In addition, as calcium channel antagonists, IV formulations of nimodipine cannot be used because of the high risk of inducing hypotension. Various controlled release and combinatorial formulations of nimodipine, for example, for immediate release (within 0-12 hours of administration) or slower release (within 12-24 hours) of administration are disclosed, for example, in US Patent Publication No. US 2010/0215737, US 2010/0239665, etc.

[0011] The commercial available nimodipine exists primarily as Form I. An orally administered immediate release formulation containing a co-precipitate of essentially amorphous nimodipine with poly-vinyl-pyrrolidone (PVP) is described in U.S. Patent No. 5,491,154. A pharmaceutical preparation containing a suspension of a mixture of nimodipine Form II crystals in a suspension solution is described in U.S. Patent No. 5,599,824. A solid dispersion of nimodipine Form II in PVP with fast release kinetics is described in Papageorgiou, G.Z. et al., "The effect of physical state on the drug dissolution rate: Miscibility studies of nimodipine with PVP", Journal of Thermal Analysis and Calorimetry, 2009, 95(3): 903-915.

[0012] Thus the formation of different polymorphic drug forms in a microparticle can impact product performance and stability. What are needed are formulation strategies that can control to formation of drug polymorphs. These needs and other needs are satisfied by the delivery systems and methods of the present invention. Additionally, the present invention describes sustained release microparticle formulations of nimodipine polymorphs with delayed release kinetics and improved stability.

SUMMARY

[0013] According to one ~~aspect~~ embodiment disclosed herein are processes for producing a substantially pure polymorphic form of a bioactive agent encapsulated into microparticles, wherein the process comprises: (a) providing a substantially pure crystalline form of the bioactive agent; (b) adding the substantially pure crystalline form of the bioactive agent to a polymer solution, thereby creating a mixture of the bioactive agent and the polymer solution; (c) homogenizing the mixture to form a disperse phase; (d) mixing the disperse phase with a

continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the bioactive agent; (e) forming and extracting the microparticles comprising the substantially pure polymorphic form of the bioactive agent; and (f) drying the microparticles.

According to one aspect, there is provided a process for producing microparticles encapsulating a crystalline polymorphic Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, the process comprising: (a) providing the polymorphic Form I of Nimodipine; (b) adding polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution; (c) homogenizing the mixture to form a disperse phase; (d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine; (e) forming and extracting the microparticles comprising the polymorphic Form I of Nimodipine; and (f) drying the microparticles, the microparticles being characterized by: (i) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and (ii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.

According to another aspect, there is provided a process for producing microparticles encapsulating a crystalline polymorphic Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC), the process comprising: (a) providing the polymorphic Form I of Nimodipine; (b) adding the polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution; (c) homogenizing the mixture to form a disperse phase; (d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine; (e) forming and extracting the microparticles comprising the polymorphic form of Nimodipine; and (f) drying the microparticles, the microparticles being characterized by: (i) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and (ii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.

[0014] According to a further ~~aspect~~embodiment, the polymer solutions of the aforementioned processes comprise a polymer and a solvent. It is understood and herein contemplated that the disclosed polymers comprise in one ~~aspect~~ embodiment polylactide,

polylactide-co-glycolide, poly(orthoester), and poly(anhydride). In a further ~~aspect~~embodiment, the polymer comprises 8515 DLG 6A, 8515 DLG 5A, 8515 DLG 4.5E, 88515 DLG 5E, 515 DLG 7A, 7525 DLG 7A, 7525 DLG 7E, 7525 DLG 5E, 6535DLG 5E, 6353 DLG 2E, 6535 DLG 4A, 5050DLG 4A, 5050 DLG2A, and 2000 MW DLPL. In another ~~aspect~~embodiment, the solvent can comprise ethyl acetate or dichloromethane.

[0015] According to another ~~aspect~~embodiment, the processes disclosed herein comprise drying the microparticle over a 4 to 48 hour period.

[0016] According to another ~~aspect~~embodiment, disclosed herein are semisolid, biodegradable, biocompatible delivery systems capable of sustained release kinetics comprising (i) a flowable microparticulate formulation comprising substantially pure crystalline form of a bioactive agent, , and (ii) a pharmaceutically acceptable carrier, wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution, wherein the bioactive agent is dispersed throughout each microparticle, and wherein the delivery system is further characterized in that the microparticulate formulation is capable of delayed release of the bioactive agent within a half life from 1 day to 30 days.

According to another aspect, there is provided a semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics comprising (i) a flowable microparticulate formulation comprising a crystalline polymorphic Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, the microparticulate formulation being characterized by: (a) a plurality of microparticles; (b) dispersal of the polymorphic Form I of Nimodipine throughout each microparticle, and (c) a load of at least 70 percent by weight relative to the total weight of Nimodipine of Form I of Nimodipine; and (ii) a pharmaceutically acceptable carrier, the delivery system being characterized by delayed release of the polymorphic Form I of Nimodipine from the delivery system, wherein one half of the polymorphic Form I of Nimodipine is released from the delivery system within 1 day to 30 days in vivo.

According to another aspect, there is provided a semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics comprising a (i) a flowable microparticulate formulation comprising a crystalline polymorphic Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC), the

microparticulate formulation being characterized by: (a) a plurality of microparticles; (b) dispersal of the polymorphic Form I of Nimodipine throughout each microparticle, and (c) a load of at least 70 percent by weight relative to the total weight of Nimodipine of Form I of Nimodipine; and (d) a pharmaceutically acceptable carrier, the delivery system being characterized by delayed release of the polymorphic Form I of Nimodipine from the delivery system, wherein one half of the polymorphic Form I of Nimodipine is released from the delivery system within 1 day to 30 days in vivo.

[0017] According to another ~~aspect~~embodiment, disclosed herein are methods for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, comprising: (a) providing a flowable sustained release microparticle composition comprising: (i) a microparticulate formulation comprising a therapeutic amount of a substantially pure crystalline form I of nimodipine having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, wherein the microparticulate formulation comprises a plurality microparticles of uniform size distribution, wherein the therapeutic amount is effective to treat a delayed complication of the constriction of a cerebral artery, and (ii) a pharmaceutical carrier; and (b) administering the

composition locally into a cerebral ventricle so that the microparticulate formation flows from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before releasing the nimodipine form I in the subrachnoid space, wherein the nimodipine form I contacts and flows around the at least one cerebral artery in the subarachnoid space without entering systemic circulation in an amount to cause unwanted side effects.

[0018] According to another ~~aspect~~embodiment, disclosed herein are methods for treating a cerebral vasospasm in a human subject, the method comprising: :(a) providing a flowable sustained release microparticle composition comprising: (i) a microparticulate formulation comprising a therapeutic amount of a substantially pure crystalline form I of nimodipine having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, wherein the microparticulate formulation comprises a plurality microparticles of uniform size distribution, wherein the therapeutic amount is effective to treat a delayed complication of the constriction of a cerebral artery, and (ii) a pharmaceutical carrier; and b) administering the pharmaceutical composition to the human subject locally via surgical injection in a cistern closest to a cerebral artery at risk for vasospasm, such that the composition flows around the cerebral artery without entering the systemic circulation in an amount to cause unwanted side effects; wherein the pharmaceutical composition produces a localized pharmacologic effect; and wherein the therapeutic amount is effective to treat the cerebral vasospasm.

According to another aspect, there is provided the use of a flowable sustained release microparticle composition comprising the semisolid, biodegradable, biocompatible delivery system as defined above in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, wherein the flowable, sustained release microparticle composition is suitable for administering locally, either (i) intraventricularly so that the microparticulate formulation is carried by cerebrospinal fluid (CSF) flow from the cerebral ventricle to the subarachnoid space before releasing the Nimodipine form I in the subrachnoid space, (ii) intracisternally into the subarachnoid space in a subarachnoid cistern closest to a cerebral artery at risk for interruption; or (iii) intrathecally into spinal subarachnoid space so the composition is carried by cerebrospinal fluid (CSF) flow from the spinal subarachnoid space to the subarachnoid space of the brain

before releasing the Form I of Nimodipine in the subarachnoid space of the brain; wherein interruption of the cerebral artery is accompanied by at least one delayed complication selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof; and wherein a therapeutic amount of the substantially pure crystalline Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11 that contacts and flows around the at least one cerebral artery in the subarachnoid space is effective to treat the delayed complication without entering systemic circulation in an amount to cause hypotension.

According to another aspect, there is provided the use of a flowable sustained release microparticle composition comprising the semisolid, biodegradable, biocompatible delivery system as defined above in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, wherein the flowable, sustained release microparticle composition is suitable for administering locally, either (i) intraventricularly so that the microparticulate formulation is carried by cerebrospinal fluid (CSF) flow from the cerebral ventricle to the subarachnoid space before releasing the Nimodipine form I in the subrachnoid space, (ii) intracisternally into the subarachnoid space in a subarachnoid cistern closest to a cerebral artery at risk for interruption; or (iii) intrathecally into spinal subarachnoid space so the composition is carried by cerebrospinal fluid (CSF) flow from the spinal subarachnoid space to the subarachnoid space of the brain before releasing the Form I of Nimodipine in the subarachnoid space of the brain; wherein interruption of the cerebral artery is accompanied by at least one delayed complication selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof; and wherein a therapeutic amount of the substantially pure crystalline Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC) that contacts and flows around the at least one cerebral artery in the subarachnoid space is effective to treat the delayed complication without entering systemic circulation in an amount to cause hypotension.

[0019] BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0021] **FIGURE 1** shows an IR spectrum of nimodipine Form I as obtained using a sample of commercially available USP nimodipine Form I RS.

[0022] FIGURE 2 shows an IR spectrum of nimodipine Form II as obtained using a sample of commercially available USP nimodipine Form II RS.

CLAIMS

What is claimed:

1. A process for producing a substantially pure polymorphic form of a bioactive agent encapsulated into microparticles, wherein the process comprises:

(a) providing a substantially pure crystalline form of the bioactive agent;

(b) adding the substantially pure crystalline form of the bioactive agent to a polymer solution, thereby creating a mixture of the crystalline form of the bioactive agent and the polymer solution;

(c) homogenizing the mixture to form a disperse phase;

(d) mixing the disperse phase with a continuous phase comprising a continuous process medium , thereby forming an emulsion comprising the bioactive agent;

(e) forming and extracting the microparticles comprising the substantially pure polymorphic form of the bioactive agent; and

(f) drying the microparticles.

2. The process according to claim 1, wherein the polymer solution comprises a solvent and a biodegradable polymer.

3. The process according to claim 2, wherein the biodegradable polymer is selected from the group consisting of polylactide, polylactide-co-glycolide, poly(orthoester), and poly(anhydride).

4. The process according to claim 3, wherein the polylactide co-glycolide comprises a 85:15, 75:25, 65:35, or 50:50 ratio of lactide to glycolide.

5. The process according to claim 4, wherein the biodegradable polymer comprises 8515 DLG 6A, 8515 DLG 5A, 8515 DLG 4.5E, 88515 DLG 5E, 515 DLG 7A, 7525 DLG 7A, 7525

DLG 7E, 7525 DLG 5E, 6535DLG 5E, 6353 DLG 2E, 6535 DLG 4A, 5050DLG 4A, 5050 DLG2A, or 2000 MW DLPL.

6. The process according to any of claims 2 to 4 wherein the solvent in the polymer solution comprises ethyl acetate or dichloromethane or a mixture thereof.

7. The process according to of any of claims 1 to 5 wherein the drying time is from 4 to 48 hours.

8. The process according to claim 1, wherein the bioactive agent is nimodipine.

9. The process according to claim 8, wherein the crystalline form of nimodipine substantially comprises nimodipine Form I.

10. The process according to claim 8, wherein the crystalline form of nimodipine substantially comprises nimodipine Form II.

11. The process according to claim 8, wherein the crystalline form of nimodipine is nimodipine Form I having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11.

12. The process according to claim 1, wherein the continuous process medium comprises water, dichloromethane, ethanol or a combination thereof.

13. The process according to claim 1, further comprising a surfactant in the continuous process medium.

14. The process according to claim 14, wherein the surfactant is polyvinyl alcohol (PVA).

15. The process according to claim 1, further comprising rinsing the microparticles prior to drying.

16. The process according to claim 1, wherein the second flow rate is 1.4 mL/min to 2.0 mL/min.

17. The process according to claim 1, wherein the dry rate is between 0.2 mLs per minute and 2 liters per minute.

18. The process according to claim 1, wherein the process further comprises:

(g) analyzing a morphology of the microparticles via X-ray powder diffraction (XRPD), Raman spectroscopy, Differential Scanning Calorimetry, or a combination thereof.

19. A semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics comprising a

(i) a flowable microparticulate formulation comprising substantially pure crystalline form of a polymorphic bioactive agent, and

(ii) a pharmaceutically acceptable carrier,

wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution

wherein the bioactive agent is dispersed throughout each microparticle, and

wherein the delivery system is further characterized in that the microparticulate formulation is capable of delayed release of the bioactive agent within a half life from 1 day to 30 days.

20. The delivery system according to claim 19, wherein the bioactive agent is Form I of Nimodipine having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11.

21. The delivery system according to claim 19, wherein each microparticle comprises a matrix.

22. The delivery system according to claim 19, wherein the microparticulate formulation comprises a powder suspension of microparticles.

23. The delivery system according to claim 19, wherein the microparticulate formulation further comprises a slow-release compound.

24. The delivery system according to claim 23, wherein the slow release compound is a biodegradable polymer.

25. The delivery system according to claim 19, wherein drug load of the composition contained within the delivery system ranges from about 25% (by weight) to 75% by weight.

26. The delivery system according to claim 25, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

27. A method for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, comprising:

(a) providing a flowable sustained release microparticle composition comprising:

(i) a microparticulate formulation comprising a therapeutic amount of a substantially pure crystalline form I of nimodipine having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, wherein the microparticulate formulation comprises a plurality microparticles of uniform size distribution, wherein the therapeutic amount is effective to treat a delayed complication of the interruption of the cerebral artery, and

(ii) a pharmaceutical carrier; and

(b) administering the composition locally into a cerebral ventricle so that the microparticulate formation flows from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before releasing the nimodipine form I in the subrachnoid space, wherein the nimodipine form I contacts and flows around the at least one cerebral artery in the subarachnoid space without entering systemic circulation in an amount to cause unwanted side effects.

28. The method according to claim 27, wherein each microparticle comprises a matrix.

29. The method according to claim 27, wherein the delayed complication is selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof.

30. The method according to claim 27, wherein the microparticulate formulation comprises a powder suspension of microparticles.

31. The method according to claim 27, wherein the microparticulate formulation further comprises a slow-release compound.

32. The method according to claim 31, wherein the slow release compound is a biodegradable polymer.

33. The method according to claim 32, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

34. The method according to claim 27, wherein administering occurs via a surgical injection apparatus.

35. The method according to claim 34, wherein the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

36. A method for treating a cerebral vasospasm in a human subject, the method comprising:

(a) providing a flowable sustained release microparticle composition comprising: (i) a microparticulate formulation comprising a therapeutic amount of a substantially pure crystalline form I of nimodipine having an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, wherein the microparticulate formulation comprises a plurality microparticles of uniform size distribution, wherein the therapeutic amount is effective to treat a delayed

complication of the constriction of a cerebral artery, and (ii) a pharmaceutical carrier; and

b) administering the pharmaceutical composition to the human subject locally via surgical injection in a subarachnoid cistern closest to a cerebral artery at risk for vasospasm, such that the composition flows around the cerebral artery without entering the systemic circulation in an amount to cause unwanted side effects;

wherein the pharmaceutical composition produces a localized pharmacologic effect; and wherein the therapeutic amount is effective to treat the cerebral vasospasm.

37. The method according to claim 36, wherein the carrier is a gel compound.

38. The method according to claim 36, wherein the carrier is a slow-release solid compound.

39. The method according to claim 36, wherein the subarachnoid cistern closest to a cerebral artery at risk for vasospasm in step (b) is from about 0.001 mm to about 10 mm from the cerebral artery.

CLAIMS

What is claimed:

1. A process for producing microparticles encapsulating a crystalline polymorphic Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, the process comprising:

(a) providing the polymorphic Form I of Nimodipine;

(b) adding polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution;

(c) homogenizing the mixture to form a disperse phase;

(d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine;

(e) forming and extracting the microparticles comprising the polymorphic Form I of Nimodipine; and

(f) drying the microparticles,

the microparticles being characterized by:

(i) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and

(ii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.

2. The process according to claim 1, wherein the polymer solution comprises a solvent and a biodegradable polymer.

3. The process according to claim 2, wherein the biodegradable polymer is selected from the group consisting of polylactide, polylactide-co-glycolide, poly(orthoester), and poly(anhydride).

4. The process according to claim 3, wherein the polylactide co-glycolide comprises a 85:15, 75:25, 65:35, or 50:50 ratio of lactide to glycolide.

5. The process according to claim 2 wherein the solvent in the polymer solution comprises ethyl acetate, dichloromethane, or a mixture thereof.

6. The process according to claim 1 wherein the drying time is from 4 to 48 hours.

7. The process according to claim 1, wherein the continuous process medium comprises water, dichloromethane, ethanol or a combination thereof.

8. The process according to claim 1, further comprising a surfactant in the continuous process medium.

9. The process according to claim 8, wherein the surfactant is polyvinyl alcohol (PVA).

10. The process according to claim 1, further comprising rinsing the microparticles prior to drying.

11. The process according to claim 1, wherein the drying rate is between 0.2 mLs per minute and 2 liters per minute.

12. The process according to claim 1, wherein the process further comprises:

(g) analyzing a morphology of the microparticles via, Raman spectroscopy, Differential Scanning Calorimetry, or a combination thereof.

13. A semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics comprising

(i) a flowable microparticulate formulation comprising a crystalline polymorphic Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11, the microparticulate formulation being characterized by:

(a) a plurality of microparticles;

(b) dispersal of the polymorphic Form I of Nimodipine throughout each microparticle, and

(c) a load of at least 70 percent by weight relative to the total weight of Nimodipine of Form I of Nimodipine; and

(ii) a pharmaceutically acceptable carrier,

the delivery system being characterized by delayed release of the polymorphic Form I of Nimodipine from the delivery system, wherein one half of the polymorphic Form I of Nimodipine is released from the delivery system within 1 day to 30 days in vivo.

14. The delivery system according to claim 13, wherein each microparticle comprises a matrix.

15. The delivery system according to claim 13, wherein the microparticulate formulation comprises a powder suspension of microparticles.

16. The delivery system according to claim 13, wherein the microparticulate formulation further comprises a biodegradable polymer.

17. The delivery system according to claim 13, wherein Nimodipine load of the formulation contained within the delivery system ranges from about 25% (by weight) to 75% by weight relative to the total weight of the formulation.

18. The delivery system according to claim 17, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

19. Use of a flowable sustained release microparticle composition comprising the semisolid, biodegradable, biocompatible delivery system according to claim 19 in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject,

wherein the flowable, sustained release microparticle composition is suitable for administering locally, either

(i) intraventricularly so that the microparticulate formulation is carried by cerebrospinal fluid (CSF) flow from the cerebral ventricle to the subarachnoid space before releasing the Nimodipine form I in the subrachnoid space,

(ii) intracisternally into the subarachnoid space in a subarachnoid cistern closest to a cerebral artery at risk for interruption; or

(iii) intrathecally into spinal subarachnoid space so the composition is carried by cerebrospinal fluid (CSF) flow from the spinal subarachnoid space to the subarachnoid space of the brain before releasing the Form I of Nimodipine in the subarachnoid space of the brain;

wherein interruption of the cerebral artery is accompanied by at least one delayed complication selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof; and

wherein a therapeutic amount of the substantially pure crystalline Form I of Nimodipine that has an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11 that contacts and flows around the at least one cerebral artery in the subarachnoid space is effective to treat the delayed complication without entering systemic circulation in an amount to cause hypotension.

20. The use according to claim 19, wherein each microparticle comprises a matrix.

21. The use according to claim 19, wherein the microparticulate formulation is a biodegradable polymer.

22. The use according to claim 21, wherein the biodegradable polymer is selected from the group consisting of polylactide polyglycolide, poly(orthoester), and poly(anhydride).

23. The use according to claim 19, wherein administering occurs via an injection apparatus.

24. The use according to claim 23, wherein the administering occurs via a needle, a cannula, a catheter or a combination thereof.

25. The semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics according to claim 13, wherein the microparticulate formulation is characterized by a Nimodipine load of from about 25% to 75% by weight relative to the total weight of the formulation and each microparticle comprises a matrix.

26. The semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics according to claim 13, wherein the flowable microparticulate formulation is prepared by a process comprising:

(a) providing the polymorphic Form I of Nimodipine with an X-ray Powder Diffraction (XRPD) spectrum substantially the same as the X-Ray Powder Diffraction (XRPD) spectrum shown in Fig. 11;

(b) adding the polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution;

wherein the polymer solution comprises a solvent and a biodegradable polymer, the solvent in the polymer solution comprises ethyl acetate or dichloromethane or a mixture thereof and the biodegradable polymer is selected from the group consisting of polylactide, polylactide-do-glycolide, poly(orthoester), and poly(anhydride);

(c) homogenizing the mixture to form a disperse phase;

(d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine;

(e) forming and extracting the microparticles comprising the polymorphic form of Nimodipine; and

(f) drying the microparticles for a time from 4 to 48 hours,

wherein the microparticulate formulation is characterized by:

(i) a plurality of microparticles;

(ii) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and

(iii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.

27. A process for producing microparticles encapsulating a crystalline polymorphic Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC), the process comprising:

(a) providing the polymorphic Form I of Nimodipine;

(b) adding the polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution;

(c) homogenizing the mixture to form a disperse phase;

(d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine;

(e) forming and extracting the microparticles comprising the polymorphic form of Nimodipine; and

(f) drying the microparticles,

the microparticles being characterized by:

(i) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and

(ii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.

28. The process according to claim 27, wherein the polymer solution comprises a solvent and a biodegradable polymer.

29. The process according to claim 28, wherein the biodegradable polymer is selected from the group consisting of polylactide, polylactide-co-glycolide, poly(orthoester), and poly(anhydride).

30. The process according to claim 29, wherein the polylactide co-glycolide comprises a 85:15, 75:25, 65:35, or 50:50 ratio of lactide to glycolide.

31. The process according to claim 28 wherein the solvent in the polymer solution comprises ethyl acetate, dichloromethane, or a mixture thereof.

32. The process according to claim 27 wherein the drying time is from 4 to 48 hours.

33. The process according to claim 27, wherein the continuous process medium comprises water, dichloromethane, ethanol or a combination thereof.

34. The process according to claim 27, further comprising a surfactant in the continuous process medium.

35. The process according to claim 34, wherein the surfactant is polyvinyl alcohol (PVA).

36. The process according to claim 27, further comprising rinsing the microparticles prior to drying.

37. The process according to claim 27, wherein the drying rate is between 0.2 mLs per minute and 2 liters per minute.

38. The process according to claim 27, wherein the process further comprises:

(g) analyzing a morphology of the microparticles via X-ray powder diffraction (XRPD), Raman spectroscopy, or a combination thereof.

39. A semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics comprising a

(i) a flowable microparticulate formulation comprising a crystalline polymorphic Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC), the microparticulate formulation being characterized by:

(a) a plurality of microparticles;

(b) dispersal of the polymorphic Form I of Nimodipine throughout each microparticle, and

(c) a load of at least 70 percent by weight relative to the total weight of Nimodipine of Form I of Nimodipine; and

(d) a pharmaceutically acceptable carrier,

the delivery system being characterized by delayed release of the polymorphic Form I of Nimodipine from the delivery system, wherein one half of the polymorphic Form I of Nimodipine is released from the delivery system within 1 day to 30 days in vivo.

40. The delivery system according to claim 39, wherein each microparticle comprises a matrix.

41. The delivery system according to claim 39, wherein the microparticulate formulation comprises a powder suspension of microparticles.

42. The delivery system according to claim 39, wherein the microparticulate formulation further comprises a biodegradable polymer.

43. The delivery system according to claim 39, wherein Nimodipine load of the formulation contained within the delivery system ranges from about 25% (by weight) to 75% by weight relative to the total weight of the formulation.

44. The delivery system according to claim 43, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

45. Use of a flowable sustained release microparticle composition comprising the semisolid, biodegradable, biocompatible delivery system according to claim 39 in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject,

wherein the flowable, sustained release microparticle composition is suitable for administering locally, either

(i) intraventricularly so that the microparticulate formulation is carried by cerebrospinal fluid (CSF) flow from the cerebral ventricle to the subarachnoid space before releasing the Nimodipine form I in the subrachnoid space,

(ii) intracisternally into the subarachnoid space in a subarachnoid cistern closest to a cerebral artery at risk for interruption; or

(iv) intrathecally into spinal subarachnoid space so the composition is carried by cerebrospinal fluid (CSF) flow from the spinal subarachnoid space to the subarachnoid

space of the brain before releasing the Form I of Nimodipine in the subarachnoid space of the brain;

wherein interruption of the cerebral artery is accompanied by at least one delayed complication selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof; and

wherein a therapeutic amount of the substantially pure crystalline Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC) that contacts and flows around the at least one cerebral artery in the subarachnoid space is effective to treat the delayed complication without entering systemic circulation in an amount to cause hypotension.

46. The use according to claim 45, wherein each microparticle comprises a matrix.

47. The use according to claim 45, wherein the microparticulate formulation is a biodegradable polymer.

48. The use according to claim 47, wherein the biodegradable polymer is selected from the group consisting of polylactide polyglycolide, poly(orthoester), and poly(anhydride).

49. The use according to claim 45, wherein administering occurs via an injection apparatus.

50. The use according to claim 49, wherein the administering occurs via a needle, a cannula, a catheter or a combination thereof.

51. The semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics according to claim 39, wherein the microparticulate formulation is characterized by a Nimodipine load of from about 25% to 75% by weight relative to the total weight of the formulation and each microparticle comprises a matrix.

52. The semisolid, biodegradable, biocompatible delivery system capable of sustained release kinetics according to claim 39, wherein the flowable microparticulate formulation is prepared by a process comprising:

(a) providing the polymorphic Form I of Nimodipine characterized by a melting range of 122° C to 127° C as measured by Differential Scanning Calorimetry (DSC);

(b) adding the polymorphic Form I of Nimodipine to a polymer solution, thereby creating a mixture of the polymorphic Form I of Nimodipine and the polymer solution;

wherein the polymer solution comprises a solvent and a biodegradable polymer, the solvent in the polymer solution comprises ethyl acetate or dichloromethane or a mixture thereof and the biodegradable polymer is selected from the group consisting of polylactide, polylactide-do-glycolide, poly(orthoester), and poly(anhydride);

(c) homogenizing the mixture to form a disperse phase;

(d) mixing the disperse phase with a continuous phase comprising a continuous process medium, thereby forming an emulsion comprising the polymorphic Form I of Nimodipine;

(e) forming and extracting the microparticles comprising the polymorphic form of Nimodipine; and

(f) drying the microparticles for a time from 4 to 48 hours,

wherein the microparticulate formulation is characterized by:

(i) a plurality of microparticles;

(ii) dispersal of the polymorphic form I of Nimodipine throughout each microparticle; and

(iii) a load of at least 70% by weight relative to the total weight of Nimodipine of Form I of Nimodipine.