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(52) UK CL (Edition V)

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WO 1999/059541 A1 **WO 1997/039050 A1**

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US 4404183 A

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(74) continued overleaf

(54) Abstract Title

Active/polymer coformulations

(57) A coformulation of an active (preferably pharmaceutically active, for instance a COX-2 enzyme inhibitor) substance and an oligomeric or polymeric excipient, containing at least 10 % w/w of the active, between 90 and 100 % w/w of which is amorphous. The amorphous phase is stable, with respect to the crystalline phase(s), for at least eighteen months after its preparation when stored at between 0 and 10 °C. The coformulation is preferably prepared by a SEDS™ particle formation process, in which a supercritical or near-critical fluid anti-solvent is used simultaneously both to disperse, and to extract a fluid vehicle from, a solution or suspension of a target substance.

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Fig. 1.

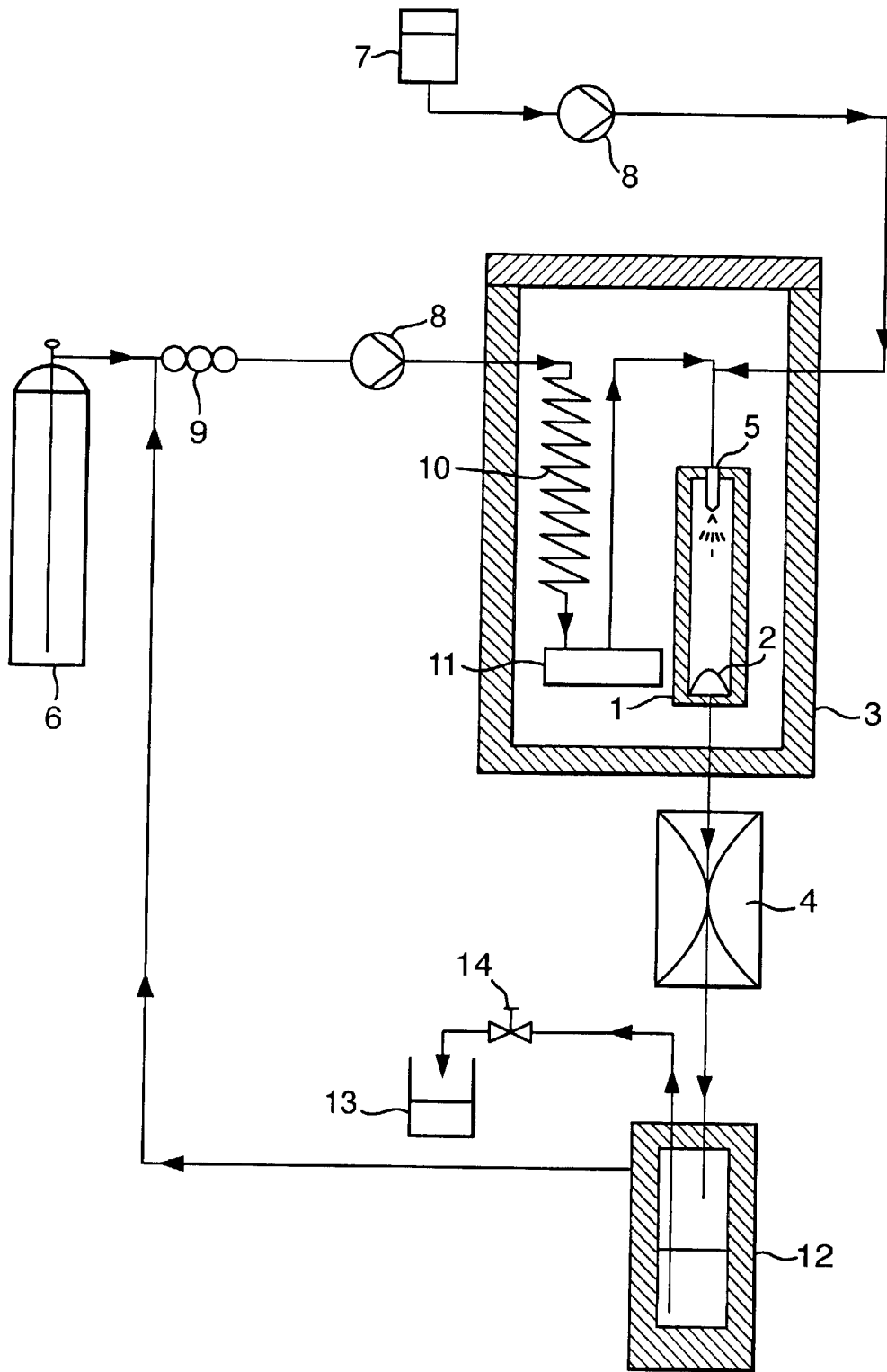


Fig.2.

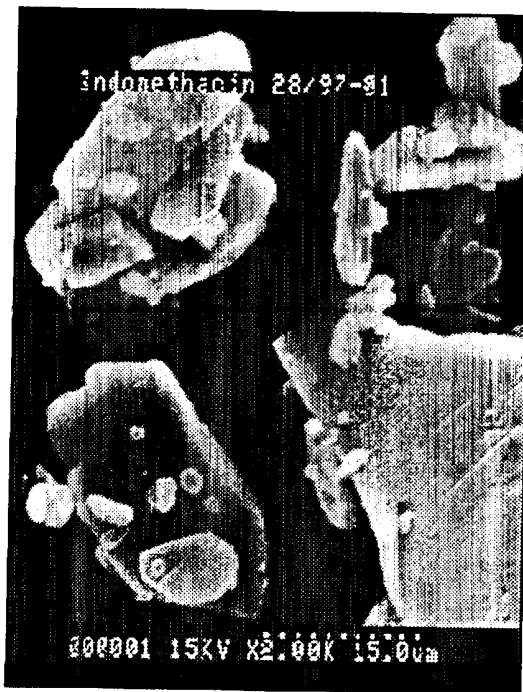


Fig.3.

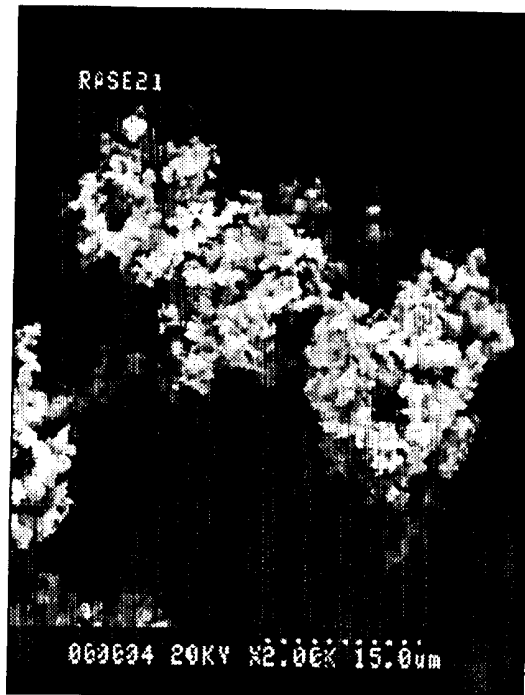


Fig.4.



Fig.5.

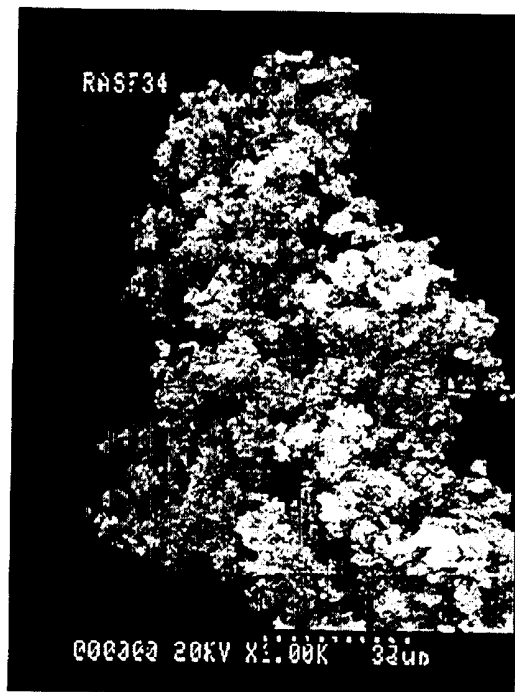


Fig.6.

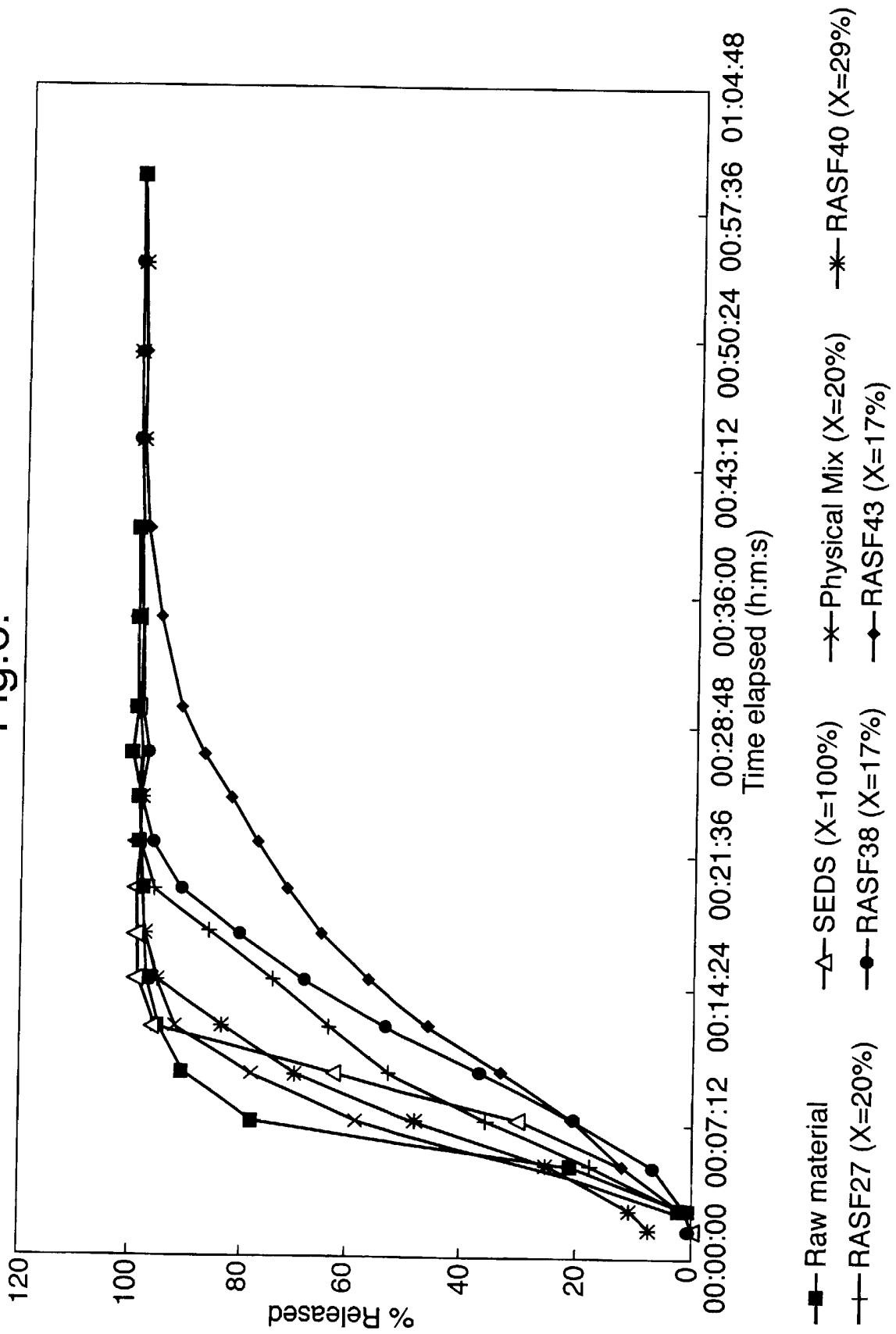


Fig.7.

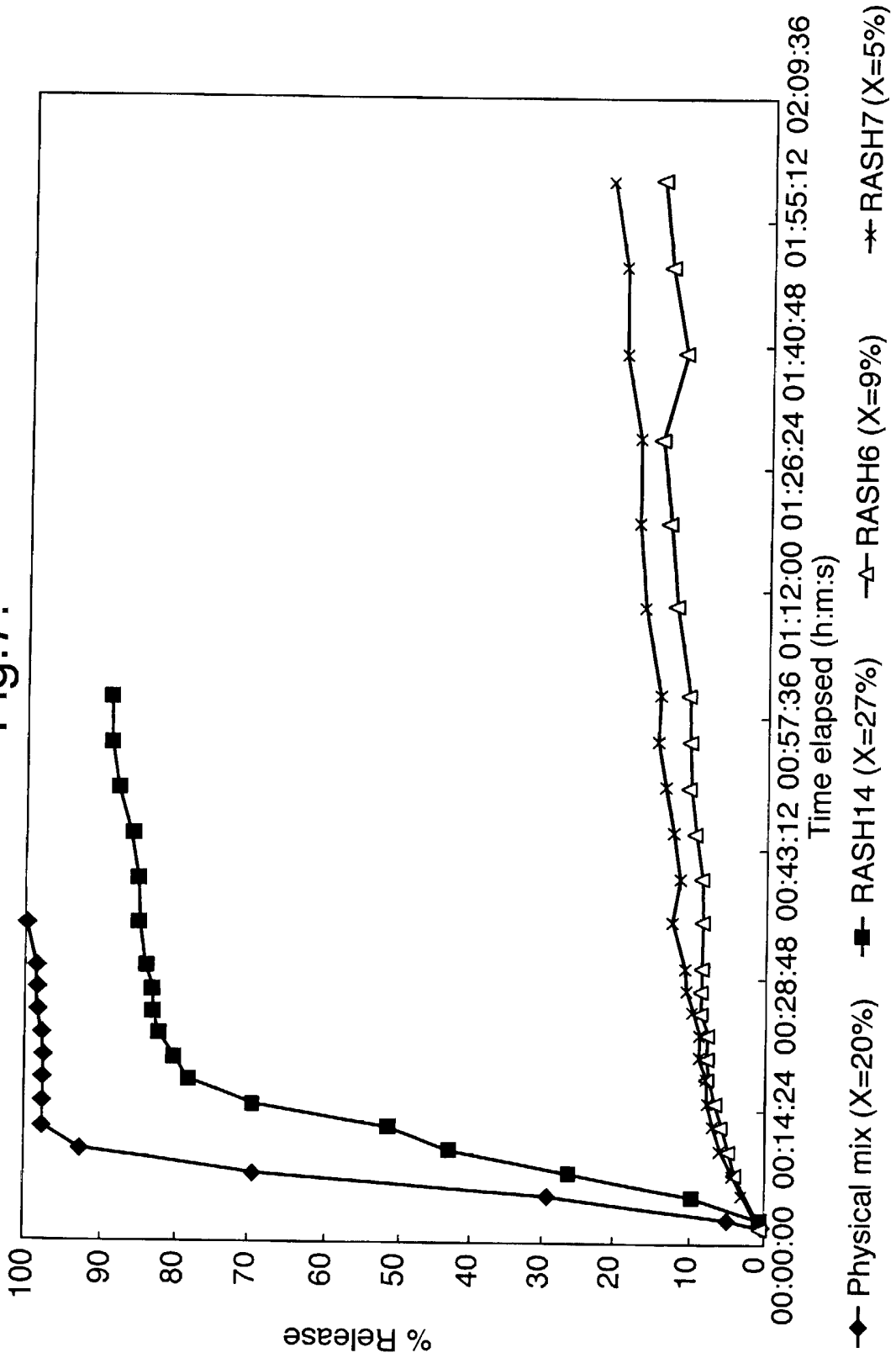


Fig.8.

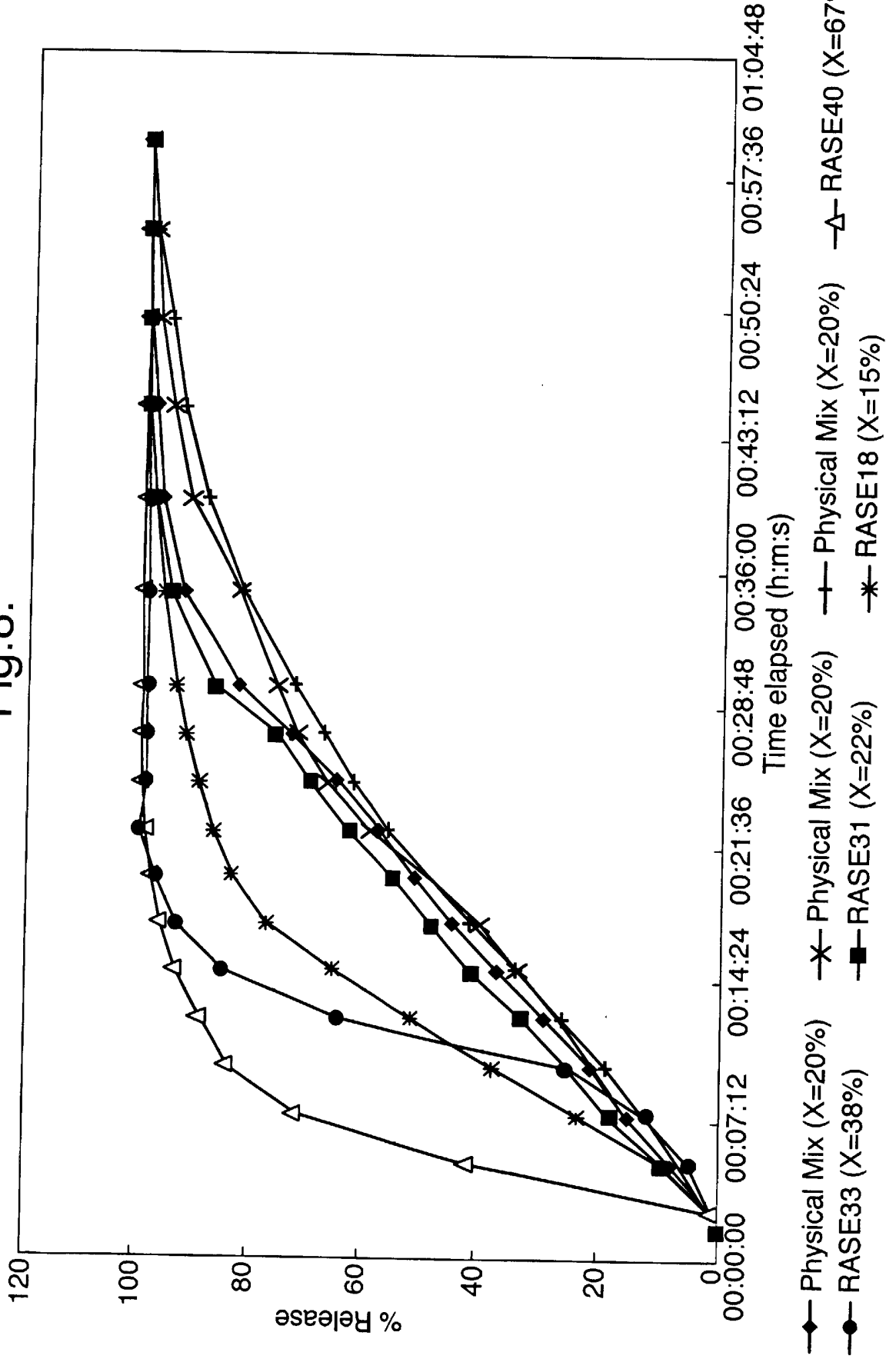


Fig.9.

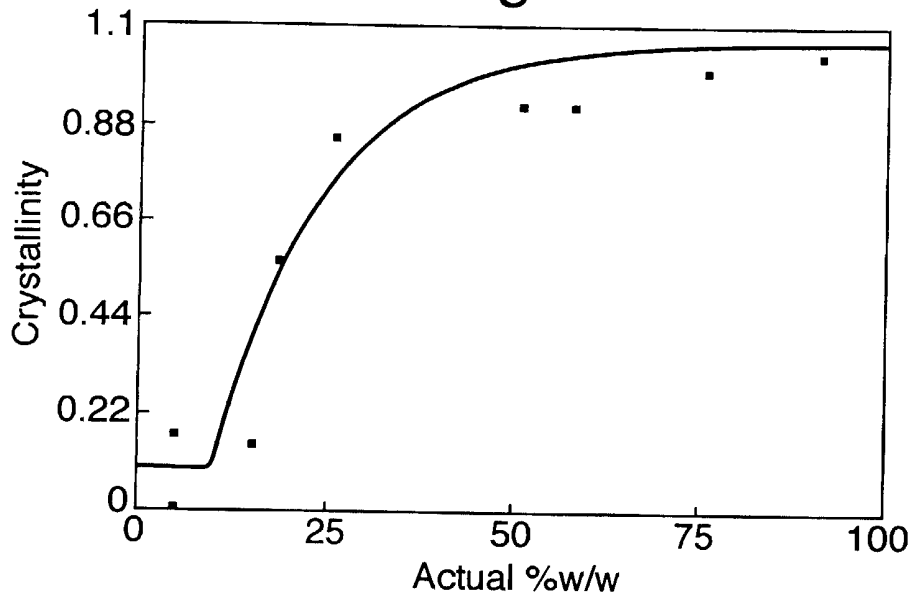


Fig.10.

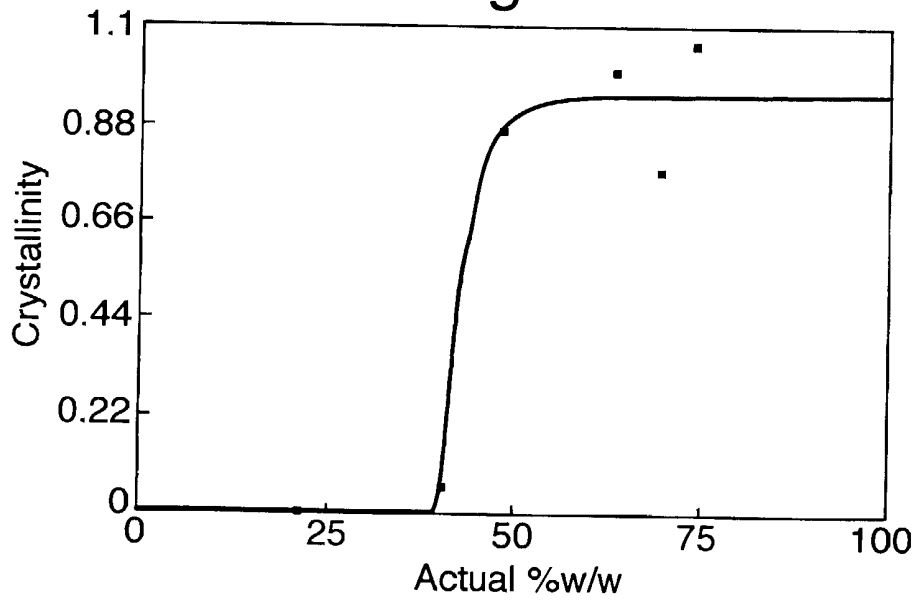


Fig.11.

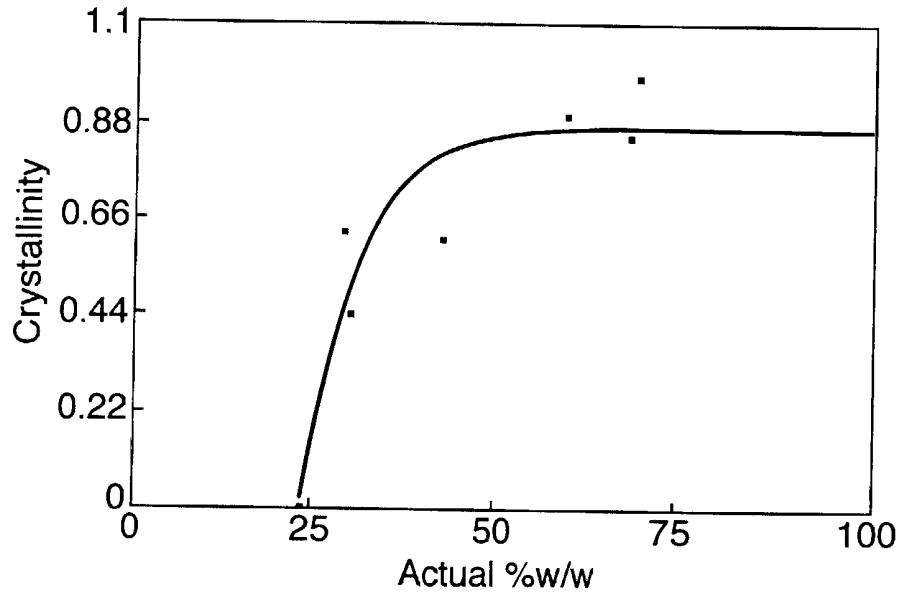


Fig.12.

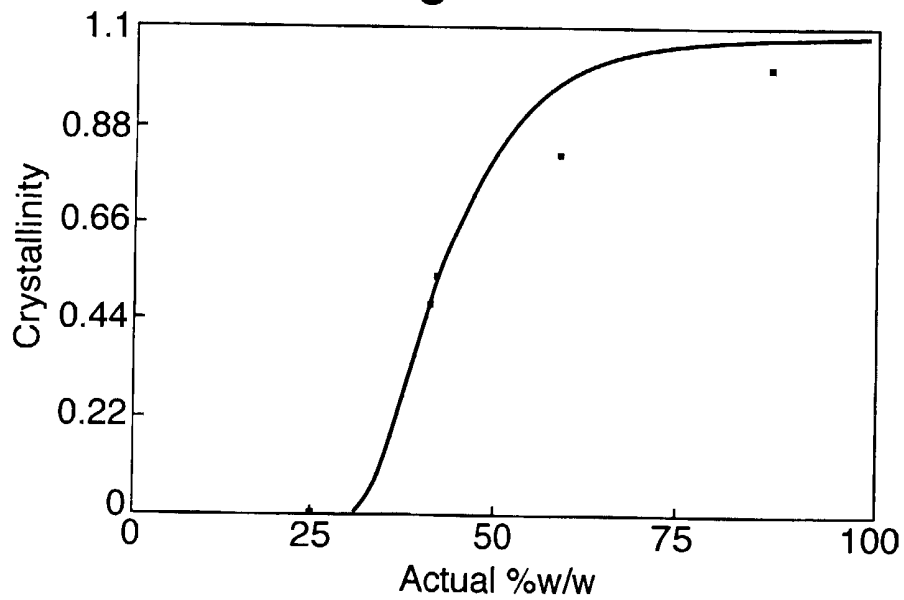


Fig.13.

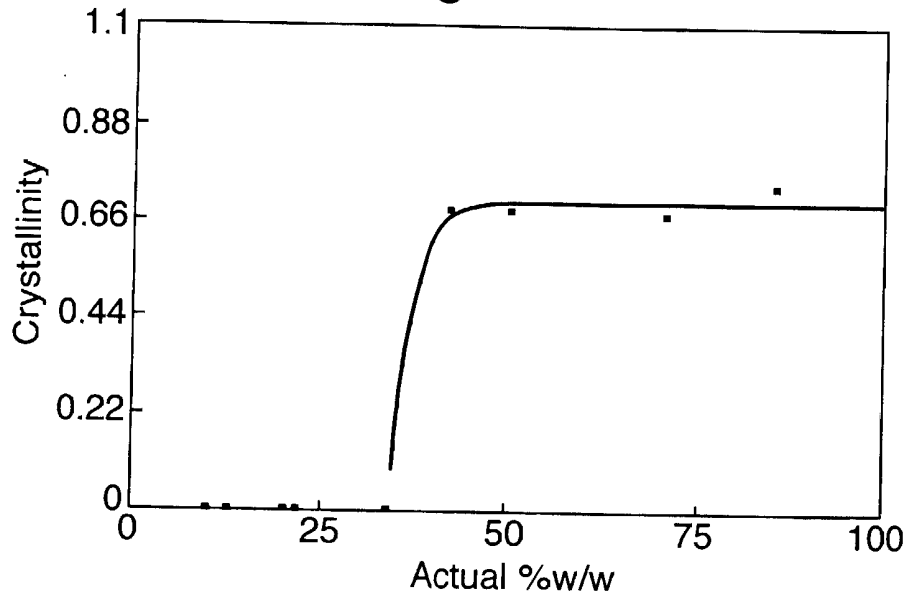


Fig.14.

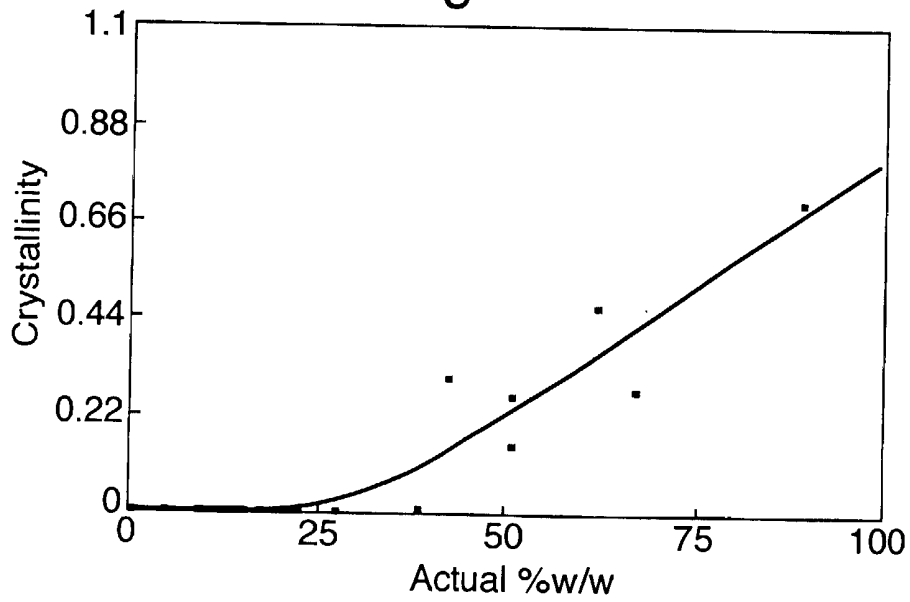


Fig.15.

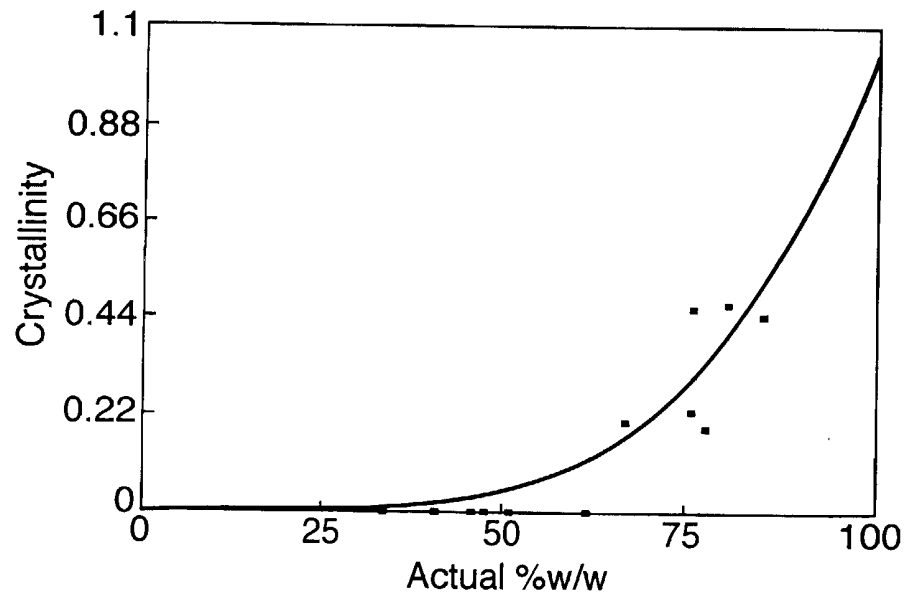


Fig.16.

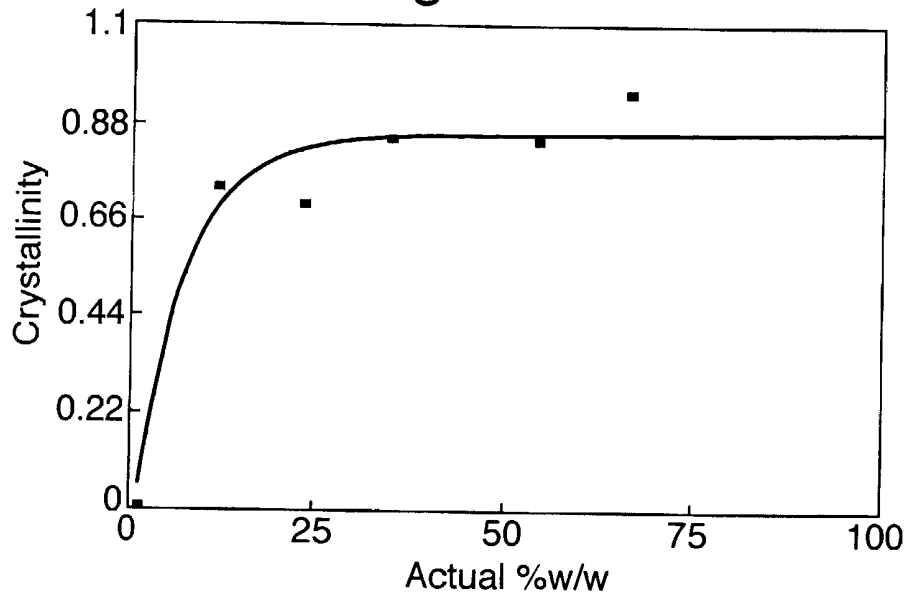


Fig.17.

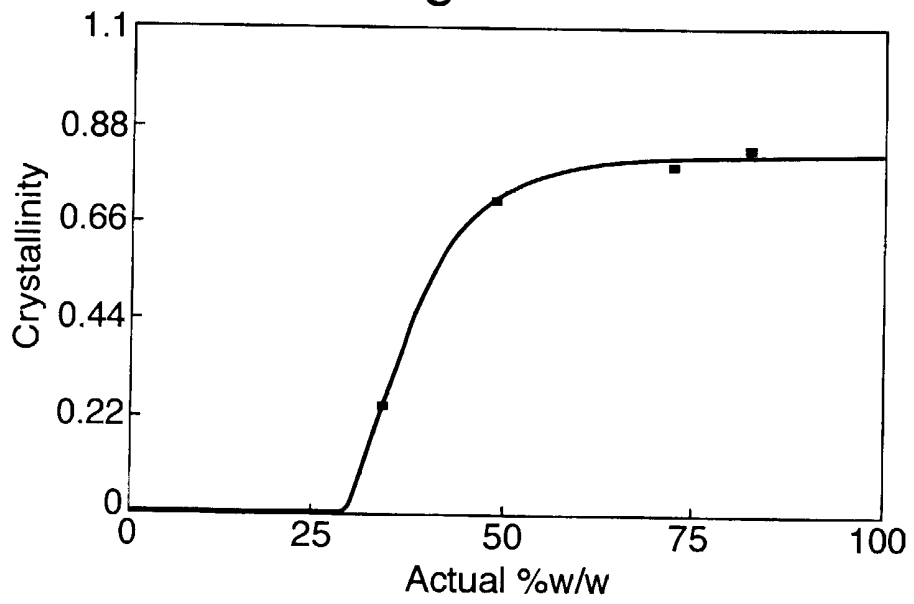


Fig.18.

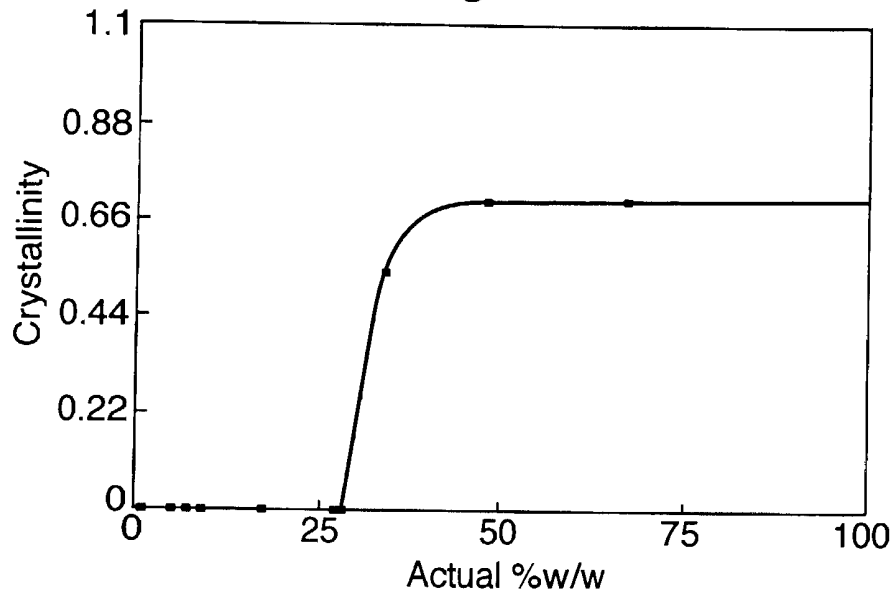


Fig.19.

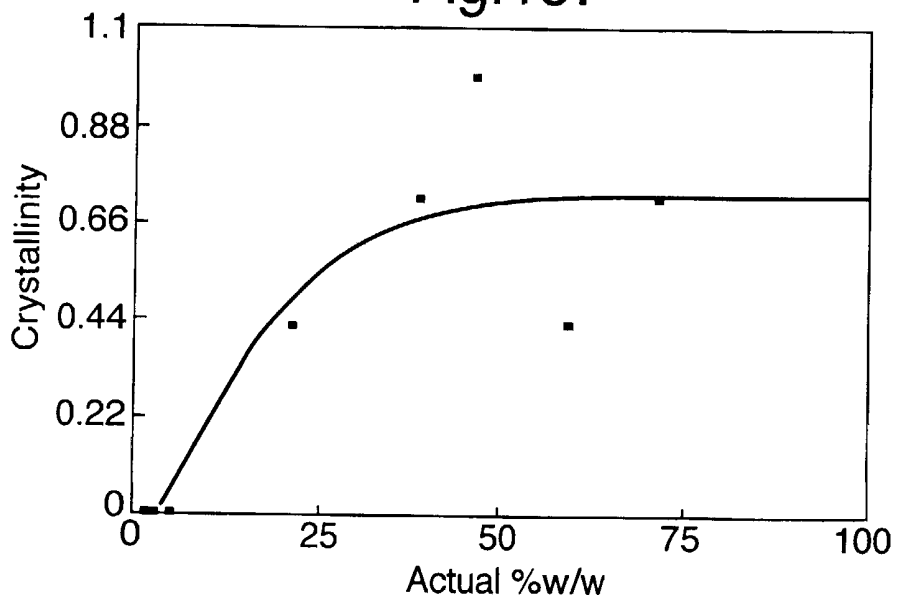


Fig.20.

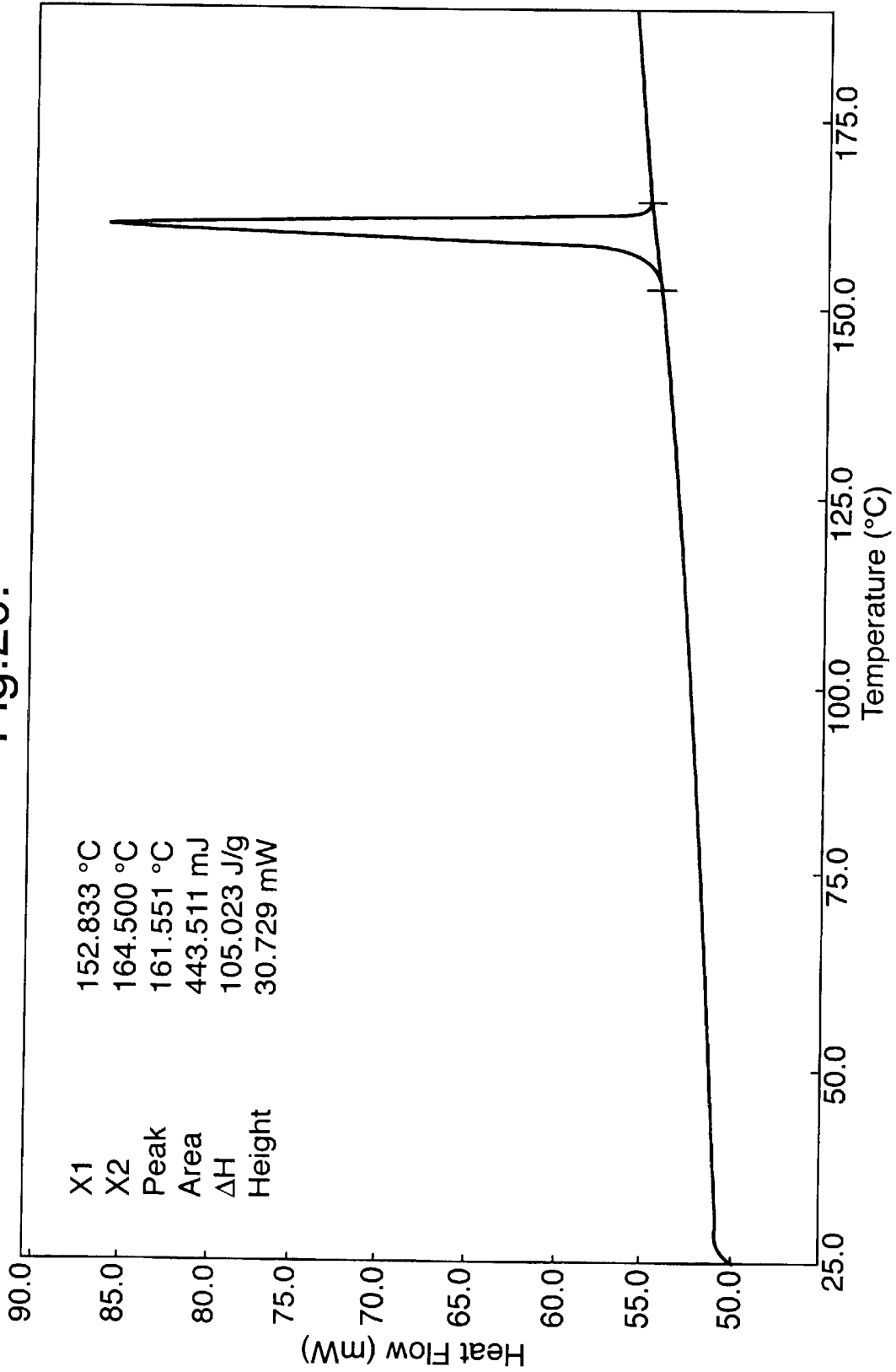


Fig.21.

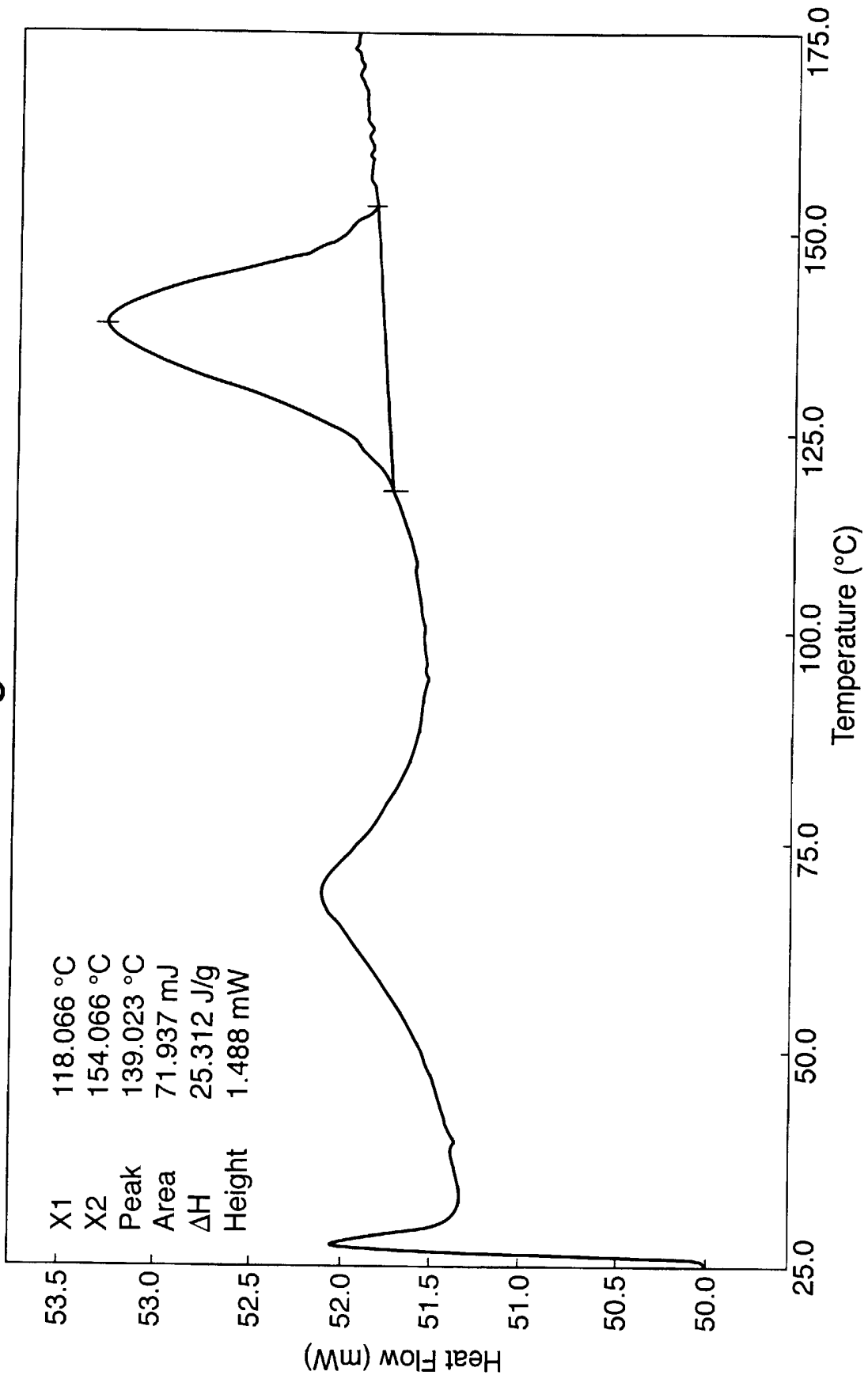
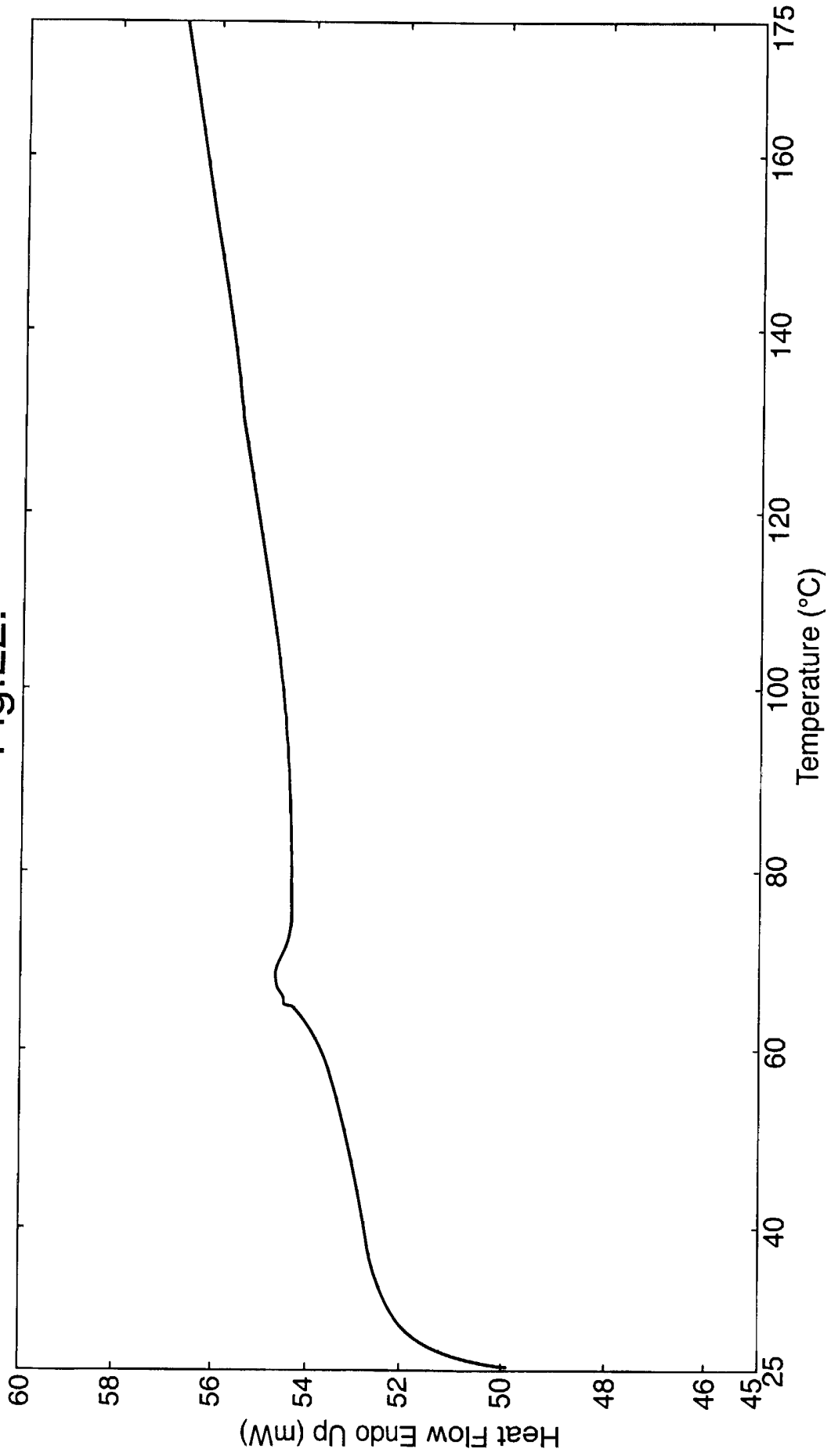


Fig.22.



(Heat from 25.00°C to 175.00°C at 10.00°C/min)

Fig.23.

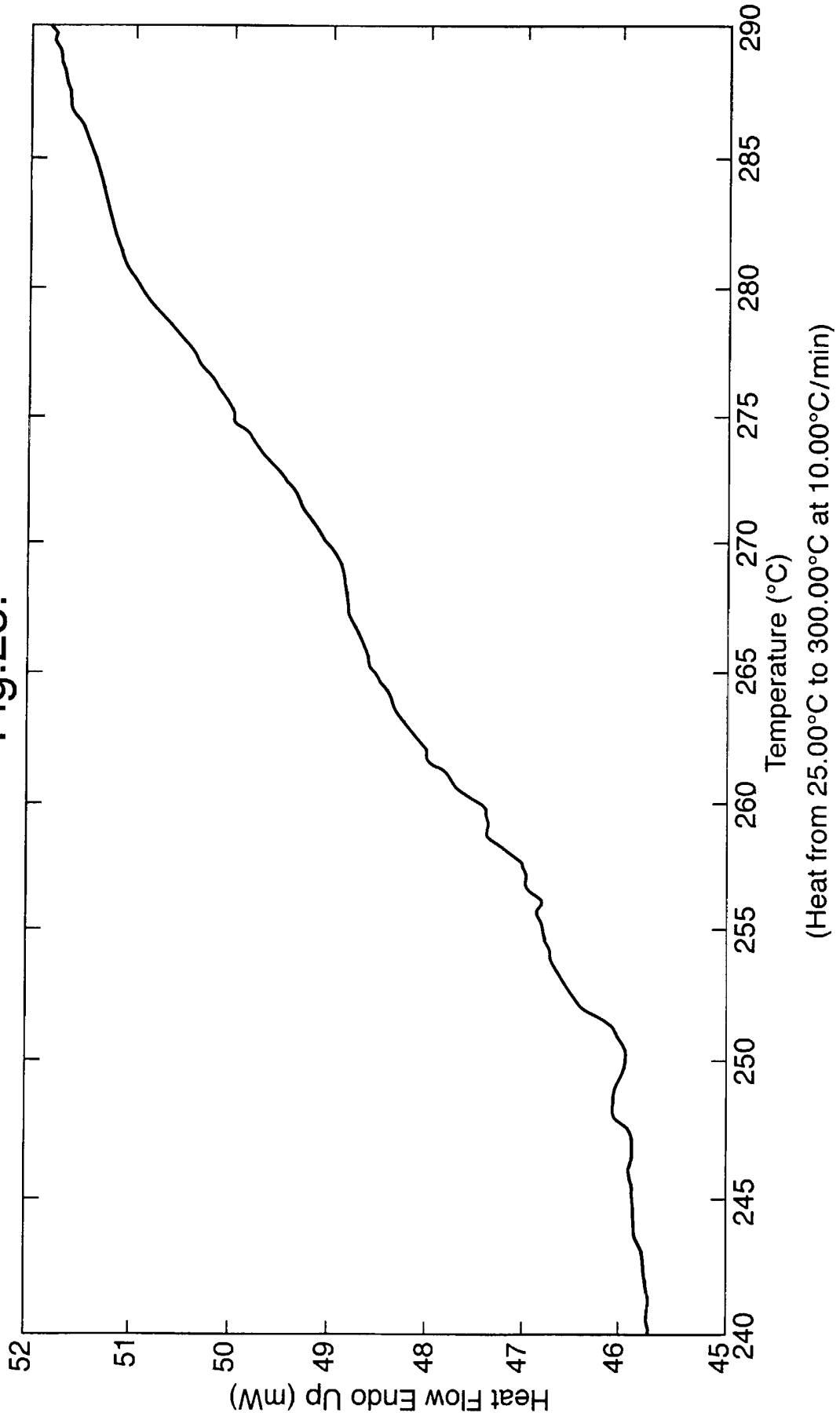
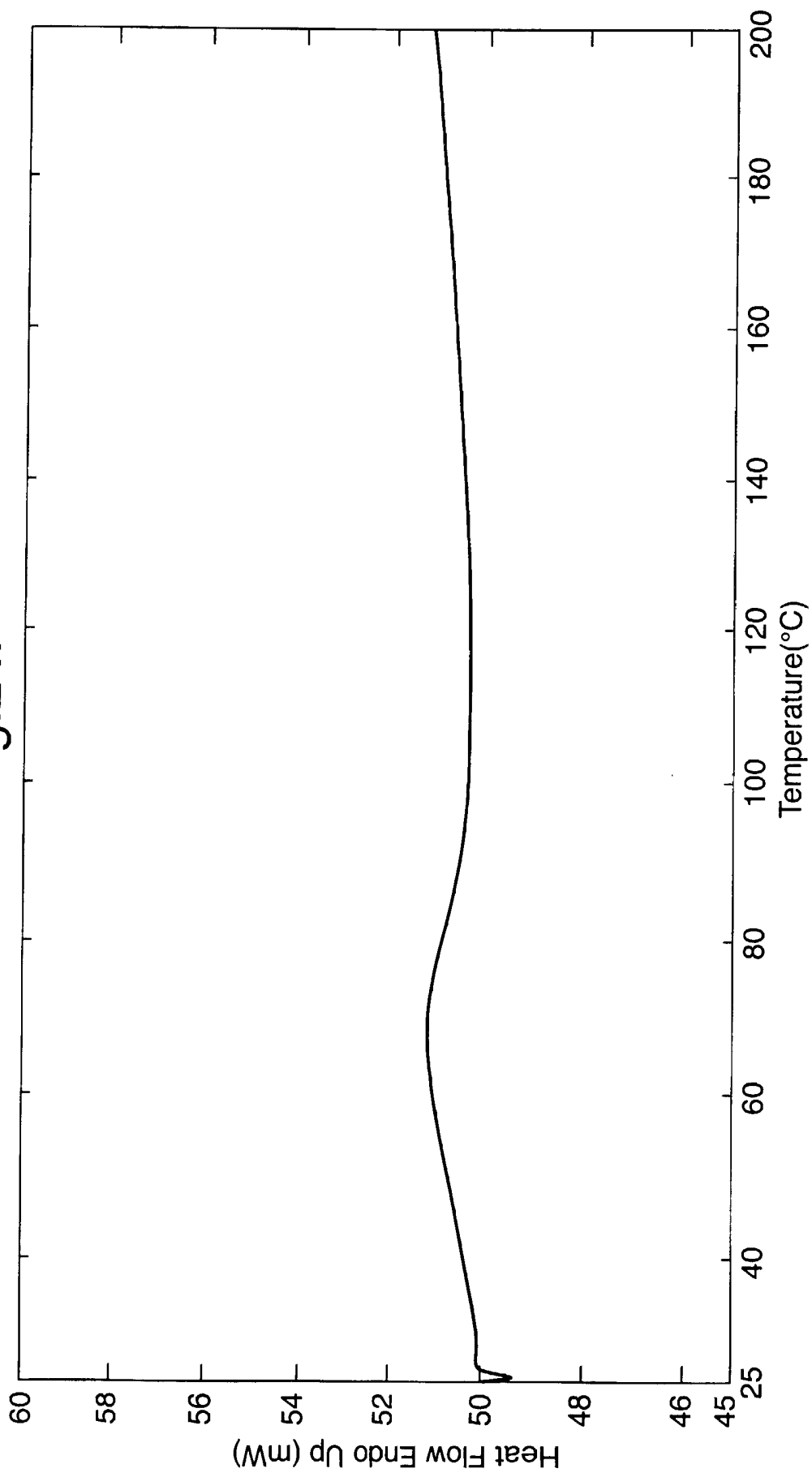


Fig.24.



(Heat from 25.00°C to 200.00°C at 20.00°C/min)

Fig.25.

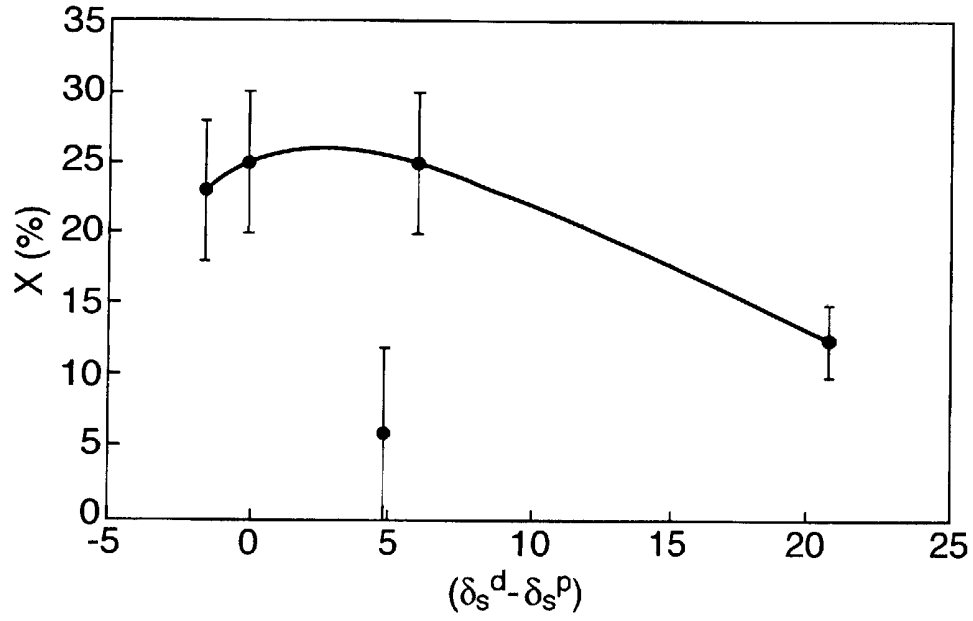


Fig.26.

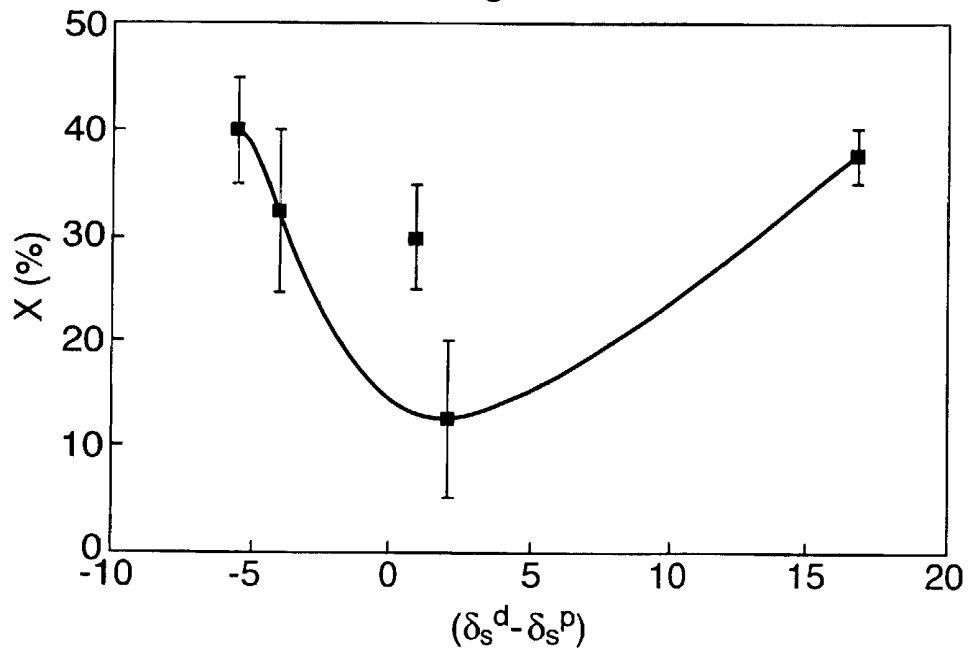


Fig.27.



Fig.28.

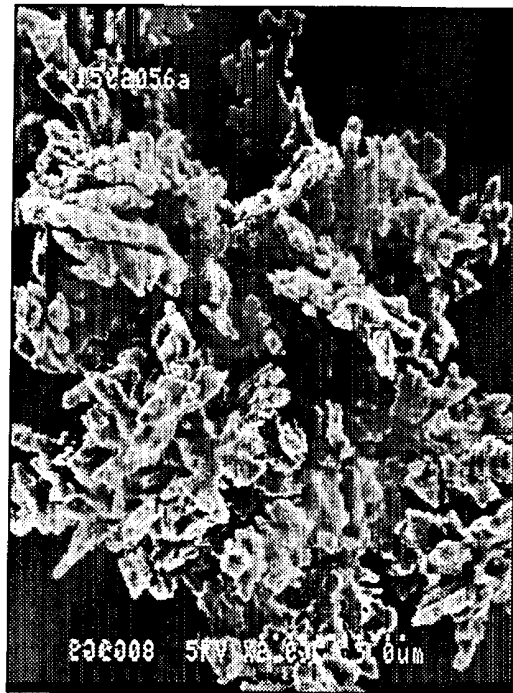


Fig.29.

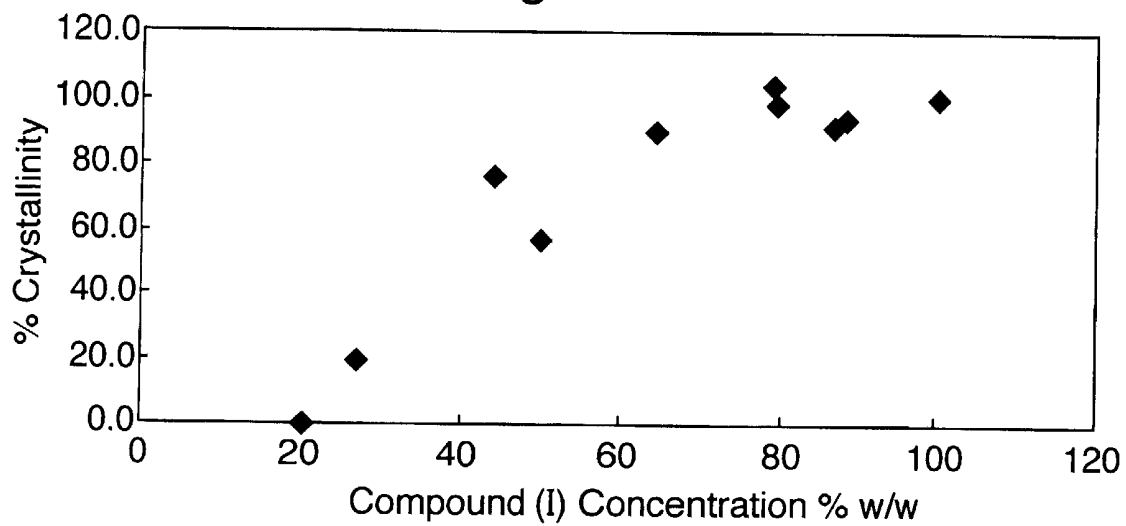


Fig.30.

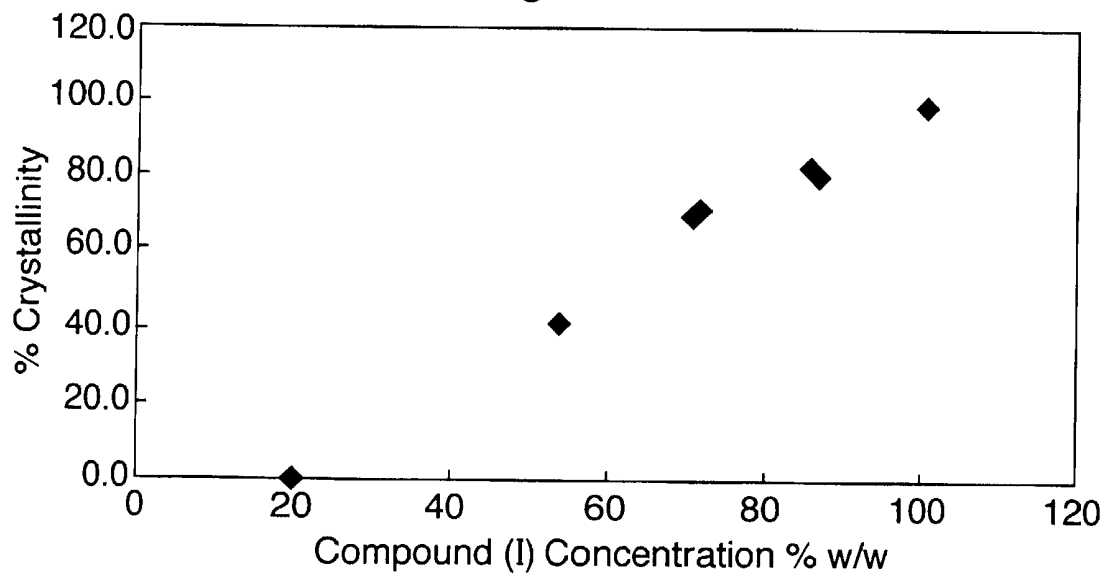
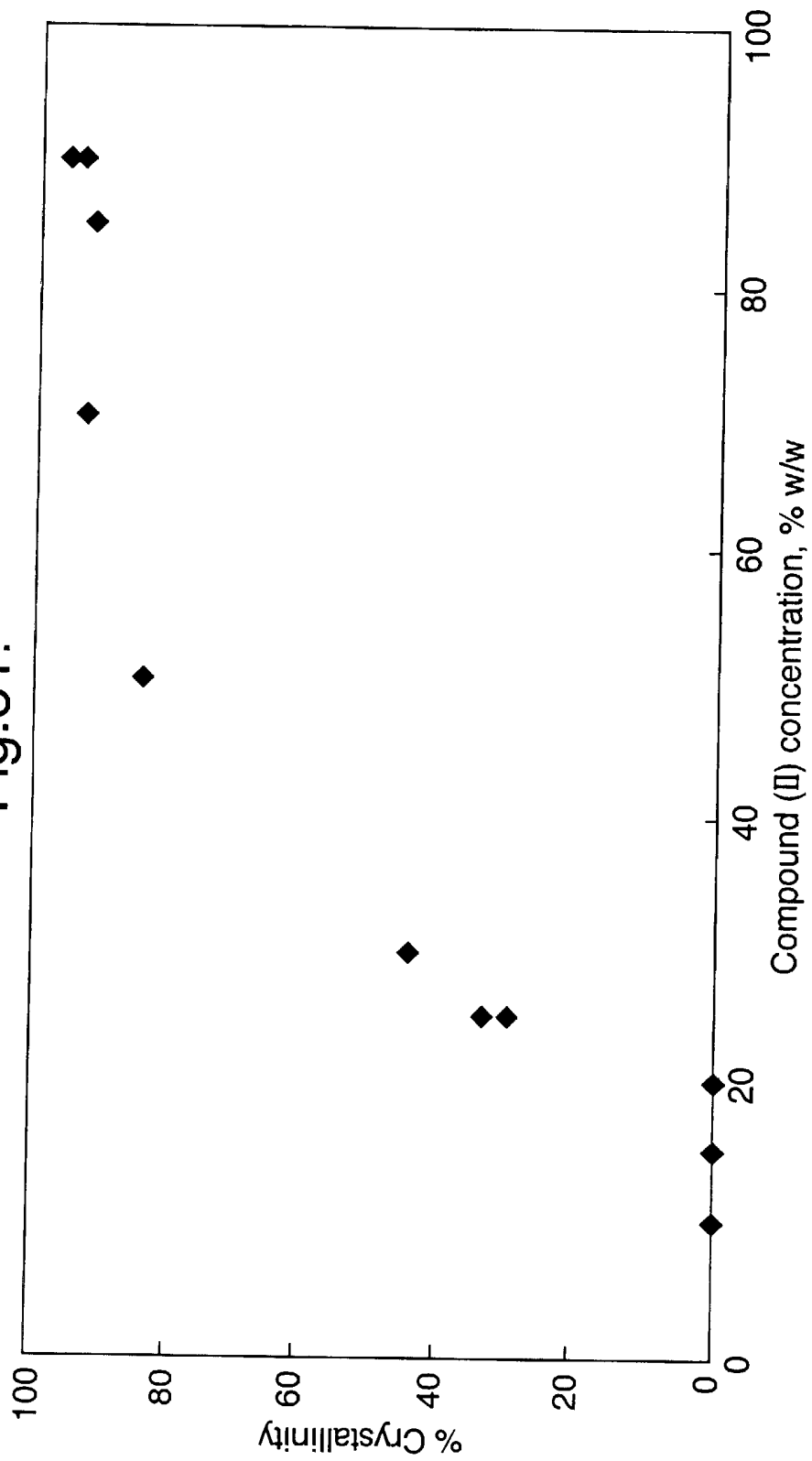


Fig.31.



Active/polymer coformulations

This invention relates to the coformulation of an active substance and an oligomeric or polymeric excipient in particulate form.

5 In particular, it relates to new applications and products of the particle formation technique known as SEDS™ (Solution Enhanced Dispersion by Supercritical fluids), which is described in WO-95/01221 and (in modified versions) in WO-96/00610, WO-98/36825, WO-99/44733 and WO-99/59710. It has been found that this technique may be used to produce novel coformulation products, especially of pharmaceutically active
10 ingredients with oligomer or polymer excipients, having advantageous physicochemical characteristics.

It is known to coformulate pharmaceuticals with polymers in order to modify their solubility profiles and hence, for example, improve the dissolution of an otherwise poorly soluble drug, or slow the dissolution of a highly soluble drug so as to control its
15 release after administration or to reduce its toxicity.

Known techniques for preparing such drug/polymer coformulations include solvent evaporation and coprecipitation, from a mixture of the drug and polymer in a common solvent system. Such approaches are often limited however by manufacturing difficulties, including environmental constraints, solvent problems such as the need for
20 multiple solvent systems and the consequent risk of phase separation, harvesting difficulties and the high levels of polymer often required. Other major limitations tend to be the poor physical properties and processing characteristics of the particulate products, which can be cohesive and difficult to handle, may contain unacceptable levels of residual solvent or non-uniform drug distributions, may suffer poor chemical and physical stability
25 and are often large particles which need to be further reduced in size before they can be processed into commercial products. It can also be difficult to control the morphology of the drug in the system, ie, the relative proportions of its crystalline and (more soluble, and hence generally preferred) amorphous phases.

There is a tendency too for amorphous phase drugs, even in the presence of
30 polymeric excipients, to be meta-stable with respect to the crystalline phase. Over extended storage periods an amorphous drug can revert to its crystalline form, with consequent changes in its dissolution profile. The degree of instability may depend on

storage temperature (in particular with respect to the glass transition temperature, T_g, of the amorphous solid) and humidity, and on relative drug and excipient concentrations. It can also be affected to some degree by the choice of excipient, and even by the manner in which the drug/polymer mixture was prepared. (See references [1] – [5].)

5 An active substance such as a drug should have stable characteristics under “normal” storage conditions, typically at room temperature and for shelf lives of at least two years. Thus for pharmaceuticals, standards are being developed which require stability for reasonable periods at 25°C. Previous attempts to coformulate drugs with excipients have generally failed to achieve an amorphous phase active with such a high
10 level of stability; in many cases recrystallisation has been observed within days, if not hours ([1] – [5], *supra*).

Matsumoto and Zografi [6] claim more recently to have stabilised the amorphous phase of the drug indomethacin, using poly vinyl pyrrolidone (PVP) as an excipient. They report storage periods of up to 20 weeks at 30°C without
15 recrystallisation, for coformulations containing up to 95% indomethacin. The properties of the system are explained in terms of hydrogen bonding between the drug and polymer, which disrupts the drug dimers associated with the crystalline phase.

The products of the present invention are coformulations of an active substance, typically a pharmaceutically active substance, with an oligomeric or polymeric material.
20 They contain significant amounts of the active substance in its amorphous form, the stability of which can be much greater than in analogous prior art coformulations. They can be used in particular in the design and manufacture of drug delivery systems, to control drug release and/or enhance bioavailability.

According to a first aspect of the present invention, there is provided a
25 coformulation of an active (preferably a pharmaceutically active) substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, wherein the amorphous phase active substance is stable, with respect to its crystalline form(s), for at least three months after its preparation when stored at between 0 and 10°C, conveniently 6°C. It is
30 preferably also stable, for the same period, when stored at 25°C.

By “stable” is meant that, over the specified time period, there is no significant change in the X-ray diffraction (XRD) pattern of the coformulation and, where

appropriate (ie, where measurable) in its differential scanning calorimetry (DSC) profile. There is preferably no significant change in the dissolution profile of the coformulated active substance. In other words, there is little or no detectable change in the amount of any crystalline form(s) present after the specified time period, preferably less than 10%,
5 more preferably less than 1%, most preferably less than 0.1% change with respect to the initial amount. Yet more preferably, the coformulation contains no detectable crystalline active substance both pre- and post-storage.

For the purpose of assessing stability, the coformulation may need to be stored in a protective atmosphere if it is particularly sensitive to humidity. Low humidity levels,
10 preferably a moisture-free environment or at least between 0 and 5% relative humidity (RH), may be achieved in conventional ways, for instance by storing in moisture resistant packaging or in a desiccator.

The amorphous phase active substance is preferably stable for at least six, more preferably nine or twelve months after its preparation, and is most preferably stable for at
15 least eighteen, twenty four or thirty six months after its preparation.

It is preferably also stable, for the periods mentioned above, when stored at 25°C and up to 60% RH. Even more preferably, it is stable when stored at 40°C, most preferably at 40°C and up to 75% RH.

A coformulation according to the invention is typically an intimate mixture of the
20 active substance dispersed in a "matrix" of the oligomer or polymer excipient, in which the solubility characteristics of the active substance are modified due to the presence of the excipient. Usually the dissolution rate of the active substance will be enhanced by coformulating it, but in some cases (for instance of use in "controlled release" drug formulations) it may be inhibited.

25 The products of the present invention, when made by a SEDS™ process, tend not only to be more stable but also generally less cohesive, more free flowing (having discrete particles) and easier to handle and process, than analogous coformulations made according to more conventional methods (in particular prior art coformulations containing amorphous or even semi-crystalline actives, which can have extremely poor
30 handling properties). The products of the invention can also be made with particle sizes down to between 0.1 and 1 µm, with relatively narrow size distributions.

Another advantage of the products of the present invention is that they can generally be prepared in the absence of additional surfactants, which many prior art formulations require as stabilisers. They also usually contain significantly reduced levels of residual solvents. Moreover, since they are precipitated rapidly from homogeneous active/excipient solutions, they tend to contain more uniform active distributions, a characteristic which is especially important when formulating low dosage drugs.

The coformulations of the invention are preferably prepared by a SEDS™ process, from one or more “target solutions” containing the active substance and/or the oligomeric or polymeric material. It has been found that SEDS™-coformulated products can contain higher levels of amorphous phase active than is often possible using prior art production methods, and more significantly that the amorphous phase is more stable, with respect to reversion to the crystalline phase, than in conventionally produced coformulations. This may be due to increased intimacy of the active substance/excipient mix, and/or to reduced levels of residual solvent, although we do not wish to be bound by these theories. It may also be the case that the SEDS™ method involves such rapid particle formation that neither the drug nor the excipient molecules are able to group themselves with any degree of order as they precipitate. The slower prior art coformulation processes, such as solvent evaporation and spray drying, may result in the formation of “microdomains”, small seed crystals that can act as nucleation sites for subsequent re-crystallisation. If a coformulation contains a significant number of such nucleation “seeds”, it will almost inevitably revert to the crystalline form on storage, often within a short period.

That SEDS™ may be used to prepare such coformulations is surprising in view of earlier literature on the process. In WO-95/01221, for example, there are examples of drug/polymer coformulations (salmeterol xinafoate and hydroxypropyl cellulose), but although these apparently demonstrate “disturbance” of crystallinity, it is clear from the appended DSC/XRD data that significant amounts of the crystalline drug are still present. Elsewhere in WO-95/01221 and WO-96/00610, there is emphasis on the ability of SEDS™ to yield crystalline materials, and most of the examples in those documents and in WO-98/36825, WO-99/44733 and WO-99/59710 show highly crystalline products when SEDS™ is used to process organic materials.

Thus, although SEDS™ is a fast precipitation process, which might otherwise have been expected to produce amorphous solids, in fact it has been shown to force the majority of organic compounds into a crystalline state. The addition of a polymer might be expected, as in Examples 10 and 16 of WO-95/01221, to reduce crystallinity levels, but it would not be predicted to achieve 100% amorphous drug systems, particularly at the relatively high drug loadings now found to be possible (in the past, high levels of polymer (80% or greater) tend to have been needed to give any significant reduction in crystallinity [2]). Moreover, the products of the invention have significantly improved long term stability (with respect to active re-crystallisation), which could not have been predicted from the prior art.

By "a SEDS™ process" is meant a particle formation technique as described in WO-95/01221, WO-96/00610, WO-98/36825, WO-99/44733 and/or WO-99/59710, in which a supercritical or near-critical (preferably supercritical) fluid anti-solvent is used simultaneously both to disperse, and to extract a fluid vehicle from, a solution or suspension of a target substance. Such a technique can provide better, and more consistent, control over the physicochemical properties of the product (particle size and size distribution, particle morphology, etc.) than has proved possible for coformulations in the past.

SEDS™ is also a one-step process; it can be used to precipitate both the active substance and the excipient at the same time, either from the same or from separate "target" solutions or suspensions, the target solution(s)/suspension(s) being co-introduced into a particle formation vessel with the anti-solvent, preferably through a coaxial nozzle with an appropriate number of concentric passages.

Other advantages of the SEDS™ process are described in prior art such as WO-95/01221, for example the ability to process sensitive active substances in a light-free and/or oxygen-free environment.

The anti-solvent used in the SEDS™ process is preferably supercritical carbon dioxide, although others (eg, as mentioned in the earlier SEDS™ literature) may be used instead or in addition.

The oligomeric (which includes dimeric) or polymeric material may be any suitable excipient for the active substance, of whatever molecular weight and whether hydrophilic - such as a polyethylene glycol, hydroxypropyl methyl cellulose (HPMC) or

polyvinyl pyrrolidone (PVP) - or hydrophobic - such as an ethyl cellulose (EC). It may be a biodegradable oligomer or polymer such as a polylactide or glycolide or a polylactide/glycolide. It may be crystalline, semi-crystalline or amorphous. It may be a homo- or co-oligomer/polymer, synthetic or naturally occurring.

5 Examples, of oligomeric or polymeric materials suitable in particular for coformulation with pharmaceutically active substances, include but are not limited to:

- 10 a) traditional “natural” source materials, their derivatives and their synthetic analogues, such as acacia, tragacanth, alginates (for instance calcium alginate), alginic acid, starch, agar, carrageenan, xanthan gum, chitosan, gelatin, guar gum, pectin, amylase or lecithin.
- b) celluloses and cellulose derivatives, such as alkyl (for instance methyl or ethyl) cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose, microcrystalline cellulose or microfine cellulose.
- 15 c) homo- and co-polymers of hydroxy acids such as lactic and glycolic acids.
- d) acrylates and their derivatives, such as the “Eudragit”™ polymers, methacrylic acids, or methacrylates such as methyl methacrylate.
- e) hydrated silicas, such as bentonite or magnesium aluminium silicate.
- f) vinyl polymers, such as polyvinyl chloride, polyvinyl alcohols, polyvinyl acetates, polyvinyl pyrrolidones, cross-linked polyvinyl pyrrolidones or
20 carboxy vinyl copolymers.
- g) polymeric surfactants, such as polyoxyethylene or polyoxypropylene, or polyalkylene oxides such as polyethylene oxides.
- h) phospholipids, such as DMPC (dimyristoyl phosphatidyl choline), DMPG
25 (dimyristoyl phosphatidyl glycerol) or DSPC (distearyl phosphatidyl choline).
- i) carbohydrates, such as lactose, dextrans, cyclodextrins or cyclodextrin derivatives.
- j) dendrimeric polymers, such as those based on 3,5 hydroxy benzyl alcohol.
- k) poly(ϵ -caprolactones), DL-lactide-co-caprolactones and their derivatives.
- 30 l) poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers, including block copolymers, such as are described in US-5,968,543 and US-5,939,453, also derivatives of such polymers, also such polymers with

incorporated esters of short chain α -hydroxy acids or glycolic-co-lactic acid copolymers.

Other suitable oligomers/polymers are listed in the literature on drug delivery systems, for example the report by Brocchini in World Markets Series "Business Briefing", Drug Delivery Supplement [7].

The oligomeric or polymeric material is preferably either a cellulosic material such as EC, HPC or HPMC (including cellulose derivatives), a vinyl polymer such as a polyvinyl pyrrolidone, a polyoxyalkylene (eg, polyoxyethylene or polyoxypropylene) polymer or copolymer or a polylactide or glycolide (including lactide/glycolide copolymers).

The active substance may be a single active substance or a mixture of two or more active substances. It may be monomeric or polymeric, organic (including organometallic) or inorganic, hydrophilic or hydrophobic. It may be a small molecule, for instance a synthetic drug like paracetamol, or a larger molecule such as a (poly)peptide, an enzyme, an antigen or other biological material. It preferably comprises a pharmaceutically active substance, although many other active substances, whatever their intended function (for instance, herbicides, pesticides, foodstuffs, nutraceuticals, etc.), may be coformulated with oligomers or polymers in accordance with the invention. In particular the active substance may be a material having low aqueous solubility, for which coformulation with an oligomeric or polymeric excipient can increase the aqueous dissolution rate and hence facilitate delivery.

In particular, it has surprisingly been found that SEDS™ may be used to coformulate an active substance with an oligomer or polymer even when their respective hydrophilicities are significantly different. Such pairings might previously have been thought incompatible for coformulation. Examples include coformulations of relatively polar actives such as paracetamol, theophylline or ascorbic acid with hydrophobic polymers such as ethyl cellulose.

For some active substances, SEDS™ enables the preparation of coformulations containing higher amorphous phase active loadings than has previously been possible. Thus, a second aspect of the present invention provides a coformulation of (i) an active substance selected from the group consisting of paracetamol, ketoprofen, indomethacin, carbamazepine, theophylline and ascorbic acid and (ii) an oligomeric or polymeric

material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, and in which the active substance represents at least 10% of the coformulation, provided that if the active substance is indomethacin or theophylline, the oligomeric or polymeric material is not polyvinyl pyrrolidone.

5 In a coformulation according to the invention, preferably between 80 and 100%, more preferably between 90 and 100% or between 95 and 100%, most preferably 100%, of the active substance is present in an amorphous as opposed to crystalline form. The active substance preferably represents at least 1%, more preferably at least 2% or 5% or 10% or 20% or 25% or 30% or 35% or 40% or 50% or 60% or 70% or 80% or 90% of
10 the system. In other words, products according to the invention can contain high loadings of the active substance, of which all or substantially all is present as a single amorphous phase.

Percentage concentrations are weight for weight unless otherwise stated.

Where the active substance is indomethacin and the excipient is ethyl cellulose
15 (EC), preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25% or 30% or 35%, of the coformulation.

Where the active substance is indomethacin and the excipient is hydroxypropyl methyl cellulose (HPMC), preferably between 95 and 100% of the indomethacin is
20 present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25% or 30% or 35% or 40%, of the coformulation.

Where the active substance is indomethacin and the excipient is polyvinyl pyrrolidone (PVP), preferably between 95 and 100% of the indomethacin is present in an
25 amorphous form, and the indomethacin represents at least 20%, more preferably at least 25% or 30% or 40% or 50% or 60% or 65% or 70%, of the coformulation.

Where the active substance is carbamazepine and the excipient is EC, preferably between 95 and 100% of the carbamazepine is present in an amorphous form, and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

30 Where the active substance is carbamazepine and the excipient is HPMC, preferably between 95 and 100% of the carbamazepine is present in an amorphous form,

and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

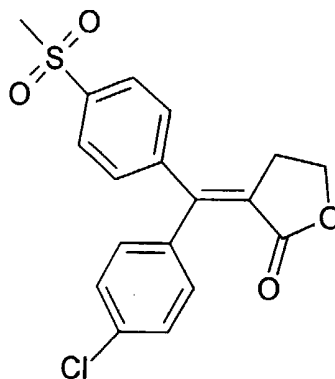
Where the active substance is theophylline and the excipient is EC, preferably between 95 and 100% of the theophylline is present in an amorphous form, and the theophylline represents at least 10%, more preferably at least 20% or 25% or 28% or 30%, of the coformulation.

Where the active substance is theophylline and the excipient is HPMC, preferably between 95 and 100% of the theophylline is present in an amorphous form, and the theophylline represents at least 1%, more preferably at least 2% or 5% or 8% or 10%, of the coformulation.

Where the active substance is ascorbic acid and the excipient is EC, preferably between 95 and 100% of the ascorbic acid is present in an amorphous form, and the ascorbic acid represents at least 1%, more preferably at least 2% or 5% or 8% or 10% or 15%, of the coformulation.

Where the active substance is ascorbic acid and the excipient is HPMC, preferably between 95 and 100% of the ascorbic acid is present in an amorphous form, and the ascorbic acid represents at least 10%, more preferably at least 20% or 25% or 30% or 35% or 40%, of the coformulation.

Where the active substance is a compound of formula (I):

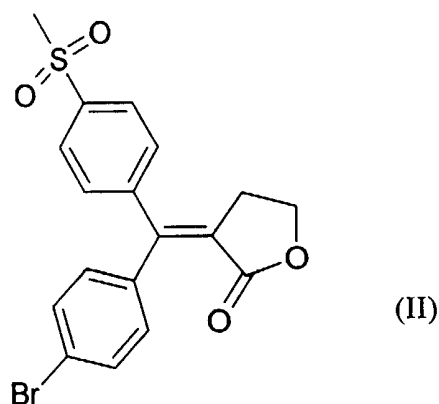


((Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulfonyl)methylene]-dihydrofuran-2-one) and the excipient is hydroxypropyl cellulose (HPC), preferably between 95 and 100% of the

Compound (I) is present in an amorphous form, and the Compound (I) represents at least 5%, more preferably at least 10% or 15% or 20% or 21%, of the coformulation.

Where the active substance is a compound of formula (I) and the excipient is a polyoxyalkylene polymer or copolymer, such as a polyoxypropylene-polyoxyethylene copolymer, preferably between 95 and 100% of the Compound (I) is present in an amorphous form, and the Compound (I) represents at least 5%, more preferably at least 10% or 15% or 20% or 24%, of the coformulation.

Where the active substance is a compound of formula (II):



10 ((Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one) and the excipient is HPC, preferably between 95 and 100% of the Compound (II) is present in an amorphous form, and the Compound (II) represents at least 5%, more preferably at least 10% or 15% or 20% or 21%, of the coformulation.

In certain cases, SEDS™ can allow formation of the amorphous phase of active substances which have (to our knowledge) previously only been prepared in their crystalline phase(s). One example of this is the preparation of paracetamol/excipient coformulations. A third aspect of the present invention therefore provides a coformulation of paracetamol and an oligomeric or polymeric material, in which between 80 and 100% of the paracetamol is present in an amorphous as opposed to crystalline form, and in which the paracetamol represents at least 1% of the coformulation.

20 In such paracetamol coformulations, preferably between 90 and 100%, more preferably between 95 and 100%, most preferably 100%, of the paracetamol is present in its amorphous form. The paracetamol preferably represents at least 2%, more preferably at least 5%, most preferably at least 8% or 10% or 20% or 25% or 28% or 30% or 35%

or 40% or 50% or 60%, of the coformulation. The oligomeric or polymeric material is preferably hydrophobic; most preferably it is an ethyl cellulose. The amorphous phase paracetamol is preferably stable, with respect to its crystalline form(s), for at least three months, preferably six months, more preferably nine or twelve or eighteen or twenty four
5 or thirty six months, after its preparation, when stored at between 0 and 10°C. It is preferably also stable, for the same period, when stored at 25°C, more preferably also at 40°C.

Aspects of the invention can also provide methods for preparing the above described coformulations, using a SEDS™ process, as well as the use of a SEDS™
10 process to prepare the coformulations. In particular, the invention provides the use of a SEDS™ process to prepare a coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, and in which the amorphous phase active substance is stable, with respect to its crystalline form(s), for at least three months after
15 its preparation when stored at between 0 and 10°C. It also provides the use of a SEDS™ process to prepare a coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form and in which the active substance represents at least 10% of the coformulation.

20 Also provided is a pharmaceutical composition containing a coformulation according to the first, second or third aspect of the invention.

The invention further provides a method for preparing a coformulation of an active (preferably a pharmaceutically active) substance and a hydrophobic oligomeric or polymeric excipient, using a SEDS™ process, in which the active substance and the
25 excipient are chosen so that the difference between their respective total specific solubility parameters, δ_s , is between -5 and +5, preferably between -2 and +2 and more preferably zero or close to zero. The excipient is preferably a cellulose or cellulose derivative such as an ethyl cellulose. The invention provides the products of such a method, and the use of a SEDS™ process in it.

30 A further aspect of the invention provides a method for preparing a coformulation of an active (preferably pharmaceutically active) substance and an oligomeric or polymeric excipient, using an anti-solvent-induced particle formation

process (preferably a SEDS™ process), wherein, under the operating conditions used, the active substance is soluble in the chosen “anti-solvent” but the excipient is not. A preferred “anti-solvent” for this method is supercritical carbon dioxide. The active substance is preferably non-polar, as for instance the drug ketoprofen, and the excipient is preferably hydrophilic, for instance HPMC. Again the invention provides the products of such a method, and the use of a SEDS™ process in it.

A yet further aspect of the invention provides a method for preparing a coformulation of indomethacin and polyvinyl pyrrolidone, using an anti-solvent-induced particle formation process, preferably a SEDS™ process. The invention provides the products of such a method, and the use of a SEDS™ process in it.

In some cases, it appears that SEDS™ can yield active/excipient mixes of sufficient intimacy that the initial “burst” of drug release, which tends to occur in the dissolution profiles of conventional systems, can be inhibited or even prevented. Certain coformulations according to the present invention can therefore be used as slow release drug formulations, providing a more uniform rate of drug release without the need for protective coatings or additional reagents. Examples include in particular coformulations of water soluble active substances such as theophylline with relatively hydrophobic excipients such as ethyl cellulose.

This finding is particularly important since the coformulation of an active substance in its amorphous phase would normally be expected to *increase* its dissolution rate. Previous attempts to inhibit dissolution have instead typically involved placing *physical* constraints on the active substance, such as by trapping its particles in a two-phase polymer matrix.

Thus, a further aspect of the invention provides a coformulation of an active (preferably a pharmaceutically active) substance and an oligomeric or polymeric excipient, comprising an intimate single-phase mixture of the active substance and the excipient in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, from which the dissolution rate of the active substance in an aqueous medium is no higher for the first 30 minutes, preferably for the first 60 or 90 or 120 minutes, than it is subsequently. Such a coformulation is again preferably prepared by a SEDS™ process.

Yet another aspect of the present invention provides a coformulation as defined above wherein the active substance is a COX-2 selective inhibitor. As used herein “COX-2 selective inhibitor” means an organic compound or pharmaceutically acceptable salt or solvate thereof which is capable of selectively inhibiting the COX-2 enzyme over the COX-1 enzyme.

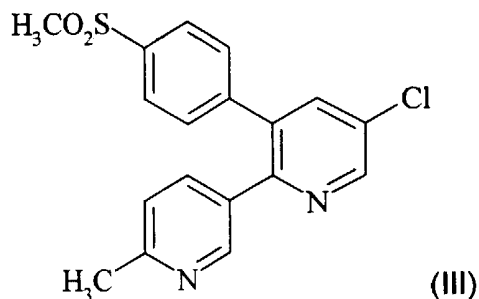
The COX-2 selective inhibitor may be a diarylheterocycle. As used herein “diarylheterocycle” means an organic compound of the diarylheterocycle genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent atoms in a five or six-membered heterocycle or both of said phenyl rings directly attached to the same carbon atom of a C₁₋₃ alkylidene linker, said C₁₋₃ alkylidene linker further attached to one atom in said five or six-membered heterocycle.

The COX-2 selective inhibitor may be a diarylfuranone. As used herein “diarylfuranone” means an organic compound of the diarylfuranone genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent carbon atoms in a furanone moiety or both of said phenyl rings directly attached to the same carbon atom of a C₁₋₃ alkylidene linker, said C₁₋₃ alkylidene linker further attached to one carbon atom in said furanone moiety.

The COX-2 selective inhibitor may alternatively be a diarylpyrazole. As used herein “diarylpyrazole” means an organic compound of the diarylpyrazole genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent atoms in a pyrazole moiety or both of said phenyl rings directly attached to the same carbon atom of a C₁₋₃ alkylidene linker, said C₁₋₃ alkylidene linker further attached to one atom in said pyrazole moiety.

The COX-2 selective inhibitor may alternatively be an arylpyridylpyridine. As used herein “arylpyridylpyridine” means an organic compound of the arylpyridylpyridine genus (or a pharmaceutically acceptable salt or solvate thereof), comprising one substituted or unsubstituted phenyl ring and one substituted or unsubstituted pyridyl moiety each directly attached to adjacent atoms in a pyridine ring or both said phenyl ring and pyridyl moiety directly attached to the same carbon atom of a C₁₋₃ alkylidene linker, said C₁₋₃ alkylidene linker further attached to one atom in said pyridine ring.

The COX-2 selective inhibitor is preferably selected from the group consisting of (Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one, (Z)-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone and the compound of Formula (III):



(Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one and (Z)-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one are COX-2 selective inhibitors useful for the treatment of acute and chronic pain. See U.S. 5,807,873 and related applications incorporated by reference herein.

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is a COX-2 selective inhibitor approved for the treatment of osteoarthritis and rheumatoid arthritis and is marketed in the U.S. under the tradename CELEBREX[®] (celecoxib). See, e.g., U.S. 5,466,823 and U.S. 5,563,165, incorporated by reference herein.

4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone is a COX-2 selective inhibitor approved for the treatment of osteoarthritis, treatment of primary dysmenorrhea and management of acute pain and is marketed in the U.S. under the tradename VIOXX[®] (rofecoxib). See e.g., U.S. 5,474, 995, incorporated by reference herein.

The compound of Formula (II) is a COX-2 selective inhibitor being developed for the treatment of acute and chronic pain. See WO 99/15503 and related applications incorporated by reference herein.

These and other COX-2 selective inhibitors falling within the biarylheterocycle genus or more particularly biarylfuranone and biarylpyrazole genera appear to have low aqueous solubility, suggesting suboptimal bioavailability. Their coformulation with

oligomeric or polymeric excipients, in accordance with the present invention, can be expected to enhance their bioavailability

The present invention will now be described, by way of example only, with reference to the following experiments and the accompanying figures, of which:

5 Figure 1 is a schematic illustration of apparatus usable to carry out methods, and obtain products, according to the invention;

Figures 2-5 are SEM (scanning electron microscope) photographs of some of the starting materials and products of Example I below;

10 Figures 6 to 8 show dissolution profiles for three of the systems investigated in Example I;

Figures 9 to 19 show plots of crystallinity against drug weight fraction for the systems investigated in Example I;

15 Figures 20 to 24 are DSC (differential scanning calorimetry) traces for, respectively, crystalline indomethacin and a number of coformulations prepared in Example I, including after 24 months' storage;

Figures 25 and 26 are plots of $(\delta_s^d - \delta_s^p)$ against X (see Table 10 below) for some of the systems investigated in Example I;

Figures 27 and 28 are SEM photographs of some of the products of Example II;

20 Figures 29 and 30 are plots of crystallinity against drug weight fraction for the products of Example II; and

Figure 31 is a plot of crystallinity against drug weight fraction for the products of Example III.

25

Examples

The following experiments demonstrate the use of a SEDS™ process to coformulate various drugs and polymers in accordance with the present invention. The physicochemical characteristics of the products, in particular the degree (if any) of drug crystallinity, the stability of the amorphous phase and the relative concentrations of the

30

drug and the polymer (ie, the drug "loading"), were tested and where possible manipulated by altering the operating conditions and solvents present.

The drugs were chosen to cover a broad range of polarities, including the highly apolar ketoprofen and, in ascending order of polarity, indomethacin, carbamazepine, paracetamol, theophylline and ascorbic acid. These drugs were coformulated with both hydrophobic (EC) and hydrophilic (HPMC) polymers.

Ketoprofen was on the whole too soluble in supercritical carbon dioxide (the chosen anti-solvent) to produce meaningful results, even under moderate processing conditions. Surprisingly, however, it could be retained to a degree when coformulated with HPMC.

In an additional investigation, PVP was coformulated with the poorly water soluble drug indomethacin.

Further experiments (Examples II and III) coformulated two cyclo-oxygenase-2 (COX-2) enzyme inhibitors with HPC and, in the case of Example II, a polyoxypropylene-polyoxyethylene block co-polymer, Pluronic™ F87.

In Example IV, the drug glibenclamide was coformulated with 75/25 DL-lactide-co-caprolactone.

20

Experimental details

The method used was essentially the SEDS™ process described in WO-95/01221. It is envisaged that modifications of SEDS™, as described in that document, WO-96/00610, WO-98/36825, WO-99/44733 and/or WO-99/59710, could be used to similar effect.

The apparatus is shown schematically in Figure 1, in which 1 is a particle formation vessel; 2 is a device (eg, a filter) for retaining the particles formed; 3 is an oven and 4 a back pressure regulator; and 5 is a nozzle for co-introducing, into the vessel 1, a supercritical anti-solvent from source 6 and a target solution from source 7. The items labelled 8 are pumps; 9 is a cooler, 10 a heat exchanger and 11 a pulse dampener. A recycling system 12 allows solvent recovery at 13 (via needle valve 14), whilst returning carbon dioxide to the cooler 9 for re-use.

The nozzles employed at 5 were two-passage coaxial nozzles of the general form depicted in Figure 3 of WO-95/01221, typical dimensions being as described in that document. Supercritical carbon dioxide was the chosen anti-solvent, introduced into a 50 ml particle formation vessel via the inner nozzle passage. The "target solution", ie, a solution of the drug or polymer, or more typically of both together, was introduced through the outer nozzle passage.

In situ mixing of separate drug and polymer solutions could have been achieved using a nozzle having three or more coaxial passages, allowing the two solutions to meet at the nozzle outlet.

Selection of a suitable solvent depended on the properties of both drug and polymer, but particularly on the latter because of the potential difficulties of processing polymeric solutions and dispersions. Polymeric dispersions can exhibit very high viscosities, even when dilute, whereas in "good" solvents the polymer matrix will relax and loosen, allowing both a greater degree of interaction and a lower viscosity, important respectively for the production of intimate drug/polymer mixtures and for the processing requirements of SEDS™ [8].

The analytical techniques employed in the experiments were as follows:

Scanning electron microscopy (SEM)

Particle size and morphology were investigated using an Hitachi™ S-520 scanning electron microscope (Hitachi, Japan). Aluminium stubs containing a small quantity of sample particulate were sputter-coated with a gold layer ~300Å thick and viewed and photographed under varying magnifications.

Differential scanning calorimetry (DSC)

This technique was used to measure sample crystallinity, given that the lower the order of the crystal lattice the less energy required for melting the sample. DSC was used to determine thermal profiles, to monitor the latent heat of fusion (ΔH_f), to identify any phase or polymorphic transitions and desolvation phenomena, and to determine melting points and glass transition temperatures.

A Perkin-Elmer™ DSC 7 (Perkin-Elmer Ltd, UK) was used. 1-5 mg samples were examined in pierced, crimped aluminium pans, under an atmosphere of nitrogen.

The analytical temperature range depended on the drug investigated. Theophylline sublimed just above the melting point, causing difficulties in measuring endotherm peak size. This problem was overcome by adopting a sealed pan method.

Relationships between product crystallinity and weight fraction of drug in the product were also investigated. Crystallinity was derived from the latent heat of fusion (ΔH_f), using the equation:

$$\% \text{ crystallinity} = \frac{\Delta H_f \text{ (coformulation)}}{\Delta H_f \text{ (100\% crystalline)}} \times \frac{100}{\text{Weight fraction of drug}}$$

10

X-ray diffraction (XRD)

This was also used to give a qualitative assessment of crystallinity. Samples were analysed on a D5000 XRD (Siemens, Germany) between 5 and 30° 2 θ .

15 UV spectrophotometry (Example I)

The weight fraction of drug in samples was measured with an Ultrospec™ 4000 spectrophotometer (Pharmacia Biotech, Cambridge, England), from reconstituted solutions of the samples. The absorbance of the polymers was negligible at the wavelengths used.

20

Dissolution test (Example I)

Dissolution testing was carried out using a stirred vessel technique and UV analysis. The apparatus consisted of a 1 litre round-bottomed vessel maintained at around 37°C in a water bath, stirred by paddle at 60 rpm. The medium was circulated using a peristaltic pump through a 10 mm flow cell. UV readings were taken every 30 seconds using an Ultrospec™ 4000 spectrophotometer (*supra*) and analysed for up to between 30 and 60 minutes.

Three systems were analysed: paracetamol/HPMC, theophylline/EC and indomethacin/HPMC. The conditions for the individual systems were:-

30 Paracetamol/HPMC: 247 nm, 37±0.5°C, 500 ml distilled water.

Theophylline/EC: 273 nm, 37±1.0°C, 350 ml distilled water.

Indomethacin/HPMC: 235 nm, 37±0.5°C, 400 ml pH 7.00±0.02 0.05M
NaH₂PO₄ aqueous buffer.

A different medium was needed for the indomethacin system due to the drug's
5 poor water solubility. The chosen medium provided a compromise between observing
drug release within a practical time span and allowing sufficient discrimination to identify
true dispersions.

The release profile characteristics were compared with physical mixes to give an
indication of polymer/drug interaction and possible complex formation. The physical
10 mixes were prepared from pre-micronised drug ground (for 1 minute in a pestle and
mortar) together with the designated polymer. Samples were transferred to hard gelatine
capsules (size 4 clear/clear, weighted by 60:40 tin/lead wire coils) for analysis. The
capsules gave no significant absorbance in the analysis region.

15 **Aerosizer-Aerodisperser™ particle size analyser (Example II)**

Particle size analysis was carried out using a time-of-flight analyser (Aerosizer™
with Aerodisperser™, TSI Inc, USA). This instrument is capable of sizing dry powder
samples over the range 0.2-700 µm. The powder is dispersed in air and the air/particle
suspension is expanded through a nozzle into a partial vacuum. The air/particle stream
20 accelerates through a measuring region, where the particles pass through two consecutive
laser beams. Smaller particles experience a greater acceleration than larger ones and
hence move more rapidly between the two beams. From measurements of the time taken
to travel between the beams and the known density of the material, the Aerosizer™
software calculates the mean size distribution of particles present in the sample. The data
25 obtained complements SEM observations. No sample preparation is required.

HELOS Sympatec™ particle size analyser (Examples II and III)

This instrument uses laser diffraction to determine particle size distributions of
solid particulate materials. It is capable of measuring across the particle size range 0.1-
30 8750 µm. A dry powder sample is introduced, via a vibrating conveyor feeder, into a dry
dispersing unit. Here the powder and any agglomerates present are fully dispersed in air.
The dispersion of single particles is then propelled by compressed air and fed through the

measuring zone, where the particle stream interacts with a monochromatic high energy beam from a He-Ne laser. The laser light is diffracted and detected by a multicomponent photodetector. The intensity of the diffracted light is then converted into an electrical signal, which is used to calculate the particle size distribution. Again, the data
5 complements SEM observations. No sample preparation is required.

High performance liquid chromatography (HPLC) (Examples II and III)

Compound (I) and (II) loadings were determined by HPLC using UV detection. An isocratic method was followed, employing a single mobile phase (0.1% phosphoric
10 acid:acetonitrile (62:38 v/v), degassed for 20 minutes before use).

Quantification was by external standardisation. Two stock solutions of Compound (I) with concentrations of 500 μgml^{-1} were prepared in the mobile phase. Appropriate volumes were alternately taken and diluted with mobile phase to produce a set of standard calibrants in the nominal range 2 to 10 μgml^{-1} . Aliquots of prepared
15 sample solutions, diluted if necessary, were then submitted to HPLC analysis, interspersed with the calibrant solutions. Using the following nominal conditions a chromatogram was generated.

| | |
|----------------------|---|
| Pump: | Capable of delivering 1.1 mlmin^{-1} |
| Sample size: | 20 μl (ATI Unicam™ autosampler) |
| Column: | 150 x 4.6 mm, ZORBAX™, RX-C8, 5 μm |
| Column temperature: | 30°C |
| Flow rate: | 1.1 mlmin^{-1} |
| Detector/wavelength: | Jasco™ UV-975 / 220 nm |
| Peak response: | Area |
| Cycle time: | Typically 17 minutes |

20 All peak area measurements and calculations were performed using Borwin™ chromatography software Version 1.22.01.

Example I

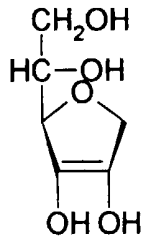
The materials used in this series of experiments were as follows; their polarities and solubility parameters are listed in Table 1 below.

| <u>Material</u> | <u>Supplier</u> | <u>Grade</u> |
|-------------------------------------|--|-------------------------------|
| L-ascorbic acid | Sigma Chemical Co, St Louis, Missouri, USA | General laboratory reagent |
| Carbamazepine | Sigma | Ditto |
| Indomethacin | Sigma | Ditto |
| Ketoprofen | Sigma | Ditto |
| Paracetamol | Sigma | 99.0%+ |
| Theophylline | Sigma | Anhyd. 99%+ |
| EC | Colorcon, Dartford, England | 7 cps |
| HPMC | Shinetsu Chemical Company, Tokyo, Japan | 3 cps (603) |
| PVP | Sigma | Av. mol. wt. 10,000 |
| Dichloromethane | BDH (Merck), Poole, England | AnalaR 99.5%+ |
| Chloroform | BDH | AnalaR 99.0-99.4% |
| Ethanol | BDH | AnalaR 99.7-100% |
| Ethanol | Rathburn Chemicals Ltd, Walkerburn, Peebleshire, Scotland | HPLC |
| Methanol | BDH | AnalaR 99.8%+ |
| Sodium dihydrogen orthophosphate | Sigma | 99.0%+ |

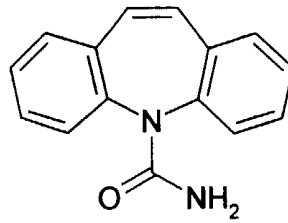
(De-ionised water was obtained from a Jencons Waterstill™ 4000X.)

5

| <u>Material</u> | <u>Chemical structure</u> |
|-----------------|---------------------------|
| L-ascorbic acid | |

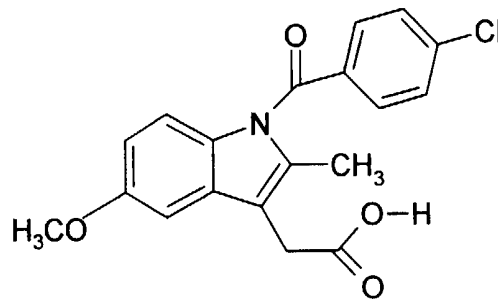


Carbamazepine

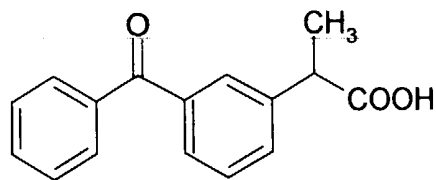


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Indomethacin



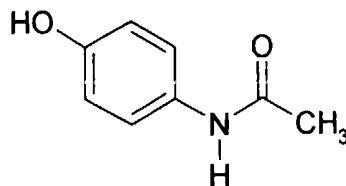
Ketoprofen



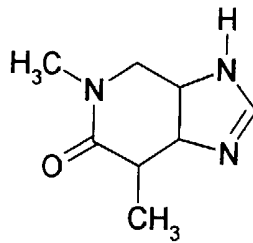
10

Paracetamol

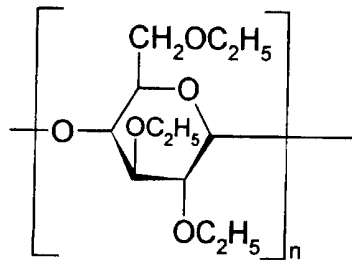
(US acetaminophen)



Theophylline

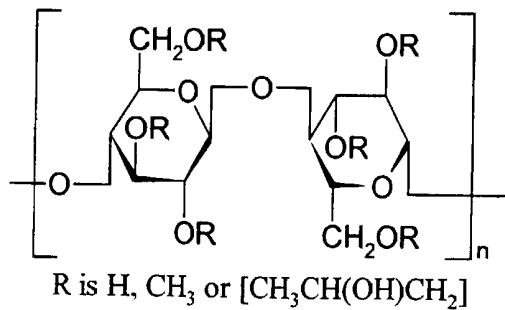


Ethyl cellulose (EC)



5

Hydroxypropyl methyl
Cellulose (HPMC)



10

Polyvinyl
Pyrrolidone (PVP)

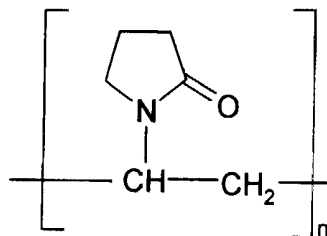


Table 1 Polarity and solubility parameters of drugs and polymers studied*

| Material | Polarity | δ_d (MPa ^{1/2}) | δ_p (MPa ^{1/2}) | δ_h (MPa ^{1/2}) | δ_s^+ (MPa ^{1/2}) | δ_t (MPa ^{1/2}) |
|-----------------------------------|----------|-------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|
| Ethyl cellulose | 0.34 | 16.7 | 2.9 | 11.7 | 12.4 | 20.6 |
| Hydroxypropyl methyl cellulose | 0.69 | 13.7 | 6.5 | 14.9 | 16.3 | 21.3 |
| Ascorbic acid | 0.71 | 21.0 | 14.0 | 30.0 | 33.1 | 39.2 |
| Carbamazepine | 0.23 | 22.0 | 7.6 | 9.6 | 12.2 | 25.2 |
| Paracetamol | 0.40 | 21.1 | 8.5 | 15.0 | 17.2 | 27.3 |
| Indomethacin | 0.19 | 21.9 | 5.6 | 9.1 | 10.7 | 24.4 |
| Theophylline | 0.53 | 17.4 | 13.1 | 12.8 | 18.3 | 25.2 |

*Values obtained from published literature

5 $^+\delta_s = (\delta_p^2 + \delta_h^2)^{1/2}$

In Table 1, δ_d , δ_p and δ_h are the partial solubility parameters representing dispersive, polar and hydrogen bonding effects respectively; δ_t is the total solubility parameter, where $\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$ [9]; δ_s is the total specific (ie, polar and hydrogen bonding) solubility parameter.

The principal operating conditions (temperature, pressure, fluid flow rates and nozzle orifice diameter) were manipulated and optimised for each drug/polymer system. Different drug:polymer concentration ratios were also tested.

It was found that temperatures in the range 34-50°C and pressures between 80 and 100 bar were preferable for processing these polymers. Anti-solvent:target solution flow rate ratios (into the particle formation vessel) were between 66:1 and 200:1, ie, an anti-solvent flow rate of 20 ml/min was used with target solution flow rates of between 0.1 and 0.3 ml/min.

Nozzle outlet internal diameters were between 100 and 500 μm , 100 μm being preferred over those greater than 200 μm .

A 1:1 mixture of ethanol and dichloromethane (or 1:1 ethanol/chloroform in the case of PVP) was used as the drug/polymer solvent. This yielded dispersions of suitably low viscosity, enabling processing without significant nozzle blockage. Similarly, ethanol was found to produce low viscosity dispersions for the EC systems. A polymer concentration of 0.5% w/v provided a balance between the ability to pump the solution at a moderate back pressure and an acceptably high material throughput.

To facilitate processing, the polymers used were selected from the lower molecular weight fractions - 3 cps HPMC, 7 cps EC and PVP of average molecular weight 10,000.

Results & discussion

The results of the various experimental runs (in particular yield, morphology and drug loading) are summarised in Tables 2 (ascorbic acid), 3 (carbamazepine), 4 & 5 (indomethacin), 6 & 7 (ketoprofen), 8 (paracetamol) and 9 (theophylline), appended.

The tables also indicate the operating conditions (temperature and pressure within the particle formation vessel, fluid flow rates, target solution concentration and nozzle tip (outlet) diameter) for each run.

The products were in the form of finely dispersed particulates; all were non-cohesive, easy-flowing powders with good handling properties. Their morphology was assessed using SEM, which revealed the non-crystalline products typically as fine, agglomerated, roughly spherical particles of the order of 0.05-1 μm diameter. The homogeneity in the appearance of the particles suggested they comprised molecular-level dispersions. Above the amorphous limits detected, mixtures of such web structures with additional, larger drug crystals were observed in many cases.

Figures 2 to 5 are SEM photographs of some of the starting materials and products of the experiments. Specifically, Figure 2 shows the indomethacin raw material (at 2000x magnification); Figure 3 shows the amorphous indomethacin/HPMC product of experimental run RASE 21 (2000x magnification); Figure 4 shows the paracetamol raw material (200x magnification) and Figure 5 shows the amorphous paracetamol/HPMC product of experimental run RASF 34 (1000x magnification).

Dissolution tests

Figures 6 to 8 show dissolution profiles for three of the systems investigated, namely paracetamol:HPMC (Figure 6), theophylline:EC (Figure 7) and indomethacin:HPMC (Figure 8). The labelling corresponds to that used in Tables 2-9 for the various experimental runs; X (%) is the maximum concentration of the amorphous phase of the drug prior to the detection of crystallinity. In all three systems, there were significant differences in drug release rates between the SEDS™-coformulated products and purely physical mixes of the relevant drug and polymer, suggesting that the products of the present invention had been formed as intimate molecular level dispersions of a drug in a polymer matrix. For instance, the release of theophylline was significantly inhibited by coformulating it with EC according to the invention, that of paracetamol was also slightly inhibited by coformulation with HPMC, whilst the dissolution rate of indomethacin was increased on coformulation with HPMC (including one sample above the amorphous detected limit).

15 *Degree of crystallinity*

Plots of drug crystallinity (determined by DSC) against drug weight fraction are shown in Figures 9 to 19. The systems illustrated are ascorbic acid/EC, ascorbic acid/HPMC, carbamazepine/EC, carbamazepine/HPMC, indomethacin/EC, indomethacin/HPMC, indomethacin/PVP, paracetamol/EC, paracetamol/HPMC, theophylline/EC and theophylline/HPMC respectively.

Although it depended very much on the drug and polymer involved, in general the proportion of amorphous to crystalline drug present in the SEDS™ products was found to be higher than that achieved using conventional processing techniques such as evaporation and coprecipitation from solvent systems [1]. For instance, maximum amorphous phase concentrations for indomethacin were 25±5% with EC, 35±5% with HPMC and 60±5% with PVP. Up to 10-15% amorphous ascorbic acid was achieved in coformulation with EC, and up to 35-40% with HPMC (Figures 9 and 10). (Note that drug concentration *ranges* are quoted at the limit of the amorphous/crystalline state boundary, due to the limitations of the method of quantifying crystallinity by DSC and the limited number of data points around the phase change concentration.)

These results are of particular significance for poorly water soluble pharmaceuticals, for which the amorphous form is generally preferred because of its superior dissolution rate.

5 *Physical and chemical stability*

The medium to long term storage stability of several of the Example I products was investigated. In all cases the physical properties of the samples were unchanged even after up to 24 months' storage; the samples remained free flowing and easy to handle.

Chemical stability (in terms of amorphous phase contents) was assessed using DSC. Looking firstly at the indomethacin/PVP system, the drug in its crystalline form exhibits a peak in DSC profiles at 150-165°C, when analysed at a scanning rate of 20°C/min. This peak shifts to lower temperature in coformulated indomethacin/PVP systems. Figures 20 and 21 show DSC profiles for, respectively, the crystalline raw material and the indomethacin/PVP system prepared in experimental run RASE 64. The peak at 139°C in Figure 20 indicates the presence of crystalline indomethacin in the sample (which contained 78% w/w indomethacin, with 30% crystallinity).

The indomethacin/PVP samples prepared in experimental runs RASE 70, RASE 69, RASE 62, RASE 66 and RASE 63 (containing 16, 20, 48, 51 and 62% indomethacin respectively), were assessed initially and after both 12 and 24 months' storage in a desiccator at between 2 and 8°C. The DSC results indicated no crystallinity in any of the samples even after 24 months. An example DSC profile for the RASE 63 sample at 24 months is shown in Figure 22; the absence of the 139°C peak indicates an absence of crystalline indomethacin.

Three theophylline/EC systems were also tested, after storage at ambient temperature and without desiccation. The DSC profiles obtained after 24 months for the products of runs RASH 6, LSDA 52 and RASH 14 (containing 9, 17 and 27% theophylline respectively, in each case 100% amorphous) again lacked definite peaks, indicating no detectable drug crystallinity. An example DSC profile, for the RASH 14 sample, is shown in Figure 23.

30 In a similar experiment, the stabilities of four of the paracetamol/HPMC products were tested over a 24 month storage period. The storage conditions were as for the theophylline/EC systems. The 24 month DSC profiles for the products of

experimental runs RASF 31, RASF 27, RASF 97 and RASF 40 (containing 19, 20, 21 and 29% paracetamol respectively, in each case 100% amorphous) indicated an absence of crystallinity. Figure 24 is an example DSC profile, for the RASF 40 sample.

Thus, coformulations according to the invention, made by a SEDS™ process, appear to possess excellent long term storage stability, with respect both to their physical properties and to re-crystallisation of the active substance.

With regard to the above stability data, it is of note that many of the systems tested were close to the point of inflexion on the graphs of crystallinity versus drug loading. In other words, they were systems containing the maximum possible drug loading before the onset of crystallinity. Other products of the invention, containing lower drug loadings, would if anything be more stable under the same storage conditions.

Solubility effects

A relationship was observed, in the systems containing the hydrophobic polymer ethyl cellulose, between the amorphous phase drug concentration and the total specific solubility parameters δ_s ($\delta_s = (\delta_p^2 + \delta_h^2)^{1/2}$ - see Table 1) of the reagents. Insofar as could be inferred from the systems studied, the trend was towards the maximum concentration of amorphous phase (and thus also the maximum drug:polymer interaction) being achieved when the δ_s of the drug and the polymer were equivalent or substantially so.

It appears that drug/polymer dispersion, and intermolecular/interpolymeric chain mixing and interaction, can be maximised by choosing the reagents so that $(\delta_s^d - \delta_s^p)$ is zero or close to zero (where δ_s^d and δ_s^p represent the total specific (ie, polar and hydrogen bonding) solubility parameters for the drug and polymer respectively). These systems would be expected to contain the maximum amount of amorphous phase drug, lower amorphous phase levels occurring as $(\delta_s^d - \delta_s^p)$ attained either a positive or a negative value.

Table 10 lists calculated values of $(\delta_s^d - \delta_s^p)$ for the systems studied, together with values of X% (mid-point and range).

30

Table 10

| Drug/Polymer | $(\delta_s^d - \delta_s^p)$ | X(%) | |
|--------------------|-----------------------------|----------|-------|
| | | Midpoint | Range |
| Ascorbic acid/EC | 20.7 | 12.5 | 10-15 |
| Ascorbic acid/HPMC | 16.8 | 37.5 | 35-40 |
| Carbamazepine/EC | -0.2 | 25.0 | 20-30 |
| Carbamazepine/HPMC | -4.1 | 32.5 | 25-40 |
| Paracetamol/EC | 4.8 | 6.0 | 1-12 |
| Paracetamol/HPMC | 0.9 | 30.0 | 25-35 |
| Indomethacin/EC | -1.7 | 23.0 | 18-28 |
| Indomethacin/HPMC | -5.6 | 40.0 | 35-45 |
| Theophylline/EC | 5.9 | 25.0 | 20-30 |
| Theophylline/HPMC | 2.0 | 12.5 | 5-20 |

The Table 10 data are plotted in Figures 25 and 26. The maximum amorphous phase contents found for drug/EC systems, with the exception of paracetamol/EC, seem to be in accord with the hypothesis (Figure 25), showing a maximum of approximately 27% amorphous content at $\delta_s^d - \delta_s^p = 0$. In contrast, for the drug/HPMC system (Figure 26), a minimum is observed at the zero point, with the paracetamol/polymer system again deviating from the trend.

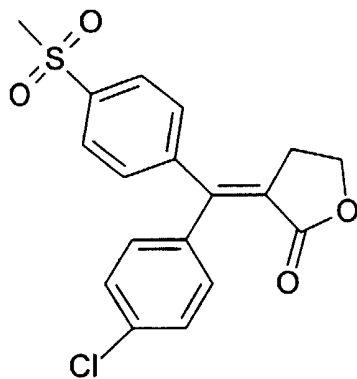
The systems containing paracetamol deviate from the trends exhibited by the other drugs. Polar systems have a greater tendency to exhibit irregular solution behaviour. Furthermore, if a molecule contains at least two active groups with differing hydrogen bonding abilities, this can lead to anomalous solubility behaviour. Commonly referred to as the "chameleonic effect", this is a combined effect of the solubility parameter and solute-solvent and solvent-solvent hydrogen bonding. Paracetamol is known to form irregular solutions in polar solvents [10-12] and contains the functional groups -OH and -NH-, which leads to varying behaviour dependent on the solvent environment.

It is of note that attempts to form amorphous paracetamol using conventional particle formation techniques have proved unsuccessful, this being attributed to the high crystallinity and crystal energy of the drug. However, using SEDS™ to coformulate

paracetamol with for instance HPMC, a particulate product containing between 25 and 35% of the amorphous drug can be prepared.

5 Example II

This series of experiments demonstrates the coformulation, using SEDS™, of a cyclo-oxygenase-2 (COX-2) inhibitor of the formula (I):

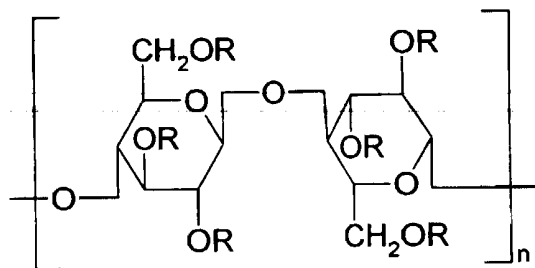


((Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulfonylmethylene)]-dihydrofuran-2-one) with:

10

(a) hydroxypropyl cellulose (HPC):

Structural Formula:



Where R is H or [-CH₂-CH(CH₃)-]_mH

and:

15

(b) "Poloxamer 237" (P-237), also known as Pluronic™ F87, which is a polyoxypropylene-polyoxyethylene block copolymer of the chemical formula HO(C₂H₄O)₆₄(C₃H₆O)₃₇(C₂H₄O)₆₄H.

The reagents used in the experiments were analytical or HPLC grade.

For (a), the solvent used was a mixture of DCM and ethanol (1:1), which could dissolve both the drug and the polymer together. The (HPC + drug) concentration was varied between 0.5 and 4.5% w/v and the DCM:ethanol ratio was altered where
5 appropriate to increase solution saturation. The ethanol helped to lower the viscosity of the HPC dispersion.

The operating conditions for (a) were 90 bar and between 50 and 70°C. Higher temperatures facilitated solvent extraction. CO₂ flows of up to 20 ml/min were used, with target solution flows of as low as 0.1 ml/min. The conditions for each experimental
10 run are summarised in Tables 11 and 12, appended.

For (b), the operating temperature was 35°C (due to the relatively low melting point of the polymer) and the pressure was varied between 75 and 100 bar. DCM was used as a solvent for both Compound (I) and the polymer together, with solution concentrations between 1 and 3% w/v. The CO₂ anti-solvent flowed at 18 ml/min and
15 the target solution at between 0.1 and 0.2 ml/min. Table 13 (appended) summarises the operating conditions for each run.

In both sets of experiments, nozzle outlet diameters of 100, 200, 400 and 750 µm were employed, and either a 50 ml or in some cases a 500 ml particle formation vessel.

Results & discussion – Compound (I) and HPC

The results are given in Tables 11 and 12, appended. The best yields and particle
20 sizes were obtained in run 14, using 85% w/w of Compound (I) – this gave a 95% yield of free flowing rounded/plate-like particles with an average diameter of 3.8 µm (Figure 27, SEM taken at 4000x magnification). At 30% w/w HPC (run 17), a 96% yield was obtained but the particles were more flake-like and agglomerated, their average size being
25 13.1 µm. HPC concentrations of 50 and 80% w/w gave large (20.7 µm) coral-like agglomerates (runs 21 (Figure 28, SEM taken at 2000x magnification) and 22). In all runs the recovery of Compound (I) was greater than 90%.

Generally, nozzle blockages were reduced at lower concentrations (eg, about 80% w/w or lower) of Compound (I). For some runs, a 50 ml vessel soon clogged with
30 precipitated solids; a 500 ml vessel was substituted to eradicate this problem.

Particle agglomeration (and hence large particle sizes) could generally be reduced by decreasing the process throughput, for instance by reducing the concentration and/or flow rate of the drug/polymer solution (whilst still maintaining a near saturated solution).

Results & discussion – Compound (I) and P-237

5 The results are given in Table 13, appended. The smallest particles of pure Compound (I) were produced in run 38, using a 2% w/v target solution with a flow rate of 0.15 ml/min. These conditions were used to produce coformulations for dissolution testing, as well as a control batch of pure Compound (I).

The recovery of Compound (I) in all samples was 100%.

10

Degree of crystallinity

Products were subjected to DSC analysis to determine the degree of crystallinity in the Compound (I) present. The results, as a function of drug concentration, are shown in Tables 14 and 15 below, for the HPC and P-237 systems respectively, and are
15 illustrated graphically in Figures 29 and 30 respectively.

Table 14 -
Crystallinity levels in HPC systems

| <u>Concentration of Compound (I)</u> <u>(% w/w) (by HPLC)</u> | <u>ΔH_f coformulation</u> <u>J/g</u> | <u>% Crystallinity</u> |
|--|--|------------------------|
| Unprocessed Compound (I) | 96.1 | 100 |
| 100 | 94.2 | 98.1 |
| 100 | 94.0 | 97.8 |
| 100 | 94.2 | 98.0 |
| 88 | 78.0 | 92.2 |
| 86.7 | 75.1 | 90.2 |
| 79 | 73.9 | 97.3 |
| 78.6 | 77.7 | 102.9 |
| 64.5 | 54.9 | 88.6 |

| | | |
|------|------|------|
| 50 | 26.9 | 56.1 |
| 43.6 | 31.7 | 75.7 |
| 26.7 | 5.1 | 20.0 |
| 20 | 0 | 0 |

Table 15 -
Crystallinity levels in P-237 systems

5

| <u>Concentration of Compound (I)</u> <u>(% w/w) (by HPLC)</u> | <u>ΔH_f coformulation</u> <u>J/g</u> | <u>% Crystallinity</u> |
|--|--|------------------------|
| Unprocessed Compound (I) | 96.0 | 100 |
| 100 | 93.6 | 97.4 |
| 86.2 | 64.9 | 78.4 |
| 85 | 66.4 | 81.4 |
| 71.3 | 48.1 | 70.3 |
| 70.7 | 46.6 | 68.7 |
| 53.7 | 20.8 | 40.3 |
| 20 | 0 | 0.0 |

The results for both systems indicate that crystallinity is significantly reduced as polymer content increases. The reduction is nearly linear for the P-237 system, but for HPC a polymer content of at least 20% w/w is needed before crystallinity levels start to decrease. For both systems, a 100% amorphous product was achieved at drug loadings of 20% w/w or less.

Physical and chemical stability

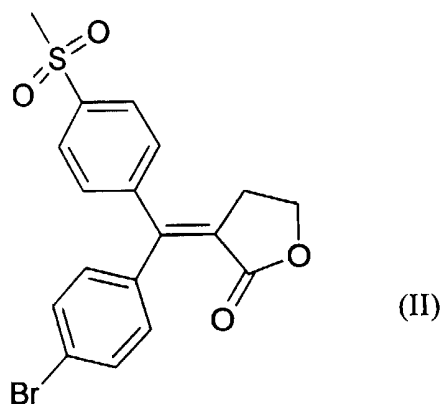
A representative sample containing 20% w/w Compound (I) and 80% w/w P-237, produced using a SEDS™ process as described above, was stored for 13 months in a screw-top glass jar, under ambient conditions (10-27°C) and in the dark. At the end of

this storage period the sample was found to have retained its initial physical properties, ie, it was still a free-flowing, easily handled powder containing discrete particles. It had also retained its 100% amorphous nature (assessed using DSC).

5

Example III

This series of experiments demonstrates the coformulation, using SEDS™, of a COX-2 inhibitor of the formula (II):



10

((Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one) with HPC.

Apparatus similar to that used in Examples I and II, but scaled up 10 fold, was used to carry out SEDS™ particle formation. Both Compound (II) and HPC (as used in Example II) were dissolved in acetone, at an optimum concentration of 2.0% w/v. The preferred operating temperature was 60°C and the pressure 120 bar. The optimum target solution flow rate was 1.0 ml/min, that for the supercritical carbon dioxide anti-solvent 200 ml/min. Products containing 10%, 20%, 30%, 50% and 70% w/w Compound (II) were prepared using these conditions, the exact conditions for each run being summarised in appended Table 16.

20

For some runs, as indicated in the table, a lower molecular weight (80,000) grade of HPC was used.

Experiments were also carried out using DCM:ethanol (35:65 v/v) as the solvent, a solution concentration of 1.0% v/v, an operating temperature and pressure of 50°C and 90 bar respectively, a target solution flow rate of 1.0 ml/min and a supercritical carbon dioxide flow rate of 200 ml/min. The operating conditions for each run are summarised in Table 17, appended; a product containing 90% w/w Compound (II) was successfully prepared.

Results & discussion

The results are given in the appended Tables 16 and 17. Sample crystallinity was assessed in each case by DSC; the results are shown in Table 18 below and represented graphically in Figure 31 (plot of crystallinity against drug loading).

Table 18

15

| <u>Compound (II) Conc. (% w/w)</u> | <u>Latent heat of fusion Coformulation (J/g)</u> | <u>% Crystallinity</u> | <u>Run N°</u> |
|--|--|------------------------|---------------|
| Starting material | 74.84 | 100 | N/A |
| 25 | 5.6 | 29.6 | 17 |
| 25 | 6.2 | 33.3 | 17 |
| 30 | 10 | 44.4 | 18 |
| 90 | 64.7 | 96.1 | 19 |
| 50 | 31.6 | 84.5 | 20 |
| 70 | 48.9 | 93.3 | 23 |
| 85 | 58.6 | 92.2 | 9 |
| 90 | 63.3 | 94 | 24 |
| 10 | 0 | 0 | 25 |
| 15 | 0 | 0 | 10 |
| 20 | 0 | 0 | 13 |

Thus, the products containing 20% w/w Compound (II) or less (run numbers 10, 13 and 25) had 0% crystallinity. After storage for approximately three months in screw top glass bottles, at ambient temperature (10-27°C) and in the dark, these samples were

20

found to have retained their 100% amorphous nature. They were also still free-flowing, easily handled powders, as initially.

5 Example IV

This series of experiments demonstrates the coformulation, using SEDS™, of glibenclamide (1-{4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulphonyl}-3-cyclohexylurea, an anti-diabetic drug) and 75/25 DL-lactide-*co*-caprolactone (Birmingham Polymers, England).

10 Supercritical nitrogen was used as the anti-solvent, since supercritical carbon dioxide would plasticise the amorphous polymer excipient. The glibenclamide was dissolved in methylene chloride. The anti-solvent flow rates were between 15 and 25 litres min⁻¹, those for the drug solution between 0.05 and 0.1 ml min⁻¹. A 500 ml particle formation vessel was used, at an operating temperature of between 35 and 60°C and a
15 pressure of 100 bar.

Results & discussion

Coformulations having drug:polymer ratios of between 1:1 and 9:1 were successfully produced under the above conditions. XRD analysis confirmed that although
20 the glibenclamide raw material was crystalline, all of the SEDS™ products contained 100% amorphous phase drug.

For all of the coformulations, residual solvent levels (measured using headspace gas chromatography (Varian™)) were below 300 ppm, surprisingly low in view of the poor mass transfer properties of supercritical nitrogen relative to supercritical carbon
25 dioxide.

Appendix

There now follow Tables 2-9 (Example I), 11-13 (Example II) and 16 and 17 (Example III), referred to above.

5

Ascorbic Acid Result Table 2

| Experiment | Drug Conc (%w/v) | Polymer | Polymer Conc (%w/v) | Solvent | Solution Flow Rate (ml/min) | CO ₂ flow (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Comments | Morphology by SEM | DSC Peaks (ΔH - J/g) | % Drug in Product by UV (Wt %) |
|-------------|------------------|-----------|---------------------|---------------------|-----------------------------|-------------------------------|-----------|----------------|--------------------------|-----------|--|---------------------------|----------------------|--------------------------------|
| RASF79 | 0.2 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 120 | 100 | 58 | Fine particulate | ND | 25.0 | 50.1 |
| RASF80 | 0.5 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 50 | Fine particulate, large nozzle blocks | ND | 108.4 | 50 |
| RASF81 | 0.5 | EC 10cps | 0.20 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | ND | CO ₂ pump problem, fine particulate | ND | 176.5 | 75 |
| RASF82 | 0.4 | EC 10cps | 0.30 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 63 | Fine particulate | ND | 123.7 | 57.1 |
| RASF83 | 0.0 | EC 10cps | 0.60 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 73 | Fine particulate | ND | 2 | 5 |
| RASF96 (SW) | 0.1 | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 62 | Fine white particulate | ND | 3.72 | 3.2 |
| RASF97 (SW) | 0.1 | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 40 | Fine white particulate | ND | 29.24 | 17.2 |
| RASF98 (SW) | 0.2 | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 29 | Fine white particulate | ND | 51.29 | 21.1 |
| RASF99 (SW) | 0.2 | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 40 | Fine white particulate | ND | 64 | 39.3 |
| LSDA18R | 0.2 | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.3 | 20 | 34 | 80 | 100 | 61 | Fine white powder | Aggregates | None | 24 |
| LSDA19 | 0.5 | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.3 | 20 | 34 | 80 | 100 | 71 | Fine white powder | Aggregates | 96 | 48 |
| LSDA20 | 1.0 | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.3 | 20 | 34 | 80 | 100 | 81 | Fine white powder | Aggregates | 123 | 69 |
| LSDA21 | 1.5 | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.3 | 20 | 34 | 80 | 100 | 41 | Fine off-white powder | Aggregates (0.5 x 0.5 µm) | 182 | 74 |
| LSDA31 | 4.5 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 58 | Fine off-white powder | ND | 226 | 86 |
| LSDA32 | 4.5 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 300 | 98 | Fine off-white powder | ND | 221 | 91 |
| LSDA33 | 4.5 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 500 | 64 | Fine off-white powder | ND | 222 | 91 |
| LSDA34 | 2.0 | EC 10cps | 0.50 | Ethanol | 1.3 | 20 | 34 | 80 | 100 | 63 | Fine off-white powder | ND | 222 | 73 |
| LSDA49 | 0.1 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 47 | Fine white powder | ND | 24 | 18 |
| LSDA50 | 0.1 | EC 10cps | 0.50 | Ethanol | 0.3 | 20 | 34 | 80 | 100 | 66 | Fine white powder | ND | None | 5 |

NA - Not applicable, ND - Not determined

All experiments used a two component nozzle

A1
38

Carbamazepine Results Table 3

| Experiment | Drug Conc (%w/v) | Polymer | Polymer Conc (%w/v) | Solvent | Solution Flow Rate (ml/min) | Pressure (bar) | CO2 flow (ml/min) | Temp °C | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm, by SEM) | Morphology (by SEM) | DSC Peaks (ΔH-J/g) | % Drug in Product by UV (Wt%) |
|------------|------------------|---------|---------------------|---------------------|-----------------------------|----------------|-------------------|---------|--------------------------|-----------|---------------------|-------------------|---------------------------------|--------------------|-------------------------------|
| LSDA6 | 2.0 | N/A | 0 | Ethanol | 0.2 | 80 | 20 | 50 | 100 | 61 | Fine white powder | ND | Acicular with some agglomerates | 101 | NA |
| LSDA7 | 0.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 100 | 38 | Fine white powder | ND | Acicular with some agglomerates | 19 | 41 |
| LSDA8 | 0.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 58 | Fine white powder | ND | Acicular | 47 | 59 |
| LSDA9 | 0.25 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 48 | Fine white powder | ND | Acicular with some agglomerates | 22 | 42 |
| LSDA10 | 1.0 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 85 | Fine white powder | ND | Acicular | 79 | 64 |
| LSDA11 | 0.167 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 45 | Fine white powder | 0.5 x 0.5 | Aggregates with some acicular | None | 25 |
| LSDA12 | 1.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 95 | Fine white powder | ND | Acicular | 87 | 87 |
| LSDA13 | 0.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 89 | Fine white powder | ND | Acicular | 26 | 43 |
| LSDA14 | 0.25 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 80 | Fine white powder | ND | Acicular | 18 | 29 |
| LSDA15 | 1.0 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 94 | Fine white powder | ND | Acicular | 53 | 60 |
| LSDA16 | 0.167 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 70 | Fine white powder | ND | Acicular | None | 24 |
| LSDA17 | 1.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 89 | Fine white powder | ND | Acicular with some agglomerates | 58 | 69 |
| LSDA38 | 0.125 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 85 | Fine white powder | ND | ND | None | 24 |
| LSDA40 | 1.167 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 94 | Fine white powder | ND | ND | 68 | 70 |
| LSDA42 | 0.215 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 500 | 49 | Fine white powder | ND | ND | 13 | 30 |
| LSDA54 | 0.215 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.2 | 80 | 20 | 50 | 200 | 82 | Fine white powder | ND | ND | None | 28 |

A two-component nozzle was used in all experiments

NA - Not applicable, ND - Not determined

Indomethacin Result Table 4

| Experiment | Drug Solvent | Drug Conc. (%w/v) | Polymer | Polymer Conc. (%w/v) | Solvent | Solution Flow Rate (ml/min) | CO ₂ Flow Rate (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm by SEM) | Morphology (by SEM) | DSC Peaks (ΔH/J) | % Drug in Product by UV (Wt.%) |
|------------|-----------------------|-------------------|----------------|----------------------|-----------------------|-----------------------------|------------------------------------|-----------|----------------|--------------------------|-----------|--|---|--|------------------------------|--------------------------------|
| RASE2 | Ethanol | 2 | NA | 0 | NA | 0.2 | 15 | 50 | 100 | 100 | 91 | Mass of fine strands | 30 x 1 | Fibres | ND | NA |
| RASE3 | Acetone | 2 | NA | 0 | NA | 0.2 | 15 | 50 | 100 | 100 | 75 | Mass of fine particulate | 15 x 2 | Acicular | ND | NA |
| RASE1B | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 39 | Fine off-white particulate | <0.1 x 0.1 | Aggregates | None | 15 |
| RASE1P | Ethanol/ DCM (1:1) | 0.25 | HPMC (3cps) | 0.75 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 73 | Fine off-white particulate | <0.1 x 0.1 | Aggregates | None | 13 |
| RASE20 | Ethanol/ DCM (1:1) | 0.25 | HPMC (3cps) | 0.75 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 100 | 500 | 75 | Fine off-white particulate | 0.1 x 0.1 | Aggregates | None | 9 |
| RASE21 | Ethanol/ DCM (1:1) | 0.25 | HPMC (3cps) | 0.75 | Ethanol/ DCM (1:1) | 0.2 | 20 | 50 | 80 | 500 | 62 | Pale yellow fine particulate | 1 x 1 | Amorphous | None | 27 |
| RASE26 | Ethanol/ DCM (1:1) | 0.25 | HPMC (3cps) | 0.75 | Ethanol/ DCM (1:1) | 0.2 | 20 | 50 | 80 | 500 | 63 | Pale yellow fine particulate | 0.5 x 0.5 | Aggregates | None | 17 |
| RASE27 | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 50 | 80 | 500 | 64 | Fine off-white particulate Very fine white particulate with yellow cob | 0.5 x 10 & 1 x 1 Wide variations 0.2 x 0.2 & 100 x 0.5 | Acicular & amorphous Aggregates, acicular & fibres | 0.7 | 55 |
| RASE30 | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 50 | 80 | 500 | 39 | Fine off-white particulate | 0.2 x 0.2 & 50 x 50, 50 x 1, 30 x 0.2 | Aggregates & fibres | 0.1 | 22 |
| RASE31 | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 75 | Fine white particulate with crystals | Wide variations | Tabular, acicular & fibres aggregates & fibres | <20 (153°C), \$31 (160°C) | 89 |
| RASE32 | Ethanol/ DCM (1:1) | 0.75 | HPMC (3cps) | 0.25 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 64 | Fine off-white particulate | Wide variations | Amorphous | 0.3 | 38 |
| RASE33 | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 37 | 80 | 500 | 25 | Fine off-white particulate | 0.5 x 0.5 | Amorphous | None | 13 |
| RASE34 | Ethanol/ DCM (1:1) | 0.5 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 37 | 80 | 500 | 72 | Fine off-white particulate | 0.1 x 0.1 | Amorphous | None | 5 |
| RASE35 | Ethanol/ DCM (1:1) | 0.167 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 73 | Fine off-white particulate | 0.1 x 0.1 | Amorphous aggregates | None | 10 |
| RASE36 | Ethanol/ DCM (1:1) | 0.167 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 37 | 80 | 500 | 52 | Fine off-white particulate | 0.2 x 0.2 | Amorphous aggregates | None | 14 |
| RASE37 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 200 | 41+ | Fine off-white particulate | 0.2 x 0.2 | Amorphous aggregates | None | 13 |
| RASE38 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 200 | 61 | Fine off-white particulate | Wide variations 0.3 x 0.3 & 30 x 0.3 | Aggregates, acicular & fibres | 12.2 | 51 |
| RASE39 | Ethanol/ DCM (1:1) | 0.75 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 64 | Fine off-white particulate | 0.1 x 0.1 | Amorphous & fibres | 29.1 | 67 |
| RASE40 | Ethanol/ DCM (1:1) | 0.75 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | -40 | Fine off-white particulate | 0.1 x 0.1 | Amorphous aggregates | None | 11 |
| RASE41 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 39 | Fine off-white particulate | 0.05 x 0.05 | Amorphous aggregates | None | 17 |
| RASE42 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 37 | 80 | 500 | 75 | Pale yellow fine particulate | 0.5 x 0.5, 5 x 0.5 & 5 x 0.3 | Aggregates, acicular & fibres | 19.6 | 42 |
| RASE43 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.1 | 20 | 50 | 80 | 500 | 74 | Pale yellow fine particulate | 15 x 10, 0.5 x 0.5 20 x 0.5, 10 x 0.2 | Amorphous (2 types), acicular & fibres | 20.7 | 51 |
| RASE44 | Ethanol/ DCM (1:1) | 0.33 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 50 | 80 | 500 | 51 | Fine off-white particulate | <0.1 x 0.1 | Amorphous aggregates | None | 12 |
| RASE45 | Ethanol/ DCM (1:1) | 0.41 | HPMC (3cps) | 0.5 | Ethanol/ DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 51 | Fine off-white particulate | <0.1 x 0.1 | Amorphous aggregates | None | 12 |

NA - Not applicable, ND - Not determined

A two-component nozzle was used in all experiments

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Indomethacin Result Table 5

| Experiment | Drug Solvent | Drug Conc (mg/ml) | Polymer Conc (%w/v) | Polymer | Solution Flow Rate (ml/min) | CO ₂ flow (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm, by SEM) | Morphology (by SEM) | DSC Peaks (ΔH/Jg) | % Drug in Product by UV (Wt %) |
|------------|----------------------------|-------------------|---------------------|-----------|-----------------------------|-------------------------------|-----------|----------------|--------------------------|-----------|--|------------------------------------|--|-------------------|--------------------------------|
| RASE58 | Ethanol | 0.5 | 0.5 | EC (7pp) | 0.1 | 20 | 37 | 80 | 100 | 12 | Fine yellow particulate | 100 x 150 | Amorphous pitted chunks | None | 34 |
| RASE59 | Ethanol | 0.5 | 0.5 | EC (7pp) | 0.05 | 20 | 37 | 80 | 100 | 19 | Fine yellow particulate | 100 x 150 | Amorphous pitted chunks | None | 46 |
| RASE60 | (1:1) Ethanol / Chloroform | 0.25 | 0.25 | EC (7pp) | 0.1 | 20 | 37 | 80 | 100 | 19 | Fine yellow particulate | 100 X 50 | Amorphous pitted chunks | None | 41 |
| RASE62 | (1:1) Ethanol / Chloroform | 0.25 | 0.25 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 25 | Fine yellow particulate with yellow flakes | 100 x 150 | Amorphous pitted chunks | None | 48 |
| RASE63 | (1:1) Ethanol / Chloroform | 0.75 | 0.25 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 16 | Fine yellow particulate with yellow flakes | 100 X 50 | Amorphous pitted chunks | None | 62 |
| RASE64 | (1:1) Ethanol / Chloroform | 0.75 | 0.25 | PVP (10k) | 0.2 | 20 | 50 | 80 | 100 | 38 | Fine yellow particulate | 50 x 50, 10 x 0.5, 10 x 5 & 5 x 5 | Amorphous pitted chunks with needles, tablets & microspheres | 25.3 | 78 |
| RASE66 | (1:1) Ethanol / Chloroform | 0.5 | 0.5 | PVP (10k) | 0.2 | 20 | 50 | 80 | 100 | 26 | Fine yellow particulate with yellow flakes | 250 X 200 | Amorphous pitted chunks | None | 51 |
| RASE68 | (1:1) Ethanol / Chloroform | 0.1 | 0.5 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 13 | Fine yellow particulate | 100 x 100 | Amorphous pitted chunks | NA | 17 |
| RASE69 | (1:1) Ethanol / Chloroform | 0.1 | 0.5 | PVP (10k) | 0.2 | 20 | 50 | 80 | 100 | 10 | Fine yellow particulate | 100 x 100 | Amorphous pitted chunks | None | 20 |
| RASE70 | (1:1) Ethanol / Chloroform | 0.1 | 0.5 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 8 | Fine yellow particulate with yellow flakes | 200 x 150 | Amorphous pitted chunks | None | 16 |
| RASE71 | (1:1) Ethanol / Chloroform | 1.8 | 0.2 | PVP (10k) | 0.2 | 20 | 50 | 80 | 100 | 73 | Fine pale yellow particulate | 50 x 50, 10 x 0.5, 3 x 2, 1 x 1 | Amorphous pitted chunks with needles, tablets & microspheres | 62.5 | 86 |
| RASE72 | (1:1) Ethanol / Chloroform | 1.8 | 0.2 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 64 | Fine pale yellow particulate | 50 x 50, 10 x 0.5, 6 x 2, 2 x 2 | Amorphous pitted chunks with needles, tablets & microspheres | 62.3 | 81 |
| RASE73 | (1:1) Ethanol / Chloroform | 0.75 | 0.25 | PVP (10k) | 0.2 | 20 | 50 | 80 | 100 | 43 | Fine pale yellow particulate | 30 x 30, 5 x 0.2, 2 x 1, 0.5 x 0.3 | Amorphous pitted chunks with needles, tablets & microspheres | 23.3 | 67 |
| RASE74 | (1:1) Ethanol / Chloroform | 0.75 | 0.25 | PVP (10k) | 0.2 | 20 | 37 | 80 | 100 | 13 | Fine yellowish white particulate | 50 x 50, 5 x 0.2, 5 x 3, 10 x 10 | Amorphous pitted chunks with needles, tablets & microspheres | 57.2 | 76 |
| RASE75 | (1:1) Ethanol / Chloroform | 0.75 | 0.25 | PVP (10k) | 0.2 | 20 | 60 | 80 | 100 | 83 | Fine yellow particulate | 20 x 5, 5 x 0.5, 4 x 2, 1 x 1 | Amorphous chunks with needles, tablets & microspheres | 29.1 | 76 |
| LSDA57 | (1:1) Ethanol / Chloroform | 0.168 | 0.5 | EC 7aps | 0.2 | 20 | 37 | 80 | 100 | 30 | Yellow powder | ND | ND | None | 10 |
| LSDA58 | (1:1) Ethanol / Chloroform | 0.170 | 0.5 | EC 7aps | 0.2 | 20 | 50 | 80 | 100 | 11 | Yellow powder | ND | ND | None | 22 |
| LSDA59 | (1:1) Ethanol / Chloroform | 0.5 | 0.5 | EC 7aps | 0.3 | 20 | 34 | 80 | 100 | 17 | Yellow powder | ND | ND | None | 20 |
| LSDA60 | Ethanol | 1.517 | 0.5 | EC 7aps | 0.2 | 20 | 34 | 100 | 100 | ND | Yellow powder | ND | ND | None | 34 |
| LSDA61 | Ethanol | 0.339 | 0.5 | EC 7aps | 0.2 | 12 | 34 | 80 | 100 | 10 | Yellow powder | ND | ND | None | 13 |
| LSDA63 | Ethanol | 1.515 | 0.5 | EC 7aps | 0.1 | 15 | 50 | 80 | 100 | 89 | Fine white powder | ND | ND | 68 | 85 |
| LSDA64 | Ethanol | 0.5 | 0.5 | EC 7aps | 0.1 | 15 | 50 | 80 | 100 | 67 | Fine off-white powder | ND | ND | 37 | 50 |
| LSDA65 | Ethanol | 1.0 | 0.5 | EC 7aps | 0.1 | 15 | 50 | 80 | 100 | 89 | Fine off-white powder | ND | ND | 51 | 70 |
| LSDA66 | Ethanol | 0.341 | 0.5 | EC 7aps | 0.1 | 15 | 50 | 80 | 100 | 4 | Fine white powder | ND | ND | 31 | 42 |

A two-component nozzle was used in all experiments

NA - Not applicable, ND - Not determined

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Ketoprofen Result Table 6

| Experiment | Drug Conc (%w/v) | Polymer | Polymer Conc'n (%w/v) | Solvent | Solution Flow Rate (ml/min) | CO ₂ flow (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm, by SEM) | Morphology (by SEM) | DSC Peaks (ΔH - J/g) | % Drug in Product by UV (Wt.%) |
|------------|------------------|-----------|-----------------------|---------------------|-----------------------------|-------------------------------|-----------|----------------|--------------------------|-----------|------------------------|-------------------|---------------------|----------------------|--------------------------------|
| R.ASG1 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 200 | 47 | Fine white particulate | <0.1 x 0.1 | Amorphous aggregate | None | 8 |
| R.ASG2 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 42 | Off-white particulate | 0.2 x 0.3 | Amorphous | 0.1 | 39 |
| R.ASG3 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 37 | 80 | 200 | 40 | Fine white particulate | 0.2 x 0.2 | Amorphous aggregate | None | 11 |
| R.ASG4 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 37 | 80 | 200 | 45 | Fine white particulate | 0.2 x 0.2 | Amorphous aggregate | None | 10 |
| R.ASG5 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 12 | 37 | 80 | 200 | 38 | Fine white particulate | 0.2 x 0.2 | Amorphous aggregate | None | 6 |
| R.ASG6 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 100 | 200 | 42 | Fine white particulate | 0.1 x 0.1 | Amorphous aggregate | None | 4 |
| R.ASG7 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 500 | 38 | Fine white particulate | 0.2 x 0.2 | Amorphous aggregate | None | 8 |
| R.ASG8 | 5 | NA | 0 | Ethanol | 0.2 | 15 | 50 | 100 | 200 | 0 | No product | NA | NA | NA | NA |
| R.ASG9 | 5 | NA | 0 | DCM | 0.2 | 15 | 37 | 80 | 200 | 0 | No product | NA | NA | NA | NA |
| R.ASG10 | 5 | NA | 0 | Acetone | 0.2 | 15 | 37 | 80 | 200 | 0 | No product | NA | NA | NA | NA |
| R.ASG11 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 200 | 39 | Fine white particulate | 0.3 x 0.3 | Amorphous aggregate | None | 20 |
| R.ASG12 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 100 | 47 | Fine white particulate | 0.1 x 0.1 | Amorphous aggregate | None | 12 |
| R.ASG13 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 100 | 45 | Fine white particulate | 0.3 x 0.3 | Amorphous aggregate | None | 22 |

NA - Not applicable, ND - Not determined

All experiments used a two component nozzle

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Ketoprofen Result Table 7

| Experiment | Drug Conc. (%w/v) | Polymer | Polymer Conc'n (%w/v) | Solvent | Solution Flow Rate (ml/min) | CO2 flow (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm, by SEM) | Morphology (by SEM) | DSC Peaks (ΔH - J/g) | % Drug in Product by UV (Wt %) |
|------------|-------------------|---------|-----------------------|---------------------|-----------------------------|-------------------|-----------|----------------|--------------------------|-----------|---------------------|-------------------|---------------------|----------------------|--------------------------------|
| RASG14 | 0.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 0 | No product | NA | NA | NA | NA |
| RASG15 | 0.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 200 | 10 | White cobs | ND | ND | ND | NA |
| LSDA22 | 0.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 100 | 31 | Fine white powder | NA | Aggregates | None | 22 |
| LSDA23 | 0.167 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 45 | Fine white powder | NA | Aggregates | None | 7 |
| LSDA24 | 0.25 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 39 | Fine white powder | NA | Aggregates | None | 11 |
| LSDA25 | 1.0 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 7 | Fine white powder | NA | Aggregates | None | 25 |
| LSDA26 | 1.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 0 | ND | ND | Aggregates | 1 | ND |
| LSDA27 | 4.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 0 | No product | NA | NA | NA | NA |
| LSDA28 | 4.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 0 | No product | NA | NA | NA | NA |
| LSDA29 | 4.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 3 | Fine white powder | ND | ND | None | 49 |
| LSDA30 | 4.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 2 | Fine white powder | ND | ND | None | 52 |
| LSDA36 | 4.5 | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.05 | 10 N | 35 | 80 | 200 | 1 | Fine white powder | ND | ND | 83 | 84 |
| LSDA39 | 2.25 | HPMC | 0.25 | Ethanol / DCM (1:1) | 0.05 | 20 N | 50 | 80 | 200 | 0 | No product | NA | NA | NA | NA |

All experiments used a two component nozzle

NA - Not applicable, ND - Not determined

N - In these two experiments, nitrogen was substituted for CO2 (flows are in l/min measured at ambient conditions)

Paracetamol Result Table 8

| Experiment | Drug Conc (%w/v) | Drug Solvent | Polymer | Polymer Conc (%w/v) | Polymer Solvent | Solution Flow Rate (ml/min) | CO2 flow (ml/min) | Temp (°C) | Pressure (bar) | Nozzle tip diameter (µm) | Yield (%) | Comments | Morphology by SEM | DSC Peaks (ΔH J/g) | % Drug in Product by IJV (Wt %) |
|---------------|------------------|---------------------|------------|---------------------|---------------------|-----------------------------|-------------------|-----------|----------------|--------------------------|-----------|--|--------------------------------|--------------------|---------------------------------|
| R.ASF27 | 0.17 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | 580 | 69 | Fine powder | 10µm diameter irregular chunks | None | 20 |
| R.ASF30 | 0.17 | Ethanol / DCM (1:1) | HPMC 15cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | none | 35 | Fine powder | spheres, some chunks | None | 4 |
| R.ASF31 | 0.17 | Ethanol / DCM (1:1) | HPMC 15cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | none | 63 | Fine powder | spheres, some chunks | None | 19 |
| R.ASF32 | 0.50 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 580 | 60 | Fine particles produced with some hard lumps | 100µm needles & spheres | 83.0 | ND |
| R.ASF34 | 0.50 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 2.5 | 37 | 80 | 580 | ND | Particulates with exudate on nozzle | 3µm irregular spheres | None | ND |
| R.ASF38 | 0.17 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | 200 | 57 | Fine powder | 10µm irregular chunks | None | 17 |
| R.ASF40 | 0.17 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 10 | 50 | 120 | 200 | 62 | Fine powder | 200nm spheres | None | 29 |
| R.ASF43 | 0.17 | Ethanol / DCM (1:1) | HPMC 6cps | 0.50 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | 200 | 60 | Fine powder (large pressure fluctuations) | web like spheres | 0 | 17 |
| R.ASF96 (RS) | 0.1 | Ethanol / DCM (1:1) | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 65 | Fine powder | ND | 64 | 48.5 |
| R.ASF97 (RS) | 0.17 | Ethanol / DCM (1:1) | EC 7cps | 0.50 | Methanol | 0.2 | 20 | 34 | 80 | 100 | 66 | Fine powder | ND | None | 21 |
| R.ASF98 (RS) | 0.25 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.2 | 20 | 34 | 80 | 100 | 48 | Fine powder | ND | 0.2 | 28 |
| R.ASF99 (RS) | 1.00 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.2 | 20 | 34 | 80 | 100 | 74 | Fine powder | ND | 105 | 72 |
| R.ASF103 (RS) | 2.00 | Ethanol / DCM (1:1) | HPMC 3cps | 0.50 | Ethanol / DCM (1:1) | 0.2 | 20 | 34 | 80 | 100 | 76 | Fine powder | ND | 125.5 | 82 |
| R.ASF104 (RS) | 0.21 | Ethanol / DCM (1:1) | EC 7cps | 0.50 | Ethanol / DCM (1:1) | 0.2 | 20 | 34 | 80 | 100 | ND | Fine powder | ND | 15.8 | 34 |
| R.ASF105 (RS) | 0.09 | Ethanol / DCM (1:1) | EC 7cps | 0.50 | Ethanol / DCM (1:1) | 0.2 | 20 | 34 | 80 | 50 | 50 | Fine powder | ND | 16.4 | 12 |
| LSDA35 | 0.026 | Ethanol | EC 10cps | 0.5 | Ethanol | 0.1 | 20 | 37 | 100 | 200 | 46 | Fine white powder | ND | 3 | 0 |
| LSDA37 | 0.026 | Ethanol / DCM (1:1) | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | 200 | 44 | Fine white powder | ND | None | 2 |
| LSDA46 | 0.317 | Ethanol | EC 10cps | 0.5 | Ethanol | 0.1 | 20 | 37 | 100 | 200 | 53 | Fine white powder | ND | 74 | 19 |
| LSDA47 | 0.066 | Ethanol / DCM (1:1) | HPMC | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 120 | 200 | 64 | Fine white powder | ND | None | 2 |
| LSDA48 | 0.079 | Ethanol | EC 10cps | 0.5 | Ethanol | 0.1 | 20 | 37 | 100 | 200 | 9 | Fine white powder | ND | 3 | 1 |
| LSDA51 | 0.079 | Ethanol | EC 7cps | 0.5 | Ethanol | 0.1 | 20 | 37 | 100 | 200 | 16 | Fine white powder | ND | None | 1 |

NA - Not applicable, ND - Not determined

All experiments used a two component nozzle

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Theophylline Result Table 9

| Experiment | Drug Conc'n (P ₀ w/v) | Polymer | Polymer Conc'n (P ₀ w/v) | Solvent | Solution Flow Rate (ml/min) | CO ₂ Flow Rate (ml/min) | Temp (°C) | Pressure (bar.g) | Nozzle tip diameter (µm) | Yield (%) | Product Description | Size (µm, by SEM) | Morphology (by SEM) | DSC Peaks °C (ΔH - J/g) | % Drug in Product by UV (Wt %) |
|------------|----------------------------------|-----------|-------------------------------------|---------------------|-----------------------------|------------------------------------|-----------|------------------|--------------------------|-----------|-----------------------------------|--------------------------------|--|-------------------------|--------------------------------|
| RASH1 | 0.17 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 200 | 60 | Fine white particulate | <0.1 x 0.1 | Amorphous aggregate | None | 3 |
| RASH2 | 0.17 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 73 | Fine white particulate | 20 x 20 x 0.1 x 0.1 | Amorphous aggregate / labular | None | 28 |
| RASH3 | 0.17 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 37 | 80 | 200 | 73 | Fine white particulate | 0.1 x 0.1 | Amorphous aggregate | None | 5 |
| RASH4 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 200 | 78 | Fine white particulate, some cobs | <0.1 x 0.1 / 20 x 5 / 30 x 1 | Amorphous aggregate / platy / acicular | 44.5 | 38 |
| RASH5 | 0.5 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 85 | Fine white particulate, some cobs | <0.1 x 0.1 / 50 x 30 / 3 x 0.1 | Amorphous aggregate / platy / acicular | 76.2 | 46 |
| RASH6 | 0.5 | EC 7cps | 0.5 | Ethanol | 0.2 | 20 | 37 | 80 | 200 | 13 | Fine white particulate, some cobs | 5 x 5 | Amorphous aggregate | None | 9 |
| RASH7 | 0.5 | EC 7cps | 0.5 | Ethanol | 0.1 | 20 | 37 | 80 | 200 | 30 | Fine white particulate | 5 x 5 | Amorphous aggregate | None | 5 |
| RASH8 | 0.33 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 37 | 80 | 200 | 69 | Fine white particulate, some cobs | 0.1 x 0.1 / 20 x 5 / 5 x 0.5 | Amorphous aggregate / platy / acicular | 14.3 | 21 |
| RASH9 | 0.33 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 74 | Fine white particulate, some cobs | 0.5 x 0.5 / 20 x 10 / 20 x 1 | Amorphous aggregate / platy / acicular | 41.2 | 59 |
| RASH10 | 0.17 | EC 7cps | 0.5 | Ethanol | 0.1 | 20 | 50 | 80 | 200 | 41 | Fine white particulate | 2 x 2 / 70 x 50 | Amorphous aggregate / platy | None | 28 |
| RASH11 | 0.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 34 | 80 | 100 | 47 | Fine white particulate | 1 x 1 / 2 x 6 | Amorphous aggregate / platy | 30.3 | 34 |
| RASH12 | 0.5 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 50 | 80 | 100 | 78 | Fine white particulate | 2 x 10 | Amorphous aggregate / platy | 55.2 | 48 |
| RASH13 | 0.17 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 50 | 80 | 100 | 43 | Fine white particulate | 2 x 2 / 6 x 2 | Amorphous aggregate / platy | ND | 17 |
| RASH14 | 0.25 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 50 | 80 | 100 | 49 | Fine white particulate | 2 x 2 / 8 x 2 | Amorphous aggregate / platy | None | 27 |
| RASH15 | 1.0 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 50 | 80 | 100 | 92 | Fine white particulate | ND | ND | 77.3 | 67 |
| LSDA1 | 0.33 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 37 | 80 | 500 | 44 | Fine white powder | ND | ND | None | 35 |
| LSDA4 | 0.056 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 200 | 6 | Fine white powder | ND | ND | None | 7 |
| LSDA5 | 0.056 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 200 | 33 | Fine white powder | ND | ND | None | 2 |
| LSDA52 | 0.125 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 200 | ND | ND | ND | ND | None | 17 |
| LSDA53 | 0.125 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.2 | 20 | 50 | 80 | 200 | 76 | Fine white powder | ND | ND | 16.0 | 20 |
| LSDA55 | 0.172 | EC 7cps | 0.5 | Ethanol / DCM (1:1) | 0.3 | 20 | 50 | 80 | 100 | 58 | Fine white powder | ND | ND | 7.9 | 26 |
| LSDA56 | 1.515 | HPMC 3cps | 0.5 | Ethanol / DCM (1:1) | 0.1 | 20 | 50 | 80 | 200 | 14 | Fine white powder | ND | ND | 83.7 | 71 |

All experiments used a two component nozzle

NA - Not applicable, ND - Not determined

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Table 11 - Compound (I) and HPC

| Run No. | Solvent | Soln. Conc. (w/v) | P:R (% Drug / HPLC) | CO ₂ Flow (ml/min) | Soln. Flow (ml/min) | P. (bar) | T. (°C) | AP. (bar) | Nozzle Size (mm) | Yield (%) | Particle Size (µm) | SEM Morphology / Description | Comments |
|---------|--------------------|-------------------|---------------------|-------------------------------|---------------------|----------|---------|-----------|------------------|-----------|--------------------|---|---|
| 1 | 1:1 v/v DCM/EtOH | 4.5 | 89:11 | 18.0 | 0.2 | 90 | 65 | 300 | 0.1 | 73 | 16.2 (A) | Clusters of rounded particles < 2µm | Small nozzle tip causing large pressure build up |
| 2 | 1:1 v/v DCM/EtOH | 4.5 | 89:11 | 18.0 | 0.2 | 90 | 52 | 300 | 0.1 | 72 | 3.3 (A) | Clusters of rounded particles < 2µm and needles < 5µm | New 0.1mm tip. Blockages again causing processing problems. |
| 3 | 1:1 v/v DCM/EtOH | 3.5 | 86:14 (86:7) | 18.0 | 0.2 | 90 | 60 | 280 | 0.1 | 70 | 7.2 (A) | Clusters of rounded particles < 2µm. Some needles. | Large pressure build up |
| 4 | 1:1 v/v DCM/EtOH | 3.5 | 86:14 (78.6) | 18.0 | 0.2 | 90 | 70 | 250 | 0.2 | 69 | 18.7 (A) | Clusters of rounded particles < 2µm. Some needles. | Larger nozzle tip does not reduce pressure build up. Higher temp. HPC only using same conditions. A tiny amount of lumps produced |
| 5 | 1:1 v/v DCM/EtOH | 0.5 | 0:100 | 18.0 | 0.2 | 90 | 70 | 30 | 0.2 | 4 | - | - | Drug only at higher temperature conditions. |
| 6 | 1:1 v/v DCM/EtOH | 3.0 | 100:0 | 18.0 | 0.2 | 90 | 70 | 300 | 0.2 | 47 | 2.8 | Clusters of rounded particles < 2µm | Reduced nozzle blockages with higher polymer content. |
| 7 | 1:1 v/v DCM/EtOH | 1.0 | 50:50 (43.8) | 18.0 | 0.2 | 90 | 70 | 15 | 0.2 | 24 | - | Clusters/agglomerates of flake like particles < 2µm | Lower nozzle blockages. Particles are more agglomerated |
| 8 | 1:1 v/v DCM/EtOH | 0.7 | 30:70 (26.7) | 18.0 | 0.2 | 90 | 70 | 10 | 0.2 | 40 | - | Agglomerated flakes/plates | Repeat of run 7 |
| 9 | 1:1 v/v DCM/EtOH | 1.0 | 50:50 | 18.0 | 0.2 | 90 | 70 | 10 | 0.2 | 53 | - | Clusters/agglomerates of flake like particles < 2µm | Large nozzle blockages. Solvent modified to increase saturation |
| 10 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20.0 | 0.2 | 90 | 67 | 120 | 0.2 | 72 | 2.6 | Clusters of rounded particles < 2µm | Sample very agglomerated, hence larger particle size results |
| 11 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 | 20.0 | 0.2 | 90 | 70 | 110 | 0.2 | 72 | 22.1 | Small particles < 2 µm, highly agglomerated. | Large nozzle blockages. Lower soln flow has reduced particle size |
| 12 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 | 20.0 | 0.1 | 90 | 70 | 200 | 0.2 | 73 | 3.8 | Clusters of rounded/plate like particles < 2µm | High concentration for greater throughput. High yield |
| 13 | 1:1 v/v DCM/EtOH | 3.5 | 89:11 | 20.0 | 0.2 | 90 | 70 | 150 | 0.2 | 97 | 10.8 | Agglomerated rounded/plate like particles < 2µm | Repeat of run 12 |
| 14 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 (79.0) | 20.0 | 0.1 | 90 | 70 | 150 | 0.2 | 95 | 3.8 | Clusters of rounded/plate like particles < 2µm | Reduced nozzle blockages with higher HPC content. |
| 15 | 35:65 v/v DCM/EtOH | 1.0 | 70:30 | 20.0 | 0.2 | 90 | 70 | 45 | 0.2 | 84 | 17.7 | Agglomerated plate like particles < 3µm, some small needles | Pure drug sample to be used as a control for dissolution. |
| 16 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20.0 | 0.1 | 90 | 70 | 150 | 0.2 | 95 | 2.5 | Agglomerated rounded particles < 2µm. No agglomeration. | Particles size smaller than in run 15. |
| 17 | 35:65 v/v DCM/EtOH | 1.0 | 70:30 (64.5) | 20.0 | 0.1 | 90 | 70 | 60 | 0.2 | 96 | 13.1 | Agglomerated plate like particles < 2µm, numerous small needles | Reduced solution flow? |

Table 12 - Compound (I) and HPC

| Run No. | Solvent | Soln. Cons. (w/v) | D:P (% Drug HPLC) | CO ₂ Flow (ml/min) | Soln. Flow (ml/min) | P (bar) | T (°C) | AP (bar) | Nozzle Size (mm) | Yield (%) | Particle Size (S) (µm) | SEM Morphology/Description | Comments |
|---------|-------------------|-------------------|-------------------|-------------------------------|---------------------|---------|--------|----------|------------------|-----------|------------------------|---|--|
| 18 | 35:65 v/v DCM/EOH | 1.0 | 50:50 | 20.0 | 0.1 | 90 | 70 | 12 | 0.2 | 73 | - | - | CO ₂ ran out mid run leaving wet material. |
| 19 | 25:75 v/v DCM/EOH | 1.0 | 50:50 (43:6) | 20.0 | 0.1 | 90 | 70 | 40 | 0.2 | 88 | 28.4 | Agglomerated/fused plate like particles | Solvent modified to achieve maximum saturation. |
| 20 | 20:80 v/v DCM/EOH | 1.0 | 50:50 | 20.0 | 0.1 | 90 | 70 | 30 | 0.2 | - | 18.0 | Agglomerated/fused plate like particles | Drug solution crashed out mid run. Run abandoned |
| 21 | 25:75 v/v DCM/EOH | 1.0 | 50:50 (53:7) | 20.0 | 0.1 | 90 | 70 | 45 | 0.2 | 74 | 20.7 | Agglomerated/fused plate like particles | 500 ml vessel used to stop material from plugging the nozzle region. |
| 22 | 20:80 v/v DCM/EOH | 1.0 | 20:80 (17:9) | 20.0 | 0.1 | 90 | 70 | 12 | 0.2 | 27 | - | Fused strings of large, > 10 µm, rounded, particles | 500ml vessel. Very low yield. |
| 23 | 35:65 v/v DCM/EOH | 1.0 | 95:5 | 20.0 | 0.1 | 90 | 70 | 50 | 0.2 | 90 | 2.8 | Clusters of small rounded / plate like particles < 2 µm | Addition of 5% HPC may improve dissolution further. Small particles |
| 24 | 35:65 v/v DCM/EOH | 1.0 | 85:15 | 20.0 | 0.2 | 130 | 60 | 25 | 0.2 | 81 | 15.3 | Larger angular particles. Some agglomeration | New P + T conditions reduce ΔP but particle morphology changes |

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Table 13 - Compound (I) and P-237

| Run No. | Solvent | Soln. Conc. (w/v) | D:R (%DMSO:HPLC) | CO ₂ Flow (ml/min) | Soln. Flow (ml/min) | P (bar) | T (°C) | AP (bar) | Nozzle Size (mm) | Yield (%) | Particle Size (S) (um) | SEM Morphology / Description | Comments |
|---------|---------|-------------------|------------------|-------------------------------|---------------------|---------|--------|----------|------------------|-----------|------------------------|--|--|
| 25 | DCM | 1.0 | 0:100 | 18.0 | 0.1 | 100 | 35 | - | 0.2 | - | - | - | Poloxamer did not precipitate under these conditions. |
| 26 | DCM | 2.5 | 70:30 (70:9) | 18.0 | 0.1 | 100 | 35 | 200 | 0.2 | 36 | 14.8 | Non-uniform plates and angular particles up to 30 um in size | Severe nozzle blockages. Low yield. |
| 27 | DCM | 1.75 | 100:0 | 18.0 | 0.1 | 100 | 35 | 35 | 0.75 | 62 | 6.4 | Non-uniform plates and angular particles up to 10 um in size | Large nozzle tip to reduce nozzle blocking. Concentration reduced. |
| 28 | DCM | 1.75 | 100:0 | 18.0 | 0.2 | 100 | 35 | 80 | 0.75 | 58 | 6.1 | Non-uniform plates and angular particles up to 10 um in size | Increase solution flow to reduce nozzle blockages. |
| 29 | DCM | 1.75 | 100:0 | 18.0 | 0.2 | 100 | 35 | 50 | - | 67 | 11.3 | Large non-uniform chunks up to 20 um in size | No nozzle tip. |
| 30 | DCM | 2.0 | 100:0 | 18.0 | 0.2 | 90 | 70 | 100 | 0.2 | 82 | 5.2 | Clusters of small rounded particles < 2 um | Temperature too high to process poloxamer. |
| 31 | DCM | 1.0 | 100:0 | 18.0 | 0.1 | 75 | 35 | 65 | 0.2 | 75 | 2.4 | Clusters of small rounded particles < 2 um | Reduced T + P, solution conc. and flow rate to get smaller particles |
| 32 | DCM | 1.0 | 70:30 (70:1) | 18.0 | 0.1 | 75 | 35 | 45 | 0.2 | 82 | 19.0 | Clusters of small plates < 6 um | Introduction of poloxamer changes morphology and particle size. |
| 33 | DCM | 1.0 | 50:50 (46:6) | 18.0 | 0.1 | 75 | 35 | 45 | 0.2 | 59 | - | Agglomerated large plates | Very agglomerated sample. |
| 34 | DCM | 1.0 | 20:80 | 18.0 | 0.1 | 75 | 35 | 40 | 0.2 | 4 | - | Agglomerated poloxamer plates | Particles are difficult to precipitate at higher poloxamer contents. |
| 35 | DCM | 1.0 | 70:30 (74:7) | 18.0 | 0.2 | 75 | 35 | 40 | 0.2 | 27 | - | Clusters of plates up to 20 um | Solution flow increased to get higher throughput. Yield reduced. |
| 36 | DCM | 1.0 | 85:15 (85:0) | 18.0 | 0.1 | 75 | 35 | 150 | 0.2 | 85 | 11.3 | Clusters of small plates < 8 um | Particles appear clustered rather than agglomerated together. |
| 37 | DCM | 3.0 | 100:0 | 18.0 | 0.2 | 90 | 68 | 350 | 0.2 | 75 | 4.5 | - | Run abandoned midway due to extreme nozzle blockages. |
| 38 | DCM | 2.0 | 100:0 | 18.0 | 0.15 | 75 | 35 | 150 | 0.2 | 92 | 2.0 | Well defined rounded particles < 2 um. No agglomeration | Repeat of run 31 but throughput increased. |
| 39 | DCM | 2.0 | 100:0 (95:8) | 18.0 | 0.15 | 75 | 35 | 250 | 0.2 | 87 | 2.1 | Well defined rounded particles < 2 um. No agglomeration | Repeat of run 38 to produce a larger batch. |
| 40 | DCM | 2.0 | 70:30 (71:3) | 18.0 | 0.15 | 75 | 35 | 250 | 0.2 | 95 | 20.9 | Agglomerated plates up to 10 um in size | Wide size distribution. Particle size increase with more poloxamer. |
| 41 | DCM | 2.0 | 70:30 (70:7) | 18.0 | 0.15 | 75 | 35 | 170 | 0.2 | 95 | 21.7 | Agglomerated plates up to 10 um in size | Material added to run 40 material. |
| 42 | DCM | 2.0 | 50:50 (53:7) | 18.0 | 0.15 | 75 | 35 | 100 | 0.2 | 77 | 32.4 | Agglomerated plates up to 20 um in size | Larger particles with increase in poloxamer. |
| 43 | DCM | 2.0 | 85:15 (86:2) | 18.0 | 0.15 | 75 | 35 | 170 | 0.2 | 96 | 12.3 | Agglomerated plates up to 10 um in size | Particle size reduced with lower poloxamer content. |

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Table 16 - Compound (II) and HPC

| Run No. | Solvent | Soln. Conc. (w/v) | Drug:Polymer (Polym. Type) | CO ₂ Flow (ml/min) | Soln. Flow (ml/min) | Pressure (bar) | Temp (°C) | ΔP (bar) | Nozzle Size (mm) | Yield (%) | Particle Size VMD (µm) | SEM Description/Morphology | Comments |
|---------|-------------------------------|-------------------|----------------------------|-------------------------------|---------------------|----------------|-----------|----------|------------------|-----------|------------------------|--|---|
| 1 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20 | 0.1 | 90 | 70 | 200 | 0.2 | 74 | 4.0 | Small discrete rounded/granular particles | Fine powder, phase-split conditions (similar to Compound (I)) |
| 2 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20 | 0.1 | 90 | 70 | 110 | 0.2 | 66 | 5.5 | Slightly aggregated plate-like/rounded particles | MeOH does not appear to help |
| 3 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20 | 0.2 | 120 | 60 | 140 | 0.2 | 78 | 4.5 | Slightly larger rounded/granular particles | More angular particles produced with homogenous conditions |
| 4 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20 | 0.2 | 150 | 50 | 200 | 0.2 | 64 | 6.6 | Small irregular chunks | Chunk like particles with higher density CO ₂ |
| 5 | 35:65 v/v DCM/EtOH | 1.0 | 100:0 | 20 | 0.1 | 150 | 50 | 250 | 0.2 | 59 | 8.5 | Irregular chunks up to 25µm | Problem with BPR during run may have caused larger particles |
| 6 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 (HPC) | 20 | 0.1 | 120 | 60 | 60 | 0.2 | 81 | 10.3 | Dual morphology. Small < 3µm and larger acicular particles | Reduced ΔP. Polymer and drug appear to crystallise separately |
| 7 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 (HPC) | 20 | 0.1 | 90 | 70 | 150 | 0.2 | 81 | 4.6 | Clusters of rounded/granular particles | Some fused particles. Sample appears to be a co-precipitate |
| 8 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 (Low Mw HPC) | 20 | 0.1 | 90 | 70 | 150 | 0.2 | 82 | 4.6 | Clusters of rounded/granular particles | Some fused particles. Sample appears to be a co-precipitate |
| 9 | 35:65 v/v DCM/EtOH | 1.0 | 85:15 (Low Mw HPC) | 20 | 0.1 | 120 | 60 | 70 | 0.2 | 85 | 11.0 | Dual morphology. Small < 3 µm and larger acicular particles | Reduced ΔP. Polymer and drug appear to crystallise separately |
| 10 | Acetone | 1.75 | 15:85 (HPC) | 20 | 0.1 | 120 | 60 | 5 | 0.2 | - | - | - | (50 ml vessel). Stringy polymer mass on nozzle tip |
| 11 | Acetone | 1.75 | 15:85 (HPC) | 20 | 0.1 | 120 | 60 | 30 | 0.1 | 46 | - | Small primary particles < 4 µm heavily aggregated/fused. True co-precipitate | (500 ml vessel). Coarse white powder covering entire vessel |
| 12 | 61:39 v/v Acetone Cyclohexane | 1.2 | 15:85 (HPC) | 20 | 0.1 | 120 | 60 | 20 | 0.1 | 34 | - | Small primary particles ~ 5 µm heavily aggregated/fused. True co-precipitate | (500 ml vessel). Coarse white powder covering entire vessel. Poor yield |
| 13 | Acetone | 2.0 | 20:80 (HPC) | 20 | 0.1 | 90 | 70 | 10 | 0.1 | 61 | 16.5 | Small primary particles < 5 µm heavily aggregated/fused. True co-precipitate | (500 ml vessel). Coarse white powder covering entire vessel |

Table 17 - Compound (II) and HPC (contd)

| Run No. | Solvent | Soln. Conc. (w/v) | Drug:Polymer (Polym. Type) | CO2 Flow (ml/min) | Soln. Flow (ml/min) | Pressure (bar) | Temp (°C) | ΔP (bar) | Nozzle Size (mm) | Yield (%) | Particle Size VMD (um) | SEM Description/Morphology | Comments |
|---------|-------------------------------|-------------------|----------------------------|-------------------|---------------------|----------------|-----------|----------|------------------|-----------|------------------------|---|---|
| 14 | Acetone | 2.1 | 30:70 (Low Mw HPC) | 20 | 0.1 | 150 | 50 | >200? | 0.1 | 37 | - | Small primary particles < 5 um heavily aggregated/fused. True co-precipitate | (500 ml vessel). Coarse white powder covering entire vessel. Problem with run (ΔP?) |
| 15 | Acetone | 2.1 | 30:70 (Low Mw HPC) | 20 | 0.1 | 120 | 60 | 20 | 0.2 | 80 | - | (50 ml vessel). Stringy polymer mass on nozzle tip | Pilot Plant. Coarse/fibrous powder covering vessel walls |
| 16 | Acetone | 2.0 | 25:75 (HPC) | 200 | 1.0 | 120 | 60 | 5 | 0.2 | 60 | 37.9 | Small primary particles < 5 um heavily aggregated/fused. True co-precipitate | Pilot Plant. Coarse/fibrous powder covering vessel walls |
| 17 | Acetone | 2.0 | 25:75 (HPC) | 200 | 1.0 | 120 | 60 | 5 | 0.2 | 62 | 12.0 | Small primary particles < 5 um heavily aggregated/fused. True co-precipitate | Pilot Plant. Coarse/fibrous powder covering vessel walls |
| 18 | Acetone | 2.0 | 30:70 (HPC) | 200 | 1.0 | 120 | 60 | 15 | 0.2 | 62 | 47.1 | Dual morphology. Small particles < 4 um and thin wafer like plates. | Pilot Plant. Coarse/fibrous powder covering vessel walls |
| 19 | 35:65 v/v DCM/EtOH | 1.0 | 90:10 (HPC) | 200 | 1.0 | 90 | 50 | 60 | 0.2 | 71 | 7.9 | Dual morphology. Small particles < 2 um but mostly thin wafer like plates. | Pilot Plant. Light, fluffy powder covering whole vessel |
| 20 | Acetone | 2.0 | 50:50 (HPC) | 200 | 1.0 | 120 | 60 | 20 | 0.2 | 66 | 33.7 | Small primary particles < 3 um heavily aggregated/fused. Appears to be co-precipitate | Pilot Plant. Coarse/fibrous powder covering vessel walls |
| 21 | 20:55 v/v Acetone/CycloHexane | 1.3 | 20:80 (P237) | 200 | 1.0 | 75 | 35 | 5 | 0.2 | <10 | - | Agglomerated/fused irregular shaped chunks | Pilot Plant. Thin white film coating walls. |
| 22 | Acetone | 2.0 | 50:50 (P237) | 200 | 1.0 | 80 | 35 | 30 | 0.2 | 20 | - | Small primary particles < 3 um heavily aggregated/fused. | Pilot Plant. Thin white powder film coating walls. |
| 23 | Acetone | 2.0 | 70:30 (HPC) | 200 | 1.0 | 120 | 60 | 60 | 0.2 | 50 | 13.4 | Small primary particles < 3 um heavily aggregated/fused. | Pilot Plant. Light, fluffy powder covering whole vessel |
| 24 | 35:65 v/v DCM/EtOH | 1.0 | 90:10 (HPC) | 200 | 1.0 | 90 | 52 | 45 | 0.2 | 65 | 6.7 | Dual morphology. Small particles < 2 um but mostly thin wafer like plates. | Pilot Plant. Light, fluffy powder covering whole vessel |
| 25 | Acetone | 2.0 | 10:90 (HPC) | 200 | 1.0 | 120 | 60 | 5 | 0.2 | 63 | >100 | Small primary particles < 3 um very heavily aggregated/fused. | Pilot Plant. Coarse/fibrous powder covering vessel walls |

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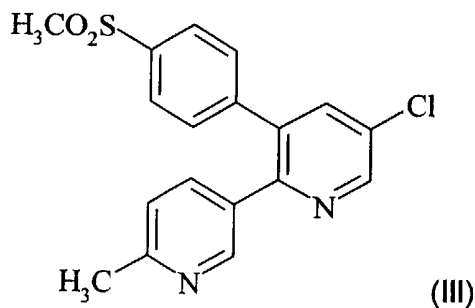
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Claims

- 1 A coformulation of an active substance and an oligomeric or polymeric material
other than poly vinyl pyrrolidone, containing at least 10 % w/w of the active substance, in
5 which between 90 and 100 % w/w of the active substance is present in an amorphous as
opposed to crystalline form, and wherein the amorphous phase active substance is stable,
with respect to its crystalline form(s) for at least eighteen months after its preparation
when stored at between 0 and 10 °C.
- 10 2 A coformulation according to claim 1, wherein the oligomeric or polymeric
material is a synthetic or naturally occurring homo- or co-oligomer/polymer selected from
the group consisting of:
- 15 a) acacia, tragacanth, alginates, alginic acid, starch, agar, carrageenan, xanthan
 gum, chitosan, gelatin, guar gum, pectin, amylase and lecithin, and derivatives
 and synthetic analogues thereof.
 - b) celluloses and cellulose derivatives.
 - c) homo- and co-polymers of hydroxy acids.
 - d) acrylates and their derivatives, methacrylic acids and methacrylates.
 - e) hydrated silicas.
 - 20 f) vinyl polymers, excluding poly vinyl pyrrolidone, and carboxy vinyl
 copolymers.
 - g) polymeric surfactants, including polyoxyalkylenes and their copolymers.
 - h) phospholipids.
 - i) carbohydrates.
 - 25 j) dendrimeric polymers.
 - k) poly(ϵ -caprolactones), DL-lactide-co-caprolactones and their derivatives.
 - l) poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers,
 including block copolymers, also derivatives of such polymers, also such
 polymers with incorporated esters of short chain α -hydroxy acids or glycolic-co-
30 lactic acid copolymers.

- 3 A coformulation according to claim 1 or claim 2, wherein the amorphous phase active substance is stable, with respect to its crystalline form(s), for at least twenty four months after its preparation, when stored at between 0 and 10 °C.
- 5 4 A coformulation according to claim 3, wherein the amorphous phase active substance is stable for at least thirty six months after its preparation, when stored at between 0 and 10 °C.
- 5 A coformulation according to any one of the preceding claims, wherein the
10 amorphous phase active substance is stable for the specified storage period, when stored at 25 °C.
- 6 A coformulation according to any one of the preceding claims, wherein the active substance comprises a pharmaceutically active substance.
- 15 7 A coformulation according to claim 6, wherein the active substance is selected from the group consisting of paracetamol, ketoprofen, indomethacin, carbamazepine, theophylline and ascorbic acid.
- 20 8 A coformulation according to claim 6, wherein the active substance is a COX-2 selective inhibitor.
- 9 A coformulation according to claim 8, wherein the COX-2 selective inhibitor is a diarylheterocycle.
- 25 10 A coformulation according to claim 8, wherein the COX-2 selective inhibitor is selected from the group consisting of (Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one, (Z)-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone and the compound of Formula (III):
- 30



- 11 A coformulation according to any one of the preceding claims, wherein the oligomeric or polymeric material is selected from the group consisting of cellulosic materials (including cellulose derivatives), vinyl polymers other than poly vinyl pyrrolidone, poly lactic or glycolic acids (including lactide/glycolide copolymers), and mixtures thereof.
- 12 A coformulation according to any one of the preceding claims, wherein the active substance is a polar substance and the oligomeric or polymeric material is hydrophobic.
- 13 A coformulation according to any one of the preceding claims, wherein 100 % w/w of the active substance is present in an amorphous as opposed to crystalline form.
- 14 A coformulation according to any one of the preceding claims, wherein the active substance represents at least 20 % w/w of the coformulation.
- 15 A coformulation according to any one of the preceding claims, comprising an intimate single-phase mixture of the active substance and the oligomeric or polymeric material, from which the dissolution rate of the active substance in an aqueous medium is no higher for the first 30 minutes than it is subsequently.
- 16 A coformulation according to claim 15, wherein the dissolution rate of the active substance in an aqueous medium is no higher for the first 60 minutes than it is subsequently.

17 A coformulation of an active substance and an oligomeric or polymeric material, the coformulation being substantially as herein described with reference to the accompanying illustrative drawings.

5 18 A pharmaceutical composition containing a coformulation according to any one of the preceding claims.



INVESTOR IN PEOPLE

Application No: GB 0220996.3
Claims searched: 1-18

Examiner: Dr William Thomson
Date of search: 26 February 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

| Category | Relevant to claims | Identity of document and passage or figure of particular relevance |
|----------|--------------------|---|
| X | 1-6 at least | GB 2053681A (YAMANOUCHI) See whole document, in particular Examples 1-9 and claims 1-8 |
| X | 1-6 at least | WO 00/56726A1 (FMC CORPORATION) See whole document, in particular |
| X | 1-6 at least | WO 97/39050A1 (EDWARD MENDELL CO., INC.) See whole document, in particular the Examples and claims 1, 8, 16, 21, 30 and 31 |
| X | 1-6 at least | WO 96/31202A1 (ELAN CORPORATION) See whole document, in particular page 2, line 29 - page 3, line 4, Examples 1 and 2 and claims 1-10 |
| X | 1-7 at least | US 4404183 (KAWATA ET AL) See whole document, in particular Examples 1-8 and claims 1-9 |
| X, P | 1-6 at least | WO 99/59541A2 (BASF AG) See whole document, in particular Examples 1-4 and claims 1-8 |
| X, P | 1-6 at least | US 5980942 (KATZHENDLER) See whole document, in particular column 3, lines 1-5 and 26-31, column 4 lines 34-67, column 5, lines 17-39 and 60-65 and column 12, lines 13-34 and claims 1-13 |

Categories:

| | | | |
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| X | Document indicating lack of novelty or inventive step | A | Document indicating technological background and/or state of the art. |
| Y | Document indicating lack of inventive step if combined with one or more other documents of same category. | P | Document published on or after the declared priority date but before the filing date of this invention. |
| & | Member of the same patent family | E | Patent document published on or after, but with priority date earlier than, the filing date of this application. |

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Application No: GB 0220996.3
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Date of search: 26 February 2003

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^v:

A5B

Worldwide search of patent documents classified in the following areas of the IPC⁷:

A61K

The following online and other databases have been used in the preparation of this search report :

CAS-ONLINE, EPODOC, JAPIO & WPI