our D2E formulations, as opposed to the more commonly obtained α -glycine in emulsion-based crystallization.¹⁵ This can be attributed to the role of the sodium ions present in the surfactant used – sodium dodecyl sulfate (SDS). Sodium ions have been reported to inhibit the growth of metastable α -glycine via interaction with the carboxylate

group of glycine zwitterions in solution, thus promoting the growth of γ -polymorph.²⁹ Control experiments using a different surfactant – ammonium lauryl sulfate (ALS) yielded α -glycine (refer Supporting Information, Section 2), thus confirming the role of SDS in the formation of γ -glycine and thus demonstrating the possibility of polymorphic control using surfactants as additives.

From the DSC thermograms (Figure 8a and 8b), an exotherm at 109°C affirms the presence of ROY and the exotherm at 250°C confirms the presence of glycine. The characteristic region of peaks observed between 180°C to 192°C, correspond to the range that defines the decomposition temperature of sucrose. The exotherm observed at 160-170°C for the 'D2E' trials may be attributed to the decomposition temperature of glucose – a product of the hydrolysis of sucrose and precursor to the Maillard reaction. The peak position is characteristic of glucose decomposition for heating rates of 2-10°C/min.³⁰ Lastly, the exotherm at 250°C confirms the presence of glycine. The DSC results reinforce the XRD results thus affirming successful co-formulation of the two API models.

In addition, we also studied the levels of residual solvent in the formulated SAs using GC analysis. Dodecane is the major component of the inner organic phase O¹, and its residual amount in the SAs was measured to be 7.5µg/mg of SAs. This is well within the acceptable limits of residual solvents on typical paraffins under class 3 classification of residual solvents.

Further evaporation studies

The aqueous continuous phase (W) was prepared by mixing 1.5% wt PVA in water. The dispersed phase (O) was one of the following three: (i) ROY in DCM (400 mg/mL), (ii) ROY-EC in DCM (320 and 80 mg/mL, respectively), (iii) CBZ-EC in DCM (240 and 60 mg/mL, respectively). W and O phases were infused from the two ends of the square capillary through the outer coaxial region using syringe pumps (Harvard PHD 22/2000 series) at flow rates of 150 and 50 µL/min respectively. The fluids were hydrodynamically flow focused through the nozzle of the round capillary resulting in the formation of the emulsion drops. 3.7 cm ID glass wells were used for sample collection and as crystallization platforms. Approximately 100 µL of O/W emulsions were dispensed directly into the glass well containing either a 'thin' (0.5 mm) or 'thick' (2 mm) film of the continuous phase. Evaporative crystallization was performed at room temperature (24 °C) and at ambient humidity (55%). Optical microscopy images were

captured using a Qimaging MicroPublisher 5.0 RTV camera mounted on an Olympus SZX7 microscope. A Leica CLS 150 XE light source was used. A thin film of continuous phase persisted at the end of all experiments.

- 5 Emulsions of ROY-EC in DCM (100 μ L) were dispensed into a glass well containing a pre-dispensed film of water-PVA solution (0.5 and 2 mm nominal film thickness) for subsequent evaporative crystallization. The entire crystallization process took $\sim$ 40 min and $\sim$ 4 hours for thin and thick film cases respectively, at ambient temperature (24 $^{\circ}$ C). Monodisperse SAs of ROY-EC of diameter 180 μ m (with a standard deviation of 5%)
10 were produced under both conditions. Polymorphic selection of nearly 100% was achieved for both conditions, as indicated by particle color and the DSC characterization (Figure 9); yellow and orange microparticles were obtained for the thin and thick film cases respectively. DSC characterization reveals the yellow polymorph to be YT04 and the orange polymorph to be orange plate (OP); here we note that YT04 is
15 thermodynamically less stable than OP among the reported polymorphs of ROY at room temperature. Figure 10 compares electron microscopy (FESEM) images of the structure of YT04 and OP SAs, highlighting the spherical shape of particles obtained in both cases. Further, FESEM images also reveal interesting structural differences between the two cases. YT04 particles have a compact structure that consists of polycrystalline,
20 presumably spherulitic domains tightly embedded within an EC matrix, whereas OP particles exhibit a void-filled porous structure with large single crystals loosely encapsulated within the pores and ribbon-like crystal flakes covering the particle surfaces.
- 25 To better understand the particle formation process, we conducted online optical microscopic monitoring of the entire crystallization process. As shown in Figure 11(a)-(e), which are time-lapse optical microscopic images of evaporating emulsion drops, we noted the occurrence of a liquid-liquid phase separation of the three component (ROY-EC-DCM) system as the solvent (DCM) evaporates. Small droplets ('domains') were
30 observed to form within the dispensed droplets and grow in size over time. The average domain size measured immediately after the first crystallization event in the droplet ensemble for the thin film case (3 μ m) was smaller than that observed in the thick film experiments (12 μ m), indicating coarsening of the domains in the latter case. As suggested by the FESEM images in Figure 10, ROY crystals formed the major
35 component in these domains whereas EC formed an interconnected scaffold surrounding the domains.

We interpret and explain our observations in terms of an interplay between simultaneous dynamic processes occurring within the evaporating emulsion drops containing API-excipient mixtures – (i) liquid-liquid phase separation of the three component system, API-excipient-solvent, due to solvent evaporation, which compartmentalizes the API rich solution into small domains surrounded by the excipient, which then provide surfaces for heterogeneous nucleation of the API and (ii) increasing supersaturation of both the API and excipient rich phases, eventually leading to solidification of the excipient, which further facilitates crystallization of API. In the thin film case, due to fast evaporation and supersaturation generation, the domains form rapidly (within ~3 minutes), resulting in a population of highly supersaturated internal droplets, where conditions are conducive to spherulitic growth. On the other hand, in the case of thick films, slow evaporation results in a milder temporal supersaturation profile and the possible coarsening of the domains. Our observation is of the less stable YT04 polymorph appearing at higher evaporation rates and the comparatively more stable OP polymorph crystallizing under a slow rate of supersaturation generation in confined spaces.

Role of the excipient in evaporation

To further investigate and validate the role of the excipient, we compared and contrasted the above results with the case of ROY crystallization in the absence of EC. 100 µL of emulsions generated from ROY-DCM solution in aqueous PVA solution were dispensed into a glass well containing a pre-dispensed film of water-PVA solution (0.5 and 2 mm film thickness) for subsequent evaporative crystallization. As compared to the case with excipient, relatively fewer monodisperse and irregular shaped particles of ROY were formed under both the thin and thick film conditions (Figure 12). The time taken for particle formation was ~1.5 hours and ~7 hours for the thin and thick film cases, respectively, which is 2-3 times longer than the above cases where EC was used along with ROY. Optical microscopy images of the ROY microparticles indicate concomitant polymorphism and thus poor control over polymorphic selection (Figure 12); DSC characterization further confirms the concomitant occurrence of both YT04 and OP polymorphs.

Liquid-liquid phase separation was also observed in this case (Figure 13); small ROY precipitates were seen appearing and growing inside the emulsion droplets within ~1 min after dispensing. In the case of an API-solvent system, this phase separation is

known as 'oiling out', and is commonly observed during the crystallization of small organic molecules. Here, the solute-solvent system transitions from a single liquid phase into a metastable liquid-liquid state (having a solute-rich and solute-lean phase), bypassing the solid-liquid zone in the phase diagram altogether. Recent pharmaceutical development has seen an increase in the number of lipophilic and non-polar API molecules, such as ROY, which do not easily self-assemble, and are prone to liquid-liquid phase separation. Further, the metastable liquid-liquid state is known to hinder primary and secondary nucleation, leading to long crystallization process times of up to 35 hours; often, special measures are needed to move the system away from this part of the phase diagram to promote nucleation and growth of crystals. This is in keeping with our observations of longer crystallization times for this case, as compared to the results with excipient. In the latter case, the formation of an excipient scaffold upon solvent evaporation provided heterogeneous sites for nucleation of ROY crystals in both the thin and thick film cases, the polymorphism ultimately being dictated by the different temporal rates of supersaturation generation.

Finally, to validate the core idea, we demonstrate controlled polymorphic selection of another model molecule - carbamazepine (CBZ) – an anticonvulsant which has multiple polymorphic forms via conformational polymorphism. An analogous protocol was followed in this case; droplets of CBZ in DCM were generated in an aqueous PVA continuous phase, and subjected to evaporative crystallization in both thin (0.5 mm) and thick films (2 mm), as for the case of ROY. The particles generated were highly monodisperse and had a smooth surface morphology. Electron microscopy of broken sections of the particles show needle shaped CBZ crystals trapped within the porous framework of ethyl cellulose (Figure 14) in both cases. Powder X-Ray diffraction (XRD) characterization reveals that particles from the thin and thick film experiments correspond to least stable form II and most stable form III polymorphs of CBZ (Form II < IV < I < III) respectively. As indicated in Figure 14g [(i) and (ii)], major peaks identified at 13.26°, 18.56°, and 24.54° are attributed to form II CBZ and peaks at 15.36°, 19.56°, 25.00°, and 27.47° to form III CBZ respectively. Dominant and unrepeatable occurrence of characteristic peaks corresponding to the two forms of CBZ provides strong evidence of polymorphic selection using our method. Finally, DSC analysis was performed to validate polymorphic selection of carbamazepine (CBZ) determined by XRD, showing Form II under thin film and Form III under thick film. DSC thermograms were recorded at 5 °C/min from 25 to 225°C, corresponding to the melting range of CBZ forms (Figure 14h). An exotherm at 188°C for the sample from the thin film experiment confirmed the

presence of form II CBZ polymorph, which has a reported melting point in the range of 188 - 192°C. The exotherm at 192°C for CBZ samples from the thick film experiment confirmed the presence of form III CBZ polymorph, which has a reported melting point in the range of 189 - 193°C.18 DSC thermograms thus reinforced our XRD results, providing strong validation for polymorphic selection of CBZ.

Conclusion

The invention described herein overcomes the challenges faced in pharmaceutical formulations wherein we demonstrate a single step formulation platform for the fabrication of monodispersed microparticles of ~200 μm size containing crystals of a hydrophobic model API (ROY) embedded within a hydrophilic excipient (sucrose) matrix ('DE' formulation), which in turn may also contain a hydrophilic model API (glycine) ('D²E' formulation).

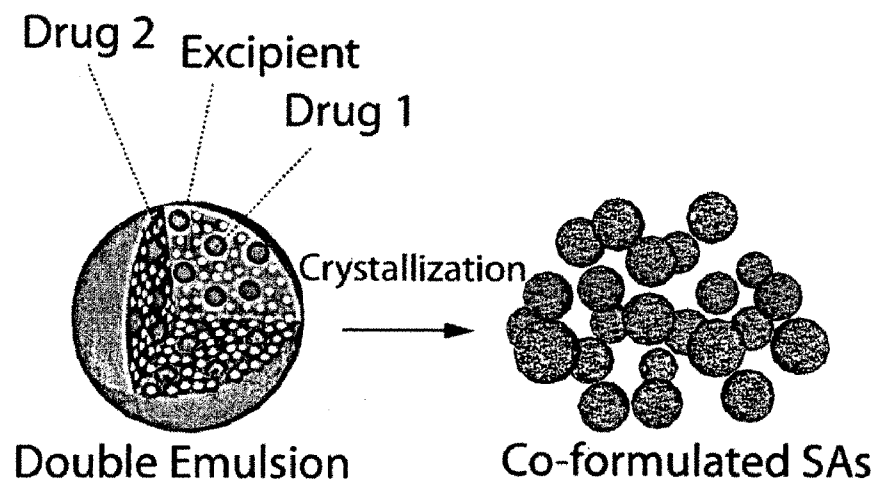
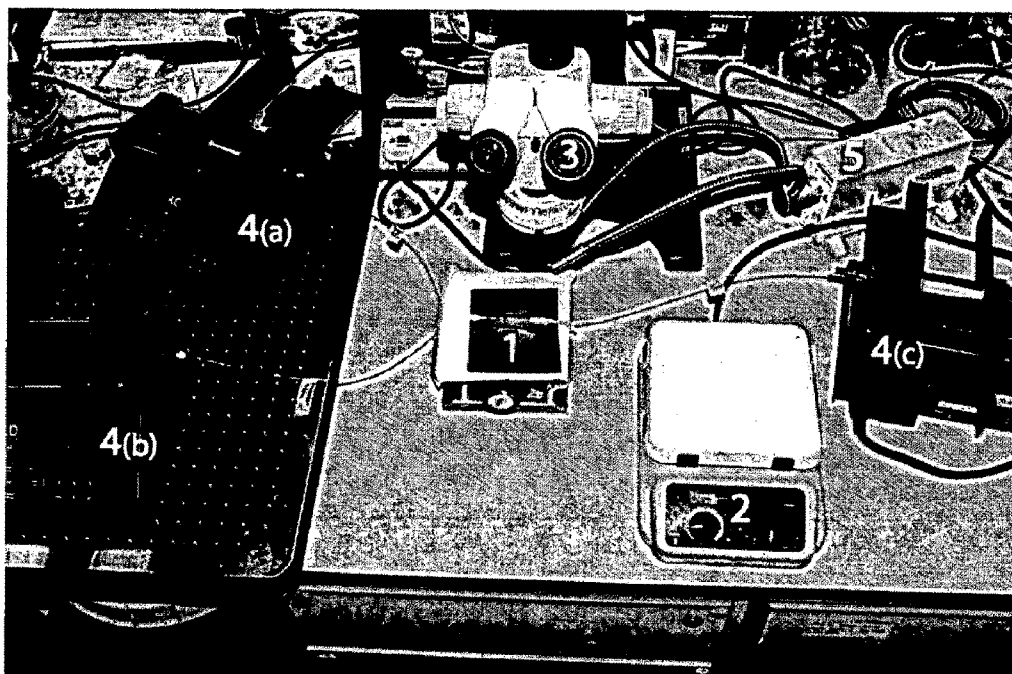
We have shown a pharmaceutical formulation process in 'bottom-up' fashion, where crystallization and formulation occur in tandem, instead of via energy intensive 'top-down' processes in traditional manufacturing. To do this we have leveraged emulsion-based spherical crystallization and microfluidic capillary-based emulsification. We dispense the components of the formulation into monodispersed oil-in-water-in-oil ($\text{O}_1/\text{W}/\text{O}_2$) or water-in-oil-in-water ($\text{W}_1/\text{O}/\text{W}_2$) double emulsions using capillary microfluidics and spherically crystallize them to form exemplary DE and D²E microparticles – the first demonstration of its kind. The method also has capabilities to completely circumvent several energy intensive and ubiquitously batch processes in traditional manufacturing, thereby offering the potential for continuous, sustainable pharmaceutical crystallization coupled with advanced formulations.

Claims

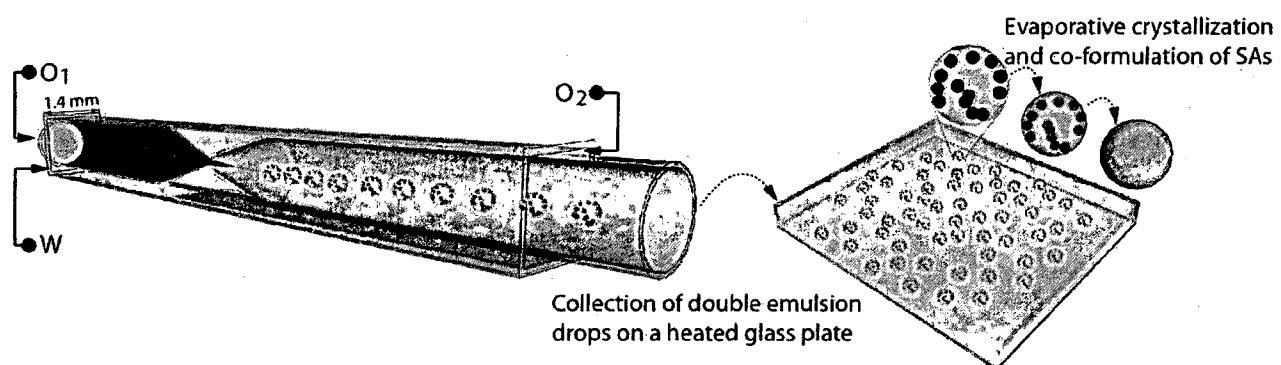
1. A method for the manufacture of a pharmaceutical product comprising:
 - i) dispersing a first pharmacologically active ingredient in a first fluid;
 - 5 ii) dispersing an excipient or carrier in a second fluid;
 - iii) mixing said first and second fluids with a third carrier fluid to form a multiple emulsion; and
 - iv) collecting the emulsion on a heated surface and allowing the emulsion to crystallize to form spherical agglomerates.
- 10 2. A method according to claim 1 wherein more than one pharmacologically active ingredient is used and the method comprises:
 - i) dispersing a first pharmacologically active ingredient in a first fluid;
 - ii) dispersing a second pharmacologically active ingredient and excipient in a second fluid
 - 15 iii) mixing said first, second fluids with a third carrier fluid to form a multiple emulsion; and
 - iv) collecting the emulsion on a heated surface and allowing the emulsion to crystallize to form spherical agglomerates.
3. The method according to claims 1 or 2 wherein said pharmacologically active
20 ingredient is either hydrophobic or hydrophilic.
4. The method according to claim 2 wherein said first pharmacologically active ingredient is hydrophobic and said second pharmacologically active ingredient is hydrophilic.
5. The method according to claim 2 wherein said first pharmacologically active
25 ingredient is hydrophilic and said second pharmacologically active ingredient is hydrophobic.
6. The method according to any one of claims 3 to 5 wherein said hydrophobic pharmacologically active ingredient is dispersed in a compatible fluid such as a non-aqueous first fluid.
- 30 7. The method according to any one of claims 3 to 5 wherein said hydrophilic pharmacologically active ingredient is dispersed in a compatible fluid such as an aqueous second fluid.
8. The method according to any one of claims 3 to 5 wherein said excipient is dispersed in a compatible fluid such as a non-aqueous or an aqueous fluid.

9. The method according to any one of the preceding claims wherein at least one further fluid is provided containing a dispersion of at least one further pharmacologically active ingredient.
- 5 10. The method according to any one of the preceding claims wherein said mixing is undertaken by passing the said fluids through a microfluidic device.
11. The method according to claim 10 wherein each fluid is introduced into the microfluidic device via a different channel each one of which converges at a mixing point where the said channels are brought together.
- 10 12. The method according to claims 10 or 11 wherein the rate of flow of said fluids through said microfluidic device or said channels is controlled or regulated in accordance with the desired formulation of the pharmacologically active ingredient(s).
13. The method according to any one of the preceding claims wherein part iv) involves collecting the emulsion on a heated surface at a selected film thickness and allowing the emulsion to crystallize to form spherical agglomerates.
- 15 14. The method according to claim 13 wherein said film thickness is between 0.5 - 2mm.
15. The method according to any one of the preceding claims wherein said spherical agglomerates are in the order of 100-300 μ m.
- 20 16. The method according to claim 15 wherein said spherical agglomerates are in the order of 200 μ m.
17. A crystalized spherical agglomerate (SA) manufactured according to the method of any one of claims 1 to 16 comprising at least one pharmacologically active ingredient (API) and an excipient or carrier.
- 25 18. A crystalized spherical agglomerate (SA) comprising at least one pharmacologically active ingredient (API) and an excipient or carrier.
19. The crystalized spherical agglomerate (SA) according to claims 17 or 18 wherein said SA comprises at least one further pharmacologically active ingredient and an excipient or carrier.
- 30 20. The crystalized spherical agglomerate (SA) according to any one of claims 16 to 18 wherein said spherical agglomerate (SA) comprises particles in the order of 100-300 μ m.
21. The crystalized spherical agglomerate (SA) according to claim 20 wherein said spherical agglomerate (SA) comprises particles in the order of 200 μ m.
- 35 22. A pharmaceutical product comprising the crystalized spherical agglomerate (SA) according to any one of claims 17 to 21.

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**Figure 1****Figure 2**

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**Figure 3**

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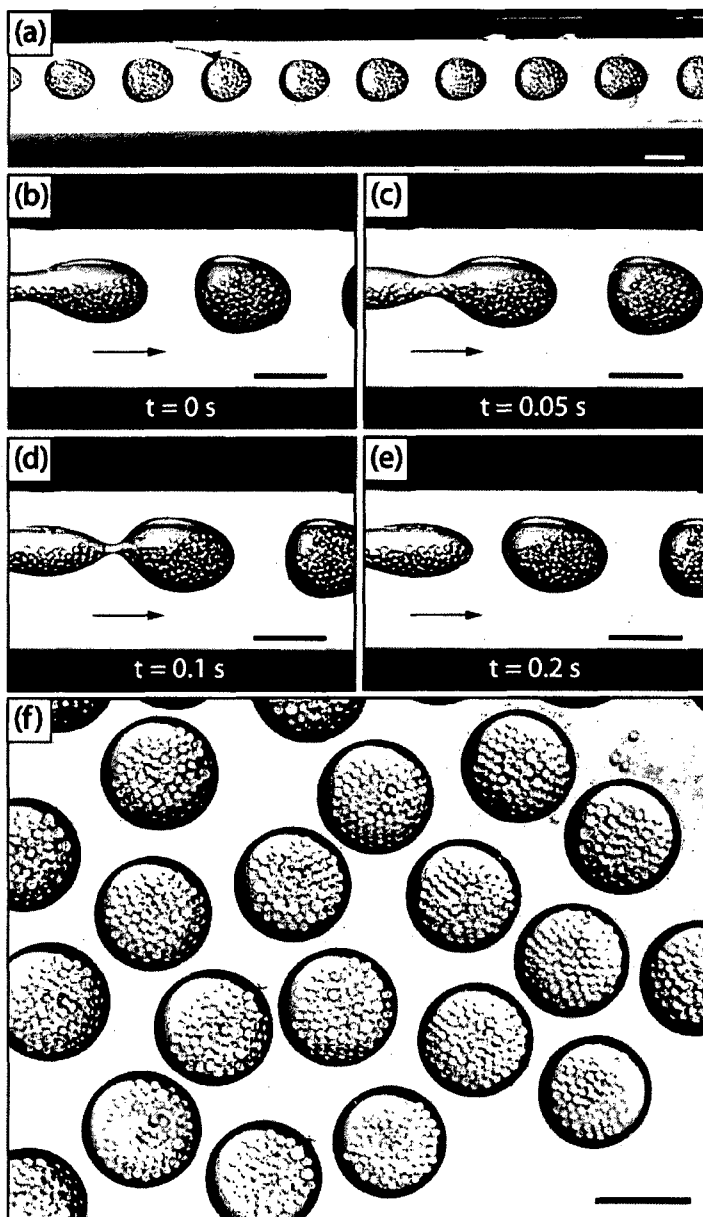


Figure 4

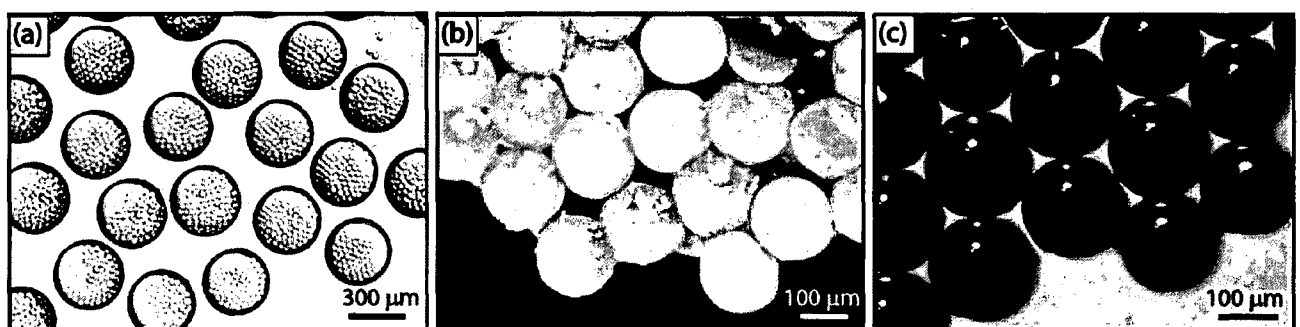
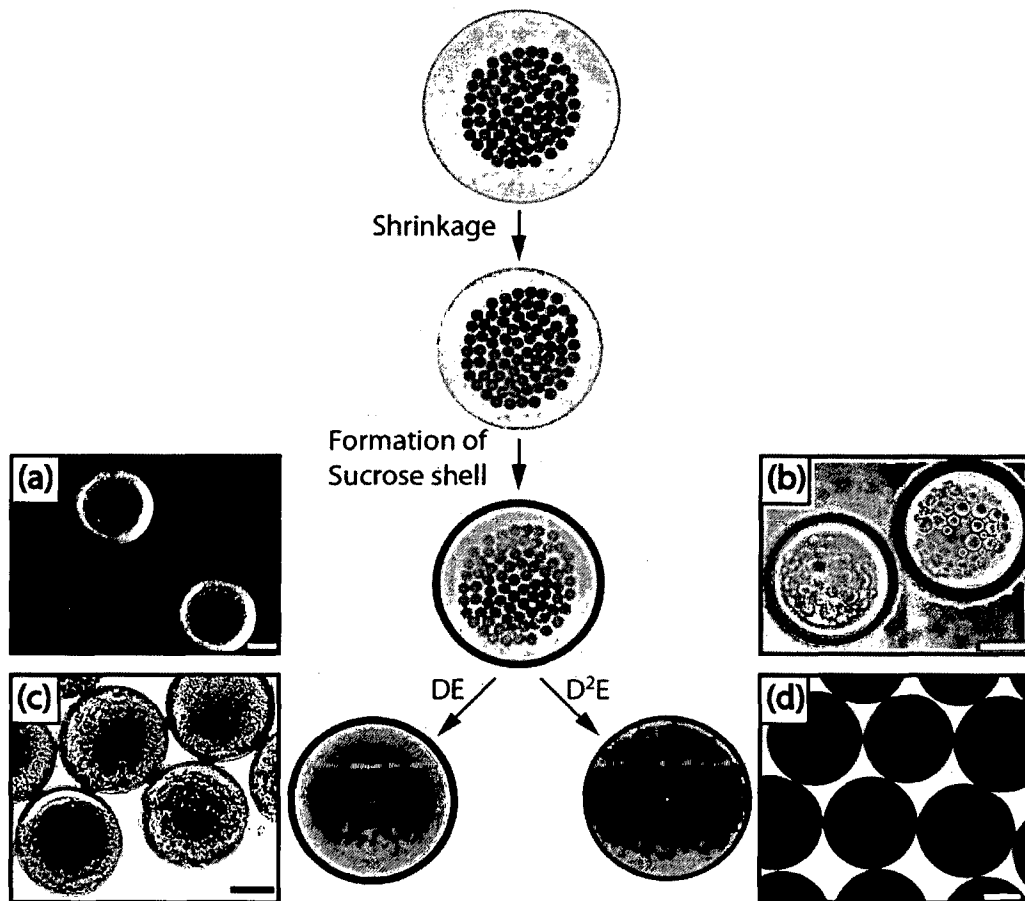


Figure 5

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**Figure 6.**

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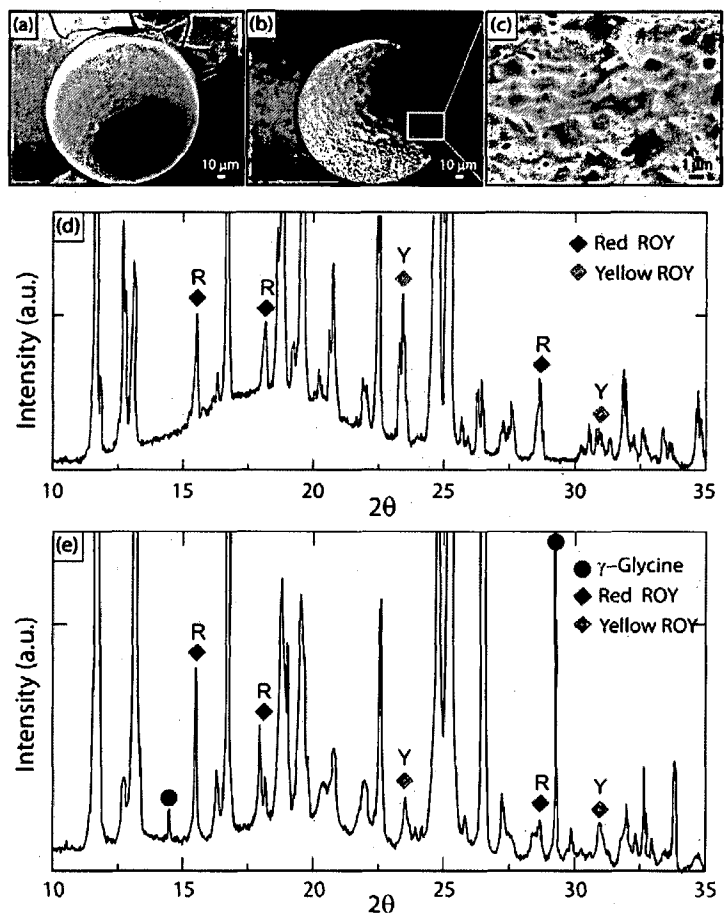


Figure 7

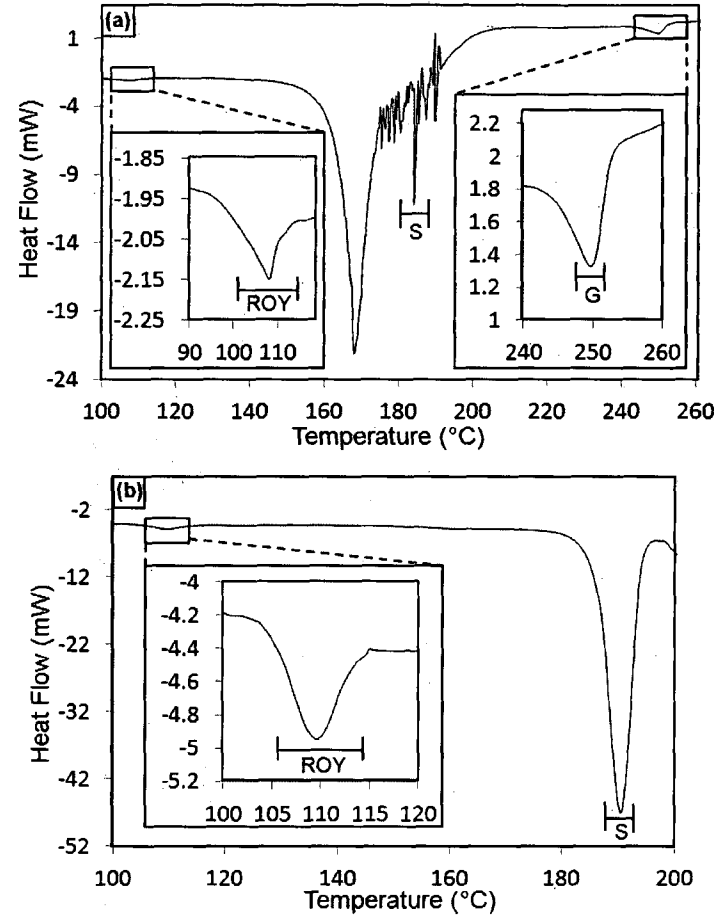


Figure 8

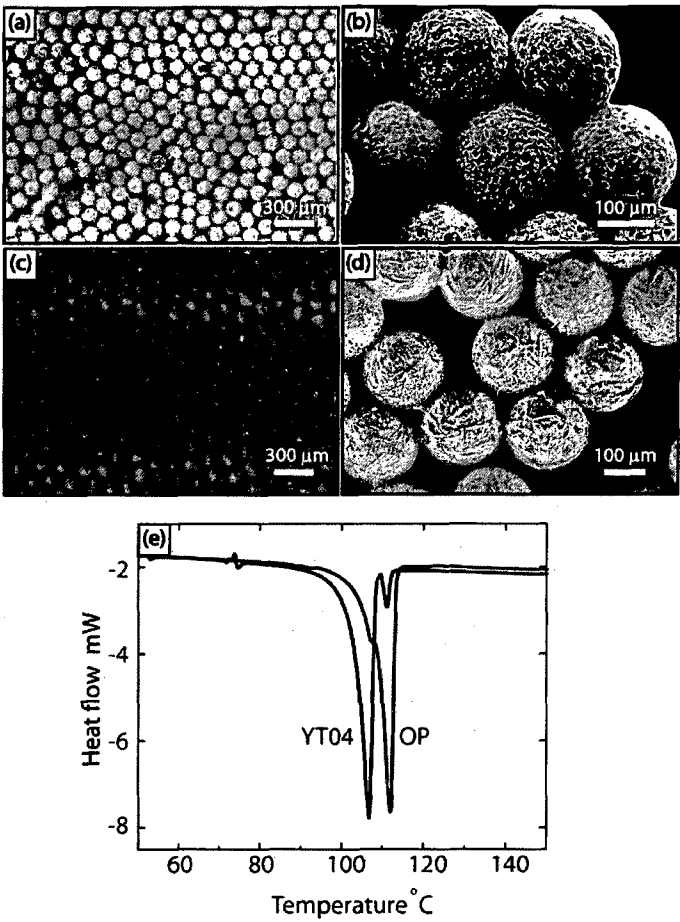


Figure 9

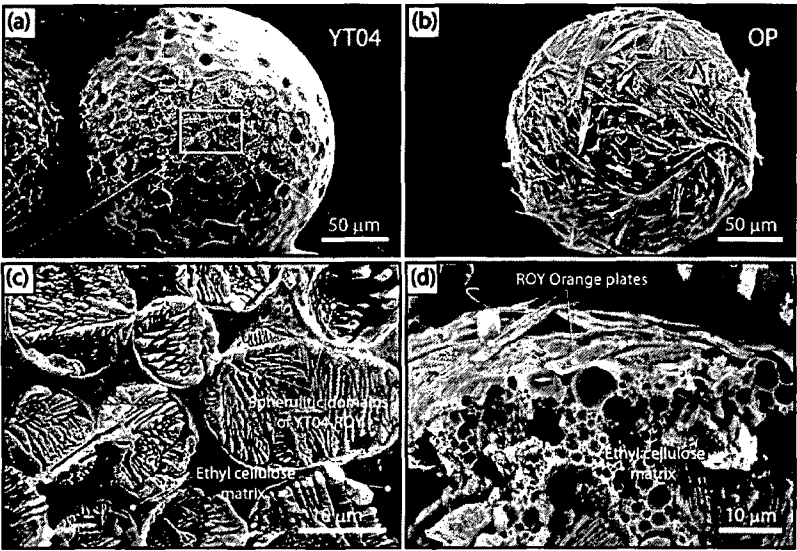


Figure 10

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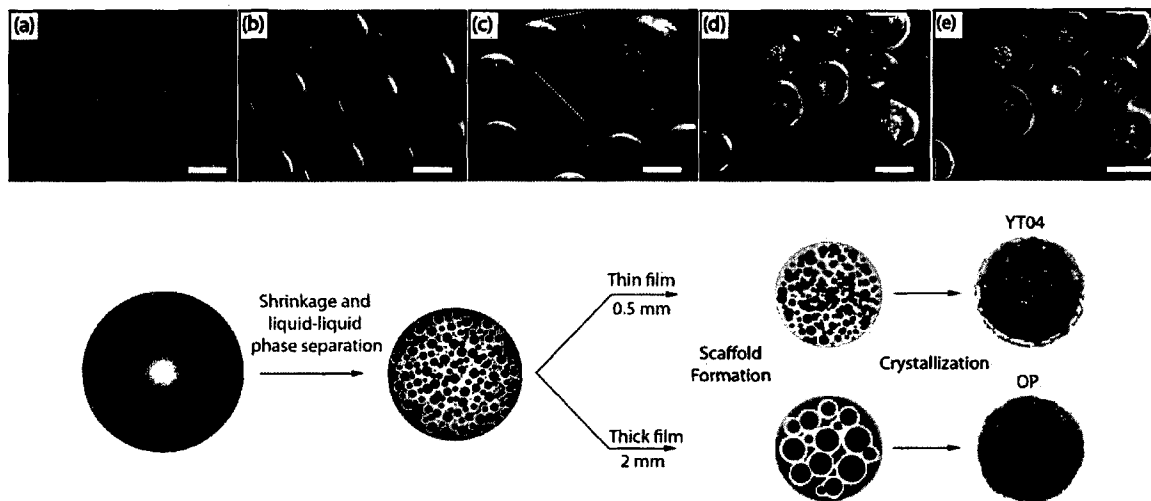


Figure 11

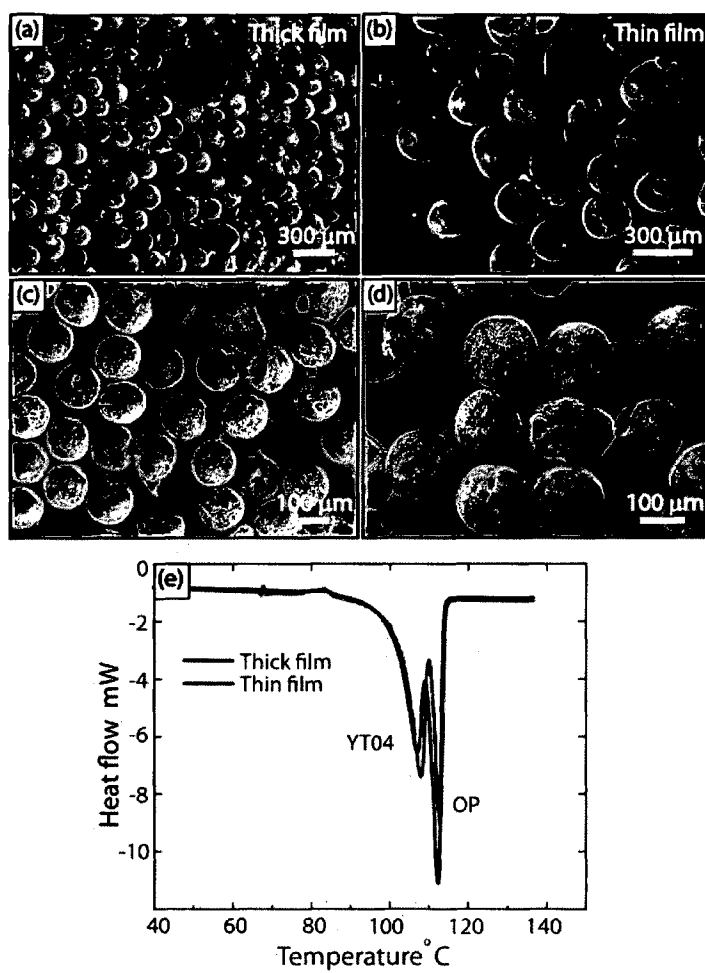


Figure 12

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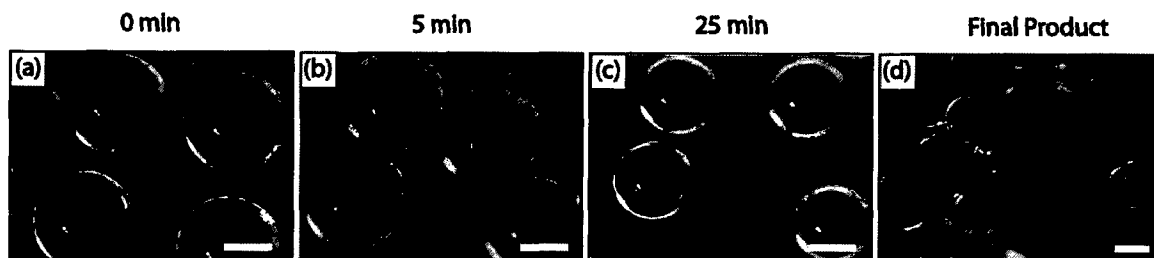


Figure 13

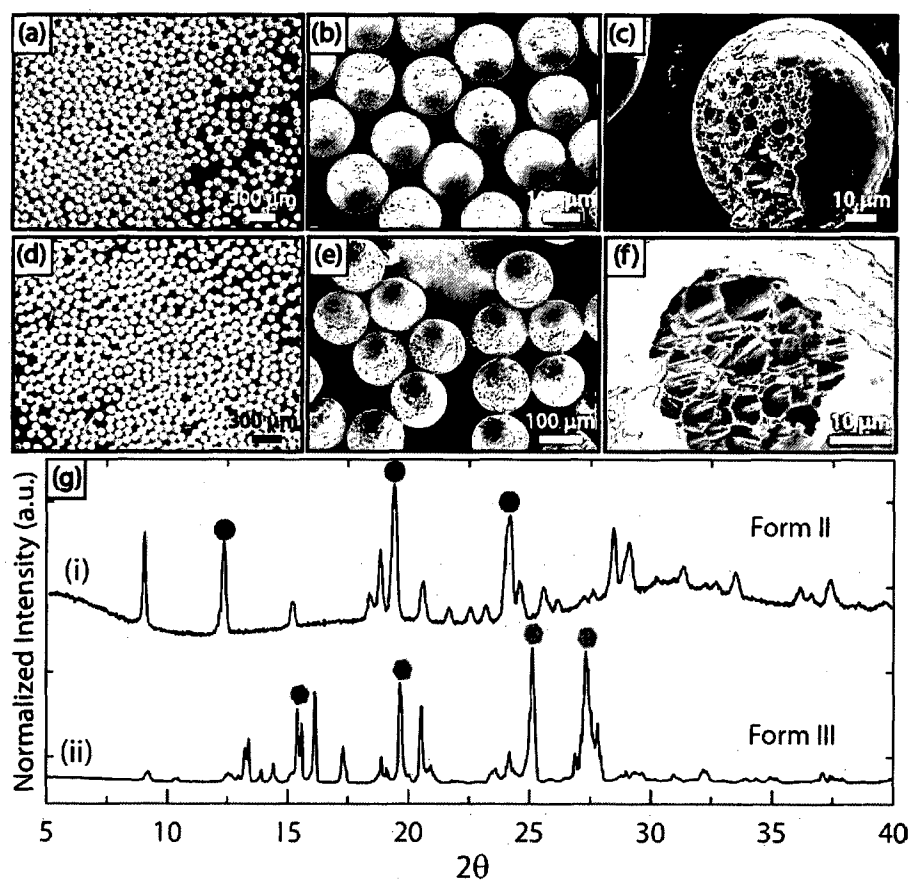


Figure 14

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/SG2014/000486

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/113 (2006.01) A61K 9/16 (2006.01)

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)

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 practicable, search terms used)

DATABASES

AUSPAT, PATENTSCOPE, GOOGLE

EPOQUE: MEDLINE, WPI, EPODOC

STN: CAPLUS, BIOSIS

SEARCH TERMS: MULTIPLE EMULSION, OIL-WATER-OIL, WATER-OIL-WATER, ACTIVE INGREDIENT, DRUG, CRYSTAL, SPHERICAL AGGLOMERATE and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 19 December 2014		Date of mailing of the international search report 19 December 2014	
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au		Authorised officer Ann Le AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832745	

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2014/000486
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	PATIL. P. et al., 'APPLICATION OF SPHERICAL AGGLOMERATION TECHNIQUE TO IMPROVE MICROMERITIC PROPERTIES AND DISSOLUTION CHARACTERISTICS OF NABUMETONE', INTERNATIONAL RESEARCH JOURNAL OF PHARMACY, 2012, Vol. 3 no.1, pages 156-162 (see abstract, pg 156-157, table 2 on page 159 and page 160). (see abstract, pg 156-157, table 2 on page 159 and page 160).	18, 19, 20, 21 and 22 1-17
X	GUPTA. M.M. et al. 'SPHERICAL CRYSTALLIZATION: A TOOL OF PARTICLE ENGINEERING FOR MAKING DRUG POWDER SUITABLE FOR DIRECT COMPRESSION', Internation Journal of Pharma. Research & Development, 2010, Issue 12 pages 1-10 (see whole document)	18 and 22
X	BHARTI. N. et al., 'Spherical Crystallization: A Novel Drug Delivery Approach', Asian Journal of Biomedical and Pharmaceutical Sciences, Available online 20 April 2013, Volume 3, Issue 18, pages 10-16 (see whole document)	18 and 22
Y	TOLDY. A.I. et al. 'Spherical Crystallization of Glycine from Monodisperse Microfluidic Emulsions', Cryst. Growth Des. 2012, vol 12, pages 3977-3982 (see whole document)	1-17

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-17 (in full) and claims 19-22 (in part) are directed to methods of producing pharmaceutical products comprising the formation of a multiple emulsion with: a pharmacologically active ingredient, excipient and carrier fluid, and heating said emulsion on a surface to form crystalized spherical agglomerates. And the crystallised spherical agglomerates that are formed specifically from said method. The feature of producing crystalized spherical agglomerates via using a multiple emulsion with: pharmacologically active ingredient, excipient and carrier fluid, and heating said emulsion on a surface to form crystalized spherical agglomerates is specific to this group of claims.
- Claim 18 (in full) and claims 19-22 (in part) are directed to a crystalized spherical agglomerate comprising at least one pharmacologically active ingredient and an excipient or carrier. The feature of a crystalized spherical agglomerate comprising at least one pharmacologically active ingredient and an excipient or carrier is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is a crystalized spherical agglomerate comprising at least one pharmacologically active ingredient.

However this feature does not make a contribution over the prior art because it is disclosed in:

D1: PATIL. P. et al., 'APPLICATION OF SPHERICAL AGGLOMERATION TECHNIQUE TO IMPROVE MICROMERITIC PROPERTIES AND DISSOLUTION CHARACTERISTICS OF NABUMETONE', INTERNATIONAL RESEARCH JOURNAL OF PHARMACY, 2012, Vol. 3 no.1, pages 156-162

Therefore in the light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.