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(54) **Titre : FORMULATIONS DE MICROSPHERES COMPRENANT DES INHIBITEURS DE BTK ET LEURS PROCEDES DE FABRICATION ET D'UTILISATION**
(54) **Title: MICROSPHERE FORMULATIONS COMPRISING BTK INHIBITORS AND METHODS FOR MAKING AND USING THE SAME**

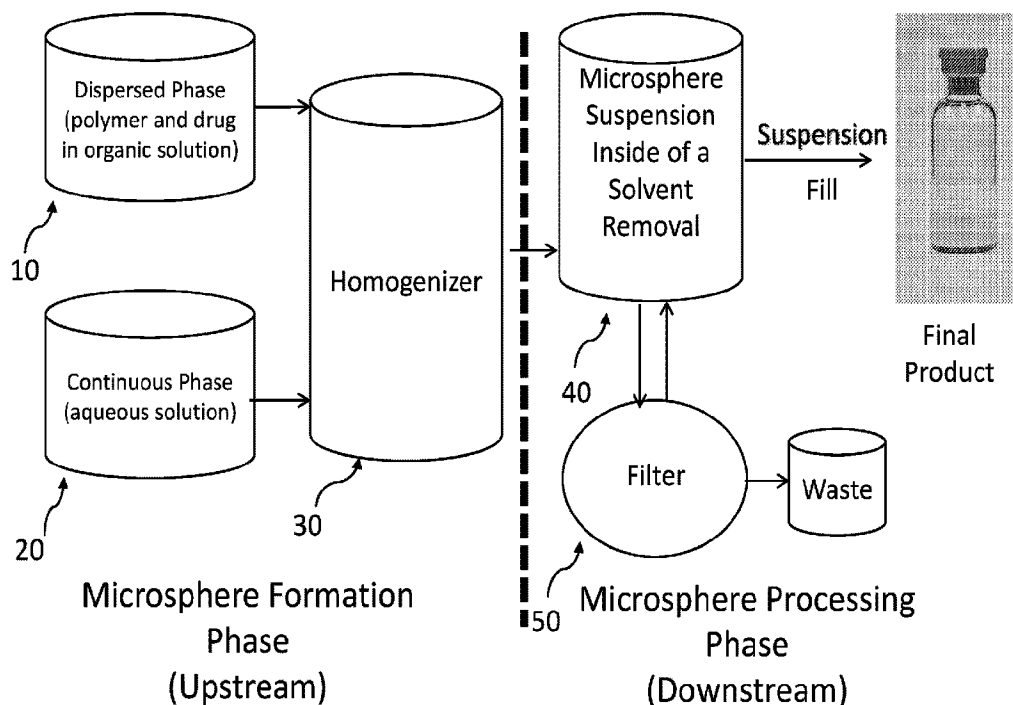


FIG. 1

(57) **Abrégé/Abstract:**

Extended-release microsphere formulations comprising a BTK inhibitor are provided. In one aspect, the microsphere formulations are characterized in that the BTK inhibitor is released in vivo in humans over a period of from about 7 to about 28 days. Methods for making and using the formulations are also provided.

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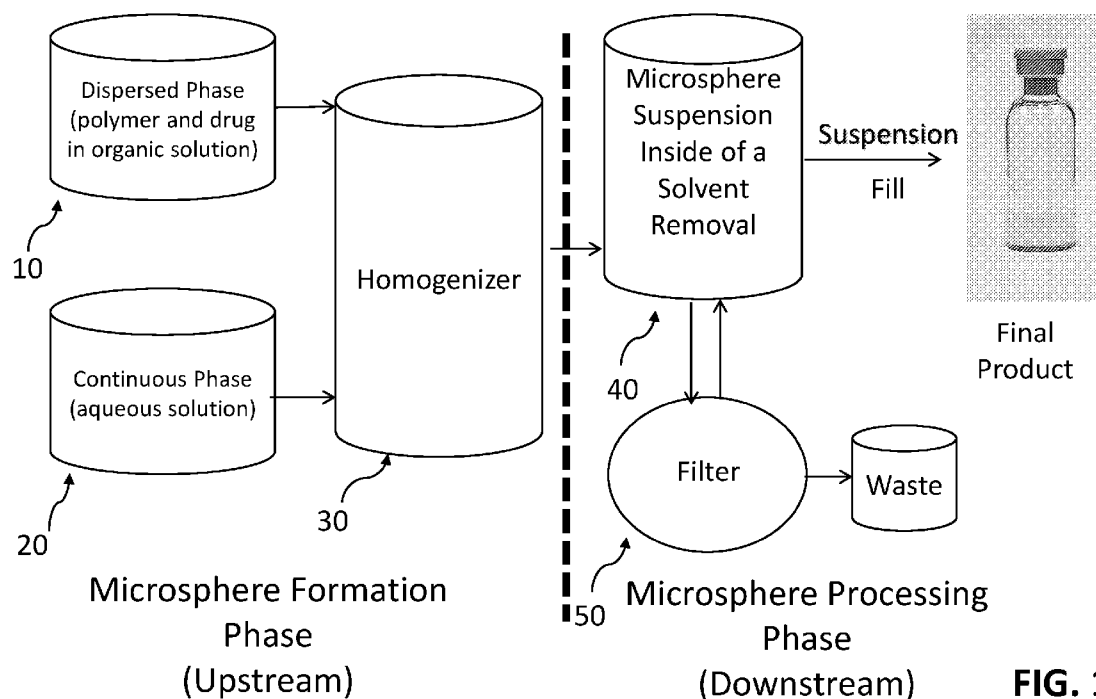


FIG. 1

(57) **Abstract:** Extended-release microsphere formulations comprising a BTK inhibitor are provided. In one aspect, the microsphere formulations are characterized in that the BTK inhibitor is released in vivo in humans over a period of from about 7 to about 28 days. Methods for making and using the formulations are also provided.

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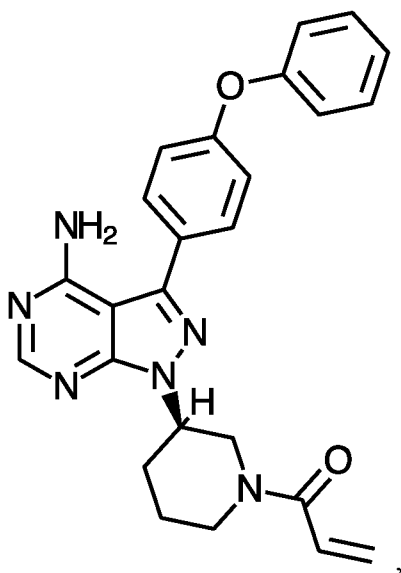
CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/156,020, filed on March 3, 2021, which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] B-cells account for up to 25% of all cells in some cancers. By inhibiting the Bruton's Tyrosine Kinase ("BTK") enzyme involved in B-cell receptor signaling, BTK inhibitors cause detachment of malignant B-cells from cancer sites into blood, which results in cell death. BTK inhibition reduces the proliferation of malignant B-cells and decreases the survival of malignant B-cells.

[0003] Ibrutinib (chemical formula $C_{25}H_{24}N_6O_2$; CAS Number 936563-96-1), characterized by the general structure:



is a BTK inhibitor. Ibrutinib, alone and in combination with other drugs, has been approved by the U.S. Food and Drug Administration (the "FDA") for the treatment of mantle cell lymphoma ("MCL"), chronic lymphocytic leukemia ("CLL"), Waldenström's macroglobulinemia, small

lymphocytic lymphoma (“SLL”), relapsed/refractory marginal zone lymphoma in patients who require systemic therapy and have received at least one prior anti-CD20-based therapy, and graft-versus-host disease, among other diseases.

[0004] Two other BTK inhibitors have been approved by the FDA: acalabrutinib (approved for treatment of relapsed MCL) and zanubrutinib (approved for treatment of MCL). Several other drugs that inhibit BTK are in clinical trials, including evobrutinib for multiple sclerosis; ABBV-105 for systemic lupus erythematosus; fenebrutinib for rheumatoid arthritis, systemic lupus erythematosus, and chronic spontaneous urticaria; GS-4059 for non-Hodgkin’s lymphoma and/or CLL; Spebrutinib (AVL-292, CC-292); and HM71224 for autoimmune diseases.

[0005] All of the currently approved BTK inhibitors are oral formulations. Oral formulations may have several disadvantages. For example, oral formulations may require closely timed, successive dosages under the supervision of a physician. Further, some BTK inhibitors may have low and variable oral bioavailability. For example, ibrutinib may have an oral bioavailability of only 2.9% in the fasted state, but this can vary from patient to patient.

[0006] A need exists for a high-bioavailability formulation comprising a BTK inhibitor that may be administered by a long-acting, sustained release injection, without the need for patients to administer closely timed, successive dosages under supervision from their physician.

SUMMARY

[0007] Microsphere formulations comprising a BTK inhibitor are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}). In another

aspect, the microsphere formulations are characterized in that they have a low initial burst release, that is, not more than 50% of the BTK inhibitor is released within about 4 hours of injection into a subject.

[0008] In one aspect, the microsphere formulations may be made by a method, the method comprising: (A) mixing: (i) the biodegradable polymer; (ii) a primary solvent; and (iii) a BTK inhibitor, to form a dispersed phase; (B) mixing: (i) water; and (ii) a surfactant, to form a continuous phase; and (C) combining the dispersed phase with the continuous phase in a homogenizer.

[0009] In one aspect, a method for treating cancer, including a B-cell malignancy, is provided. The method may comprise administering by intramuscular or subcutaneous injection to a patient in need thereof a microsphere formulation made according to the methods described herein.

[0010] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}), in the manufacture of a medicament for the treatment of cancer, including a B-cell malignancy.

[0011] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}), is provided for use as a medicament for the treatment of cancer, including a B-cell malignancy.

[0012] In another aspect, a kit is provided, the kit comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}).

BRIEF DESCRIPTION OF THE FIGURES

[0013] **Figure 1** is a schematic depicting a method for making BTK inhibitor-encapsulated polymer microspheres.

[0014] **Figure 2** is a graph showing in vitro cumulative ibrutinib release over time from ibrutinib-encapsulating polymer microspheres comprising a 50:50 poly (D,L-lactide-co-glycolide) (“PLGA”) as the biodegradable polymer.

[0015] **Figure 3** is a graph showing in vitro cumulative ibrutinib release over time from ibrutinib-encapsulating polymer microspheres comprising a 75:25 PLGA with an inherent viscosity (“IV”) of 0.26 dL/g as the biodegradable polymer.

[0016] **Figure 4** is a graph showing in vitro cumulative ibrutinib release over time from ibrutinib-encapsulating polymer microspheres comprising a 75:25 PLGA with IVs between 0.41 dL/g and 0.70 dL/g as the biodegradable polymer.

[0017] **Figure 5** is a graph showing in vitro cumulative ibrutinib release over time from ibrutinib-encapsulating polymer microspheres comprising an 85:15 PLGA as the biodegradable polymer.

[0018] **Figure 6** is a graph showing in vitro cumulative ibrutinib release over time from ibrutinib-encapsulating polymer microspheres comprising a poly(D,L-lactide) (“PLA”) as the biodegradable polymer.

DETAILED DESCRIPTION

[0019] Microsphere formulations comprising a BTK inhibitor are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}). In another aspect, the microsphere formulations are characterized in that they have a low initial burst release, that is, not more than 20% of the BTK inhibitor is released within about 24 hours of injection into a subject.

[0020] In one aspect, the microsphere formulations may be made by a method, the method comprising: (A) mixing: (i) the biodegradable polymer; (ii) a primary solvent; and (iii) a BTK inhibitor, to form a dispersed phase; (B) mixing: (i) water; and (ii) a surfactant, to form a continuous phase; and (C) combining the dispersed phase with the continuous phase in a homogenizer.

BTK inhibitors

[0021] In one aspect, the BTK inhibitor is selected from the group comprising, consisting essentially of, or consisting of ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ABBV-105, fenebrutinib, GS-4059, or spebrutinib, or combinations thereof.

[0022] In one aspect, the composition consists essentially of ibrutinib. In one aspect, the ibrutinib is supplied by ScinoPharm or MSN. In one aspect, the ibrutinib is hydrophobic. In one aspect, the ibrutinib is supplied as a free base. In another aspect, the ibrutinib is supplied as a pharmaceutically acceptable salt. In one aspect, the ibrutinib is characterized by an aqueous solubility of <2.5 mg/g. In one aspect, the ibrutinib is characterized by a solubility in

dichloromethane (“DCM”) of >300 mg/g. In one aspect, the ibrutinib is characterized by a pKa of about 3.74.

[0023] The BTK inhibitor may be in various polymorphic forms. Polymorphic forms may include hemihydrates, monohydrates, dihydrates, and other polymorphic forms as known in the art. Salts may include hydrochloride, sulfate, acetate, phosphate, diphosphate, chloride, maleate, citrate, mesylate, nitrate, tartrate, gluconate, or other salts as known in the art. In one aspect, the BTK inhibitor is in an amorphous form.

[0024] In an aspect wherein the BTK inhibitor comprises ibrutinib or another BTK inhibitor with similar solubility characteristics, a complex salt may be used to decrease solubility, such as, for example, palmitate, benzoic acid, tosylic acid, camphor-sulfonic acid, or other salt complexes as one of skill in the art can readily envision.

Biodegradable Polymers

[0025] In one aspect, the dispersed phase may include a biodegradable polymer, such as a PLGA or a PLA, although it is contemplated that other suitable biodegradable polymers may be used. The biodegradable polymer may be hydrophobic or hydrophilic.

[0026] In some aspects, the biodegradable polymer comprises a PLGA. In one aspect, the PLGA comprises a lactide:glycolide ratio of 50:50, 75:25, or 85:15. In one aspect, the PLGA is acid-terminated. In one aspect, the PLGA is ester-terminated. In one aspect, the PLGA has an IV of from about 0.1 dL/g to about 0.8 dL/g, including from about 0.1 dL/g to about 0.3 dL/g, from about 0.16 dL/g to about 0.24 dL/g, from about 0.2 dL/g to about 0.4 dL/g, from about 0.4 dL/g to about 0.6 dL/g, from about 0.6 dL/g to about 0.8 dL/g, about 0.20 dL/g, 0.26 dL/g, 0.41 dL/g, 0.56 dL/g, 0.66 dL/g, 0.7 dL/g, and any value or range between any two of those IV values.

[0027] In one aspect, the PLGA comprises Resomer® 502 H, poly(D,L-lactide-co-glycolide), acid terminated, lactide:glycolide 50:50, manufactured by Evonik, having IV = 0.20 (“502 H”). In one aspect, the PLGA comprises Resomer® 502, poly(D,L-lactide-co-glycolide), ester terminated, lactide:glycolide 50:50, manufactured by Evonik, having IV = 0.20 (“502”). In one aspect, the PLGA comprises Viatel™ DLG 7503 A, poly(D,L-lactide-co-glycolide), acid terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.26 (“7503 A”). In one aspect, the PLGA comprises Viatel™ DLG 7503 E, poly(D,L-lactide-co-glycolide), ester terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.26 (“7503 E”). In one aspect, the PLGA comprises Viatel™ DLG 7505 A, poly(D,L-lactide-co-glycolide), acid terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.56 (“7505 A”). In one aspect, the PLGA comprises Viatel™ DLG 7505 E, poly(D,L-lactide-co-glycolide), ester terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.41 (“7505 E”). In one aspect, the PLGA comprises Viatel™ DLG 7507 A, poly(D,L-lactide-co-glycolide), acid terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.70 (“7507 A”). In one aspect, the PLGA comprises Viatel™ DLG 7507 E, poly(D,L-lactide-co-glycolide), ester terminated, lactide:glycolide 75:25, manufactured by Ashland, having IV = 0.66 (“7507 E”). In one aspect, the PLGA comprises Viatel™ DL 8503 A, poly(D,L-lactide-co-glycolide), acid terminated, lactide:glycolide 85:15, manufactured by Ashland, having IV = 0.24 (“8503 A”). In one aspect, the PLGA comprises Viatel™ DL 8503 E, poly(D,L-lactide-co-glycolide), ester terminated, lactide:glycolide 85:15, manufactured by Ashland, having IV = 0.25 (“8503 E”).

[0028] In some aspects, the biodegradable polymer is a PLA. In one aspect, the PLA is acid-terminated. In one aspect, the PLA is ester-terminated. In one aspect, the PLA has an IV of

between about 0.1 dL/g and about 0.4 dL/g, including about 0.16 dL/g, about 0.18 dL/g, and about 0.32 dL/g, and any value or range between any two of those IV values.

[0029] In one aspect, the PLA comprises a Viatel™ DL 02 A, poly(D,L-lactide), acid terminated, manufactured by Ashland, having IV = 0.16 (“DL 02 A”). In one aspect, the PLA comprises a Viatel™ DL 02 E, poly(L-lactide), ester terminated, manufactured by Ashland, having IV = 0.18 (“DL 02 E”). In one aspect, the PLA comprises a Viatel™ DL 03 A, poly(L-lactide), acid terminated, manufactured by Ashland, having IV = 0.32 (“DL 03 A”).

[0030] In one aspect, the biodegradable polymer is mixed with the BTK inhibitor to form microspheres, which are injectable and formulated to release the BTK inhibitor to the patient over the intended duration of release. In another aspect, the biodegradable polymer is used to encapsulate the BTK inhibitor into microspheres, which are injectable and formulated to release the BTK inhibitor to the patient over the intended duration of release, via a controlled rate of release from the spheres, or release from different spheres at different times based upon particle size, thickness of the biodegradable polymer encapsulating the BTK inhibitor, molecular weight of the biodegradable polymer, polymer composition such as co-monomer ratio, end-cap, and drug load, or combinations of such release-affecting factors.

Dispersed Phase

[0031] In one aspect, the dispersed phase comprises a primary solvent. In one aspect, the primary solvent comprises DCM. The dispersed phase may also include up to about 50% by weight of a co-solvent capable of optimizing the solubility of the BTK inhibitor in the primary solvent. In one aspect, the co-solvent may be benzyl alcohol, dimethyl sulfoxide, dimethyl formamide, dimethyl acetamide, acetonitrile, ethanol, N-methyl pyrrolidone, ethyl acetate, or any other solvent that increases the solubility of the BTK inhibitor in the dispersed phase containing

DCM. A microsphere is “essentially free” of organic solvent if the microsphere meets the standards set forth in the “ICH Harmonised Guideline, Impurities: Guideline for Residual Solvents Q3C(R8), Current Step 4 version dated 22 April 2021,” which is incorporated herein by reference in its entirety.

Continuous Phase

[0032] The dispersed phase may be combined with an aqueous continuous phase that comprises water and, optionally, a buffer, a surfactant, or both.

[0033] In one aspect, the buffer may be added to the continuous phase to maintain a pH of the solution of about 7.0 to about 8.0. In one aspect, the buffer may be a phosphate buffer or a carbonate buffer. In one aspect, the buffer may be a 10 mM phosphate or carbonate buffer solution and may be used to create and maintain a system pH level of about 7.6.

[0034] The surfactant component may be present in the continuous phase in an amount of about 0.35% to about 1.0% by weight in water. In one aspect, the surfactant component comprises polyvinyl alcohol (“PVA”) in a concentration of 0.35% by weight in water.

[0035] In some aspects, the dispersed phase flow rate to the homogenizer may be from about 10 mL/min to about 30 mL/min, including about 20 mL/min and about 25 mL/min. In some aspects, the continuous phase flow rate to the homogenizer may be about 2 L/min. Thus, in one aspect, the continuous phase:dispersed phase ratio may be from about 66:1 to about 200:1, including about 100:1 and about 80:1. Larger scale batches may require higher flow rates.

[0036] The continuous phase may be provided at room temperature or above or below room temperature. In some aspects, the continuous phase may be provided at about 40 °C, about 37 °C, about 35 °C, about 30 °C, about 25 °C, about 20 °C, about 15 °C, about 10 °C, about 5 °C, about 0 °C, and any value or range between any two of those temperature values.

Homogenizer

[0037] For brevity, and because the methods are equally applicable to either, the phrase “homogenizer” contemplates a system or apparatus that can homogenize the dispersed phase and the continuous phase, emulsify the dispersed phase and the continuous phase, or both, which systems and apparatuses are known in the art. For example, in one aspect, the homogenizer is an in-line Silverson Homogenizer (commercially available from Silverson Machines, Waterside UK) or a Levitronix® BPS-i100 integrated pump system used, e.g., as described in U.S. Patent No. 11,167,256, which is incorporated by reference herein in its entirety. In one aspect, the homogenizer is a membrane emulsifier or a static mixer. In one aspect, the homogenizer runs at an impeller speed of about 1,000 to about 4,000 revolutions per minute (“RPM”), including about 2,000 RPM, about 3,000 RPM, and any value or range between any two of those RPM values.

Drug Load

[0038] The drug load of each polymer microsphere in a drug to polymer ratio, expressed as a percentage, may be greater than 40 wt/wt%, including from about 40 wt/wt% to about 70 wt/wt%, from about 45 wt/wt% to about 70 wt/wt%, from about 45 wt/wt% to about 65 wt/wt%, from about 50 wt/wt% to about 65 wt/wt%, greater than 50 wt/wt%, and any value or range between any two of those drug loads.

[0039] In some particular aspects, it is contemplated that the drug load may be as low as 20 wt/wt%.

Particle Size

[0040] In one aspect, the polymer microspheres may have an average particle size of less than 110 μm (D_{50}), including between about 30 μm (D_{50}) and about 60 μm (D_{50}), between about 30 μm (D_{50}) and about 50 μm (D_{50}), between about 35 μm (D_{50}) and about 60 μm (D_{50}), between about

45 μm (D_{50}) and about 60 μm (D_{50}), about 30 μm (D_{50}), about 35 μm (D_{50}), about 40 μm (D_{50}), about 45 μm (D_{50}), about 50 μm (D_{50}), about 55 μm (D_{50}), about 60 μm (D_{50}), less than about 60 μm (D_{50}), and any value or range between any two of those average particle sizes.

[0041] In some particular aspects, it is contemplated that average particle sizes may be as large as 150-200 μm .

Extended Release

[0042] In one aspect, the microsphere formulations are characterized in that they have an in vivo duration of release of less than about 7 days in humans. In one aspect, the microsphere formulations are characterized in that they have an in vivo duration of release of between about 7 days to about 14 days in humans. In one aspect, the microsphere formulations are characterized in that they have an in vivo duration of release of between about 14 days to about 28 days in humans. In one aspect, the microsphere formulations are characterized in that they have an in vivo duration of release of about 28 days in humans. In one aspect, the microsphere formulations are characterized in that they have an in vivo duration of release of greater than about 28 days in humans.

[0043] In one aspect, the microsphere formulations are characterized in that at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or 100%, and any range between any of those values, of the BTK inhibitor is released within <7, 7-14, 14-28, or >28 days (as described in the preceding paragraph) of injection into a subject. For example, in one aspect, the microsphere formulations are characterized in that about 75% to 100% of the BTK inhibitor is released over the designated period after injection into a subject. In another aspect, the microsphere formulations are characterized in that they have a low initial burst release, that is, not

more than about 20% of the BTK inhibitor is released within about 24 hours of injection into a subject.

[0044] A further aspect includes a sustained release injectable formulation of ibrutinib that is pharmacologically comparable to oral doses of: 70 mg, 140 mg, 280 mg, 420 mg, and 560 mg, in sustained release injectable formulations that release over approximately 7, 14, 21, or 28 days.

[0045] Another aspect includes a method of treating a human patient for MCL, CLL/SLL, and other diseases or conditions that may be treated by the BTK inhibitors. The method may comprise providing an injectable form of ibrutinib in a dosage strength that is pharmacologically comparable to 70 mg, 140 mg, 280 mg, 420 mg, and 560 mg per day orally, the injectable form with a duration of continuous release such that patient compliance is assured, the medical consequences of missing a dose or doses are avoided, and the pharmacokinetic profile is improved as compared with the oral dosage form.

Therapeutic Benefits

[0046] Possible conditions that may be treated using the microsphere formulations comprising a BTK inhibitor include cancer, including B-cell malignancies, including MCL, CLL, and SLL. In one aspect, a B-cell malignancy may be treated using the microsphere formulations comprising a BTK inhibitor, wherein the microsphere formulations are administered about every <7, 7-14, 14-28, or >28 days.

[0047] In one aspect, a method for treating cancer, including a B-cell malignancy, is provided. The method may comprise administering by intramuscular or subcutaneous injection to a patient in need thereof a microsphere formulation made according to the methods described herein.

[0048] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable

polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}), in the manufacture of a medicament for the treatment of cancer, including a B-cell malignancy.

[0049] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}), is provided for use as a medicament for the treatment of cancer, including a B-cell malignancy.

[0050] In another aspect, a kit is provided, the kit comprising polymer microspheres, each polymer microsphere comprising: (i) a BTK inhibitor; and (ii) a biodegradable polymer, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}).

EXAMPLES

Example 1 – General preparation of polymer microspheres comprising a BTK inhibitor

[0051] Microsphere Formation Phase. With reference to **Figure 1**, a dispersed phase (“DP”) 10 is formed by dissolving a polymer matrix (such as a PLGA or PLA polymer) in an organic solvent system (such as DCM), followed by the addition of the BTK inhibitor with mixing until completely dissolved. The DP 10 is filtered using a 0.2 μm sterilizing PTFE or PVDF membrane filter (such as EMFLON, commercially available from Pall or SartoriusAG) and pumped into a homogenizer 30 at a defined flow rate. A continuous phase (“CP”) 20 comprising water,

surfactant, and, optionally, a buffer is also pumped into the homogenizer 30 at a defined flow rate. The speed of the homogenizer 30 is generally fixed to achieve a desired polymer microsphere size distribution. A representative continuous “upstream” microsphere formation phase is described in U.S. Pat. No. 5,945,126, which is incorporated by reference herein in its entirety.

[0052] Microsphere Processing Phase. The formed or forming microspheres exit the homogenizer 30 and enter a solvent removal vessel (“SRV”) 40. Water may be added to the SRV 40 during microsphere formation to minimize the solvent level in the aqueous medium. See, e.g., U.S. Patent No. 9,017,715, which is incorporated by reference herein in its entirety. After the DP 10 has been exhausted, the CP 20 and water flow rates are stopped, and the washing steps are initiated. Solvent removal is achieved using water washing and a hollow fiber filter (commercially available as HFF from Cytiva) 50. A representative “downstream” microsphere processing phase is described in U.S. Pat. No. 6,270,802, which is incorporated by reference herein in its entirety.

[0053] The washed microspheres are collected and freeze-dried in a lyophilizer (Virtis) to remove any moisture. The resulting microspheres are a free-flowing off-white bulk powder.

Example 2 – Preparation of Ibrutinib-Encapsulated Polymer Microspheres Comprising a 50:50 PLGA – Batch Nos. 1 and 2 (“Group A”)

[0054] Following the general procedure described in Example 1 and illustrated in **Figure 1**, the DP was formed by dissolving 2.5 g of either 502 H polymer (Batch No. 1) or 502 polymer (Batch No. 2) (IV = 0.20 dL/g) in 11.67 g of DCM, followed by addition of ibrutinib (2.5 g) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,000 RPM. The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0055] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0056] Batch No. 1 had an average particle size of 36 μm (D_{50}), a drug load of 47.6 wt%, and a molecular weight of 17.6 kDa. The microspheres contained residual DCM of 3.0%. Batch No. 2 had an average particle size of 44 μm (D_{50}), a drug load of 47.8 wt%, and a molecular weight of 17.7 kDa. The microspheres contained residual DCM of 3.0%. The parameters and results are shown tabularly in **Table 1**:

Lot	Batch Number		1	2
	Symbol		○	Δ
Formulations	Polymer Supplier/Name		Evonik	
	Co-Monomer Ratio		50:50	
	Polymer IV (dL/g)		0.20	
	Polymer Endcap		Acid	Ester
	Batch Size (g)		5	
	Mixing Speed (RPM)		3000	
	Target Drug Load (%)		50.0	
Analytical	Drug Load (%)		47.6	47.8
	Encapsulation Efficiency (%)		95.2	95.6
	Residual Solvent DCM (%)		3.0	3.0
	Particle Size (μm)	D_{v10}	17	18
		D_{v50}	36	44
		D_{v90}	59	79
	Sample MW (kDa)		17.6	17.7
	Polymer MW (kDa)		17.4	17.6

Table 1

[0057] **Figure 2** is a graph showing in vitro cumulative ibrutinib release over time from the Group A ibrutinib-encapsulating polymer microspheres.

Example 3 – Preparation of Ibrutinib-Encapsulated Polymer Microspheres Comprising a 75:25 PLGA with a low polymer IV – Batch Nos. 3, 4, 6, 7, and 11 (“Group B”)

[0058] Following the general procedure described in Example 1 and illustrated in **Figure 1**, the DP was formed by dissolving 2.5 g (Batch Nos. 3, 4, and 11), 2.0 g (Batch No. 6), or 1.5 g (Batch No. 7) of either 7503 A polymer (Batch Nos. 3, 6, 7, and 11) or 7502 E polymer (Batch No. 6) (IV = 0.26 dL/g) in 11.67 g of DCM, followed by addition of ibrutinib (sufficient to provide a DP weight of 16.67 g, i.e., 2.5 g for Batch Nos. 3, 4, and 11; 3.0 g for Batch No. 6; and 3.5 g for Batch No. 7) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,000 RPM (Batch Nos. 3, 4, 6, and 7) or 2,000 RPM (Batch No. 11). The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0059] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0060] Batch No. 3 had an average particle size of 39 μm (D_{50}), a drug load of 48.2 wt%, and a molecular weight of 29.4 kDa. The microspheres contained residual DCM of 3.1%. Batch No. 4 had an average particle size of 35 μm (D_{50}), a drug load of 48.9 wt%, and a molecular weight of 25.5 kDa. The microspheres contained residual DCM of 2.1%. Batch No. 6 had an average particle size of 34 μm (D_{50}), a drug load of 60.6 wt%, and a molecular weight of 31.0 kDa. The microspheres contained residual DCM of 2.7%. Batch No. 7 had an average particle size of 30 μm (D_{50}), a drug load of 65.6 wt%, and a molecular weight of 30.1 kDa. The microspheres contained residual DCM of 1.5%. Batch No. 11 had an average particle size of 61 μm (D_{50}), a

drug load of 51 wt%, and a molecular weight of 28.9 kDa. The microspheres contained residual DCM of 1.4%. The parameters and results are shown tabularly in **Table 2**:

Lot	Batch Number		3	4	6	7	11
	Symbol		○	△	□	◇	X
Formulations	Polymer Supplier/Name		Ashland				
	Co-Monomer Ratio		75:25				
	Polymer IV (dL/g)		0.26				
	Polymer Endcap		Acid	Ester	Acid		
	Batch Size (g)		5				
	Mixing Speed (RPM)		3000				2000
	Target Drug Load (%)		50.0	50.0	60.0	70.0	50.0
Analytical	Drug Load (%)		48.2	48.9	60.6	65.6	51.0
	Encapsulation Efficiency (%)		96.4	97.8	101.0	93.7	102.0
	Residual Solvent DCM (%)		3.1	2.1	2.7	1.5	1.4
	Particle Size (μm)	D _v 10	17	15	12	10	29
		D _v 50	39	35	34	30	61
		D _v 90	65	59	58	53	103
	Sample MW (kDa)		29.4	25.5	31.0	30.1	28.9
Polymer MW (kDa)		30.7	25.8	30.7	30.7	28.6	

Table 2

[0061] **Figure 3** is a graph showing in vitro cumulative ibrutinib release over time from the Group B ibrutinib-encapsulating polymer microspheres.

Example 4 – Preparation of Ibrutinib-Encapsulated Polymer Microspheres Comprising a 75:25 PLGA with a high polymer IV – Batch Nos. 5, 12, 13, and 14 (“Group C”)

[0062] Following the general procedure described in Example 1 and illustrated in **Figure 1**, the DP was formed by dissolving 2.5 g (Batch Nos. 5 and 12) or 2.0 g (Batch Nos. 13 and 14) of either 7505 A polymer (Batch No. 5) (IV = 0.56 dL/g), 7505 E polymer (Batch No. 12) (IV = 0.41 dL/g), 7507 A polymer (Batch No. 13) (IV = 0.7 dL/g), or 7507 E polymer (Batch No. 14) (IV = 0.66 dL/g) in 11.67 g of DCM, followed by addition of ibrutinib (sufficient to provide a DP weight of 16.67 g, i.e., 2.5 g for Batch Nos. 5 and 12; and 3.0 g for Batch Nos. 13 and 14) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,000 RPM. The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0063] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0064] Batch No. 5 had an average particle size of 53 μm (D_{50}), a drug load of 47.5 wt%, and a molecular weight of 66.4 kDa. The microspheres contained residual DCM of 4.1%. Batch No. 12 had an average particle size of 47 μm (D_{50}), a drug load of 51.2 wt%, and a molecular weight of 49.8 kDa. The microspheres contained residual DCM of 0.8%. Batch No. 13 had an average particle size of 52 μm (D_{50}), a drug load of 62.2 wt%, and a molecular weight of 87.7 kDa. The microspheres contained residual DCM of 1.3%. Batch No. 14 had an average particle size of 53 μm (D_{50}), a drug load of 61.0 wt%, and a molecular weight of 90.8 kDa. The microspheres contained residual DCM of 1.3%. The parameters and results are shown tabularly in **Table 3**:

Lot	Batch Number	5	12	13	14
	Symbol	○	△	□	◇
Formulations	Polymer Supplier/Name	Ashland			
	Co-Monomer Ratio	75:25			
	Polymer IV (dL/g)	0.56	0.41	0.70	0.66
	Polymer Endcap	Acid	Ester	Acid	Ester
	Batch Size (g)	5			
	Mixing Speed (RPM)	3000			
	Target Drug Load (%)	50.0		60.0	
Analytical	Drug Load (%)	47.5	51.2	62.2	61.0
	Encapsulation Efficiency (%)	95.0	102.4	103.7	101.7
	Residual Solvent DCM (%)	4.1	0.8	1.3	1.3
	Particle Size (µm)	D _v 10	15	17	14
		D _v 50	53	47	52
		D _v 90	102	84	106
	Sample MW (kDa)	66.4	49.8	87.7	90.8
	Polymer MW (kDa)	66.2	50.0	91.0	92.9

Table 3

[0065] Figure 4 is a graph showing in vitro cumulative ibritinib release over time from the Group C ibritinib-encapsulating polymer microspheres.

Example 5 – Preparation of Ibritinib-Encapsulated Polymer Microspheres Comprising an 85:15 PLGA – Batch Nos. 18 and 19 (“Group D”)

[0066] Following the general procedure described in Example 1 and illustrated in Figure 1, the DP was formed by dissolving 2.5 g of either 8503 A polymer (Batch No. 18) (IV = 0.24 dL/g)

or 8503 E polymer (Batch No. 19) (IV = 0.25 dL/g) in 11.67 g of DCM, followed by addition of ibrutinib (2.5 g) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,000 RPM. The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0067] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0068] Batch No. 18 had an average particle size of 36 μm (D_{50}), a drug load of 49.8 wt%, and a molecular weight of 22.7 kDa. The microspheres contained residual DCM of 0.5%. Batch No. 19 had an average particle size of 35 μm (D_{50}), a drug load of 49.2 wt%, and a molecular weight of 25.8 kDa. The microspheres contained residual DCM of 0.3%. The parameters and results are shown tabularly in **Table 4**:

Lot	Batch Number		18	19
	Symbol		□	◇
Formulations	Polymer Supplier/Name		Ashland	
	Co-Monomer Ratio		85:15	
	Polymer IV (dL/g)		0.24	0.25
	Polymer Endcap		Acid	Ester
	Batch Size (g)		5	
	Mixing Speed (RPM)		3000	
	Target Drug Load (%)		50	
Analytical	Drug Load (%)		49.8	49.2
	Encapsulation Efficiency (%)		99.6	98.4
	Residual Solvent DCM (%)		0.5	0.3
	Particle Size	D_{v10}	15	13

	(μm)	D _v 50	36	35
		D _v 90	62	61
	Sample MW (kDa)		22.7	25.8
	Polymer MW (kDa)		22.7	26.4

Table 4

[0069] **Figure 5** is a graph showing in vitro cumulative ibrutinib release over time from the Group D ibrutinib-encapsulating polymer microspheres.

Example 6 – Preparation of Ibrutinib-Encapsulated Polymer Microspheres Comprising a PLA – Batch Nos. 8, 9, 10, 16, and 17 (“Group E”)

[0070] Following the general procedure described in Example 1 and illustrated in **Figure 1**, the DP was formed by dissolving 2.5 g (Batch Nos. 8, 9, 16, and 17) or 2.0 g (Batch No. 10) of either DL 02 A polymer (Batch Nos. 8 and 17) (IV = 0.16 dL/g), DL 02 E polymer (Batch Nos. 9 and 10) (IV = 0.18 dL/g), or DL 03 A polymer (Batch No. 16) (IV = 0.32 dL/g) in 11.67 g of DCM, followed by addition of ibrutinib (sufficient to provide a DP weight of 16.67 g, i.e., 2.5 g for Batch Nos. 8, 9, 16, and 17; and 3.0 g for Batch No. 10) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at either 3,000 RPM (Batch Nos. 8, 9, 10, and 16) or 2,000 RPM (Batch No. 17). The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0071] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0072] Batch No. 8 had an average particle size of 32 μm (D₅₀), a drug load of 51.7 wt%, and a molecular weight of 12.0 kDa. The microspheres contained residual DCM of 0.4%. Batch No.

9 had an average particle size of 29 μm (D_{50}), a drug load of 51.8 wt%, and a molecular weight of 11.7 kDa. The microspheres contained residual DCM of 0.1%. Batch No. 10 had an average particle size of 29 μm (D_{50}), a drug load of 64.2 wt%, and a molecular weight of 11.7 kDa. The microspheres contained residual DCM of 0.2%. Batch No. 16 had an average particle size of 40 μm (D_{50}), a drug load of 48.9 wt%, and a molecular weight of 30.1 kDa. The microspheres contained residual DCM of 0.6%. Batch No. 17 had an average particle size of 49 μm (D_{50}), a drug load of 50.2 wt%, and a molecular weight of 12.4 kDa. The microspheres contained residual DCM of 0.8%. The parameters and results are shown tabularly in **Table 5**:

Lot	Batch Number		8	9	10	16	17
	Symbol		○	△	□	◇	X
Formulations	Polymer Supplier/Name		Ashland				
	Co-Monomer Ratio		100:0				
	Polymer IV (dL/g)		0.16	0.18		0.32	0.16
	Polymer Endcap		Acid	Ester		Acid	
	Batch Size (g)		5				
	Mixing Speed (RPM)		3000				2000
	Target Drug Load (%)		50.0		60.0	50.0	
	Analytical	Drug Load (%)		51.7	51.8	64.2	48.9
Encapsulation Efficiency (%)		103.4	103.6	107.0	97.8	100.4	
Residual Solvent DCM (%)		0.4	0.1	0.2	0.6	0.8	
Particle Size (μm)		D _v 10	15	12	14	18	25
		D _v 50	32	29	29	40	49
		D _v 90	53	50	50	66	81
Sample MW (kDa)		12.0	11.7	11.7	30.1	12.4	

	Polymer MW (kDa)	11.9	11.8	11.8	29.5	11.7
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Table 5

[0073] **Figure 6** is a graph showing in vitro cumulative ibrutinib release over time from the Group E ibrutinib-encapsulating polymer microspheres.

[0074] In use, the microspheres may be suspended in a diluent for administration (injection). The diluent may generally contain a thickening agent, a tonicity agent, and a wetting agent. The thickening agent may include carboxymethyl cellulose-sodium (CMC-Na) or other suitable compounds. An appropriate viscosity grade and suitable concentration of CMC-Na may be selected so that the viscosity of the diluent is 3 cps or higher. Generally, a viscosity of about 10 cps is suitable; however, a higher viscosity diluent may be preferred for larger microspheres to minimize the settling of microspheres in the suspension.

[0075] Uniform microsphere suspension without particle settling will result in a consistent delivered dose during drug administration by injection. To have a tonicity of the diluent closer to the biological system, about 290 milliosmole (mOsm), solutes such as mannitol, sodium chloride, or any other acceptable salt may be used. The diluent may also contain a buffer salt to maintain the pH of the composition. Typically, the pH is maintained around a physiologically relevant pH by adjusting the buffer content as needed (pH about 7 to about 8).

[0076] The aspects disclosed herein are not intended to be exhaustive or to be limiting. A skilled artisan would acknowledge that other aspects or modifications to instant aspects can be made without departing from the spirit or scope of the invention. The aspects of the present disclosure, as generally described herein and illustrated in the figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are contemplated herein.

[0077] Unless otherwise specified, “a,” “an,” “the,” “one or more of,” and “at least one” are used interchangeably. The singular forms “a,” “an,” and “the” are inclusive of their plural forms. The recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.). The terms “comprising” and “including” are intended to be equivalent and open-ended. The phrase “consisting essentially of” means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method. The phrase “selected from the group consisting of” is meant to include mixtures of the listed group.

[0078] When reference is made to the term “each,” it is not meant to mean “each and every, without exception.” For example, if reference is made to microsphere formulation comprising polymer microspheres, and “each polymer microsphere” is said to have a particular BTK inhibitor content, if there are 10 polymer microspheres, and two or more of the polymer microspheres have the particular BTK inhibitor content, then that subset of two or more polymer microspheres is intended to meet the limitation.

[0079] The term “about” in conjunction with a number is simply shorthand and is intended to include $\pm 10\%$ of the number. This is true whether “about” is modifying a stand-alone number or modifying a number at either or both ends of a range of numbers. In other words, “about 10” means from 9 to 11. Likewise, “about 10 to about 20” contemplates 9 to 22 and 11 to 18. In the absence of the term “about,” the exact number is intended. In other words, “10” means 10.

CLAIMS

What is claimed is:

1. A microsphere formulation, comprising:
polymer microspheres, each polymer microsphere comprising:
 - (i) a BTK inhibitor; and
 - (ii) a biodegradable polymer,wherein each polymer microsphere comprises a drug load of the BTK inhibitor of greater than 40% by weight of the polymer microsphere, and
wherein the polymer microspheres have an average particle size of less than 110 μm (D_{50}).
2. The microsphere formulation of claim 1, wherein the BTK inhibitor comprises ibrutinib.
3. The microsphere formulation of claim 1 or 2, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide).
4. The microsphere formulation of any of claims 1-3, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of 50:50.
5. The microsphere formulation of any of claims 1-3, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of 75:25.
6. The microsphere formulation of any of claims 1-3, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of 85:15.
7. The microsphere formulation of claim 1 or 2, wherein the biodegradable polymer comprises a poly(D,L-lactide).
8. The microsphere formulation of any of the preceding claims, wherein the biodegradable polymer is acid-terminated.

9. The microsphere formulation of any of claims 1-7, wherein the biodegradable polymer is ester-terminated.
10. The microsphere formulation of any of claims 1-6, 8, or 9, wherein the biodegradable polymer has an inherent viscosity between about 0.2 dL/g and 0.6 dL/g.
11. The microsphere formulation of any of claims 1, 2, 7, 8, or 9, wherein the biodegradable polymer has an inherent viscosity between about 0.1 dL/g and 0.4 dL/g.
12. The microsphere formulation of any of the preceding claims, wherein each polymer microsphere comprises a drug load of the BTK inhibitor of from about 45% to about 65% by weight of the polymer microsphere.
13. The microsphere formulation of any of the preceding claims, wherein the polymer microspheres have an average particle size of about 30 μm (D_{50}) to about 60 μm (D_{50}).
14. The microsphere formulation of any of the preceding claims, characterized in that about 75% to 100% of the BTK inhibitor is released over a period of between about 7 and 28 days of injection into a subject, but not more than about 20% of the BTK inhibitor has been released within about 24 hours of injection into the subject.
15. A pharmaceutical composition comprising the microsphere formulation of any of the preceding claims.
16. The microsphere formulation of any of the preceding claims for use in the treatment of a B-cell malignancy.
17. A method for making a microsphere formulation, the method comprising the steps:
 - (i) contacting a BTK inhibitor with a biodegradable polymer comprising a poly(D,L-lactide-co-glycolide) having a co-monomer ratio of between about 50:50 and 85:15 and an

inherent viscosity of between about 0.2 dL/g and 0.6 dL/g in the presence of an organic solvent system to form a dispersed phase;

(ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion;

(iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and

(iv) subjecting the substantially organic solvent-free microsphere formulation to a drying process.

18. The method of claim 17, wherein the surfactant comprises polyvinyl alcohol.

19. The method of claim 17 or 18, wherein the surfactant comprises polyvinyl alcohol, and wherein the polyvinyl alcohol concentration in the aqueous phase prior to the combining is about 0.35% by weight.

20. A method for making a microsphere formulation, the method comprising the steps:

(i) contacting a BTK inhibitor with a biodegradable polymer comprising a poly(D,L-lactide) having an inherent viscosity of between about 0.1 dL/g and 0.4 dL/g in the presence of an organic solvent system to form a dispersed phase;

(ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion;

(iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and

(iv) subjecting the substantially organic solvent-free microsphere formulation to a drying process.

21. The method of claim 20, wherein the surfactant comprises polyvinyl alcohol.

22. The method of claim 20 or 21, wherein the surfactant comprises polyvinyl alcohol, and wherein the polyvinyl alcohol concentration in the aqueous phase prior to the combining is about 0.35% by weight.

23. A kit, comprising:

polymer microspheres, each polymer microsphere comprising:

- (i) ibrutinib; and
- (ii) a biodegradable polymer comprising a poly(D,L-lactide-co-glycolide) having an inherent viscosity between about 0.2 dL/g and 0.6 dL/g,

wherein each polymer microsphere comprises a drug load of ibrutinib of from about 45% to about 65% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of from about 30 μm (D_{50}) to about 60 μm (D_{50}).

24. A method for treating a B-cell malignancy, the method comprising:

administering by intramuscular or subcutaneous injection to the subject a microsphere formulation with a dosing schedule of from about every 7 to about every 28 days, the microsphere formulation comprising:

- (i) ibrutinib; and
- (ii) a biodegradable polymer comprising a poly(D,L-lactide-co-glycolide) having an inherent viscosity between about 0.2 dL/g and 0.6 dL/g,

wherein each polymer microsphere comprises a drug load of ibrutinib of from about 45% to about 65% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 30 μm (D_{50}) to about 60 μm (D_{50}).

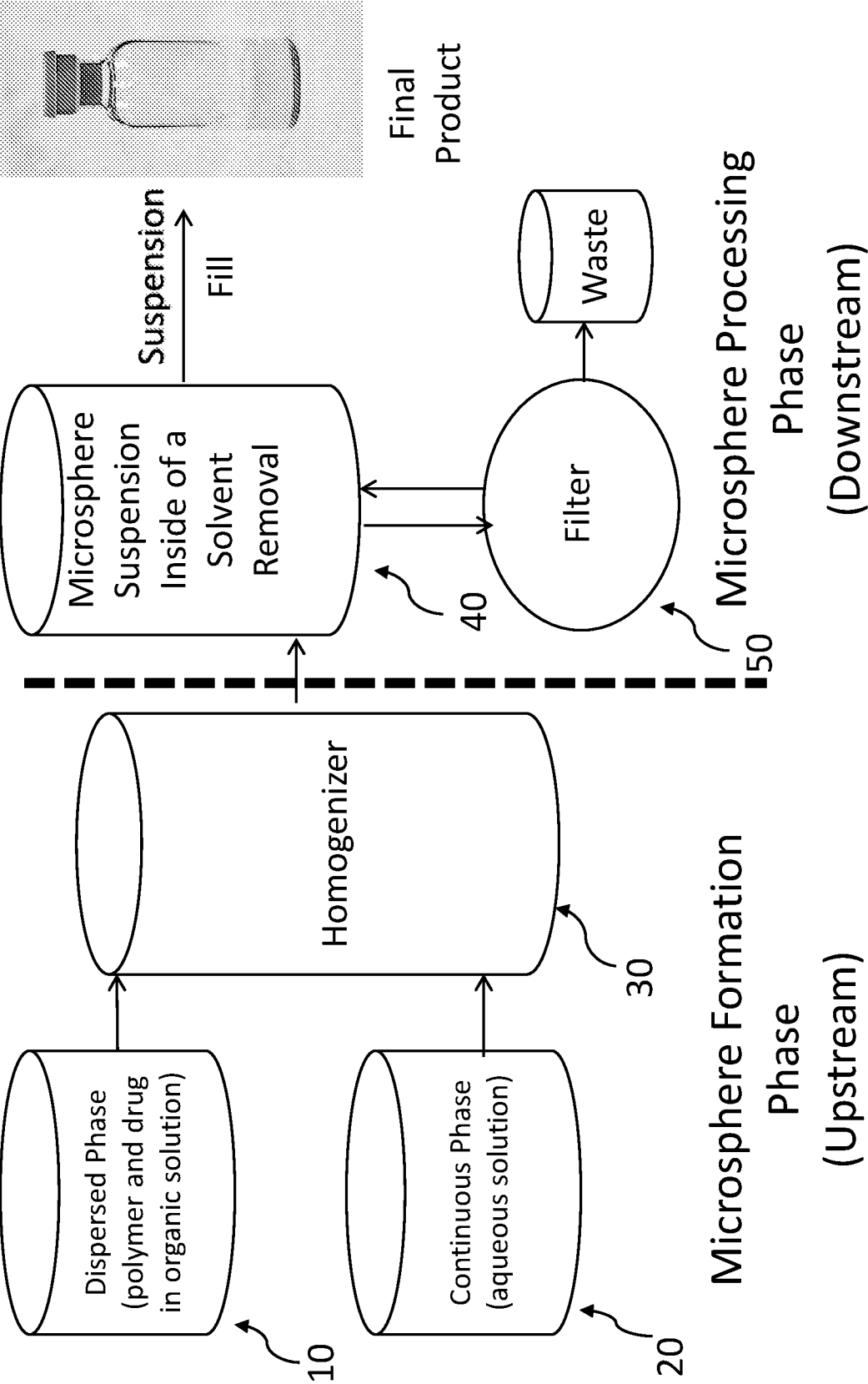
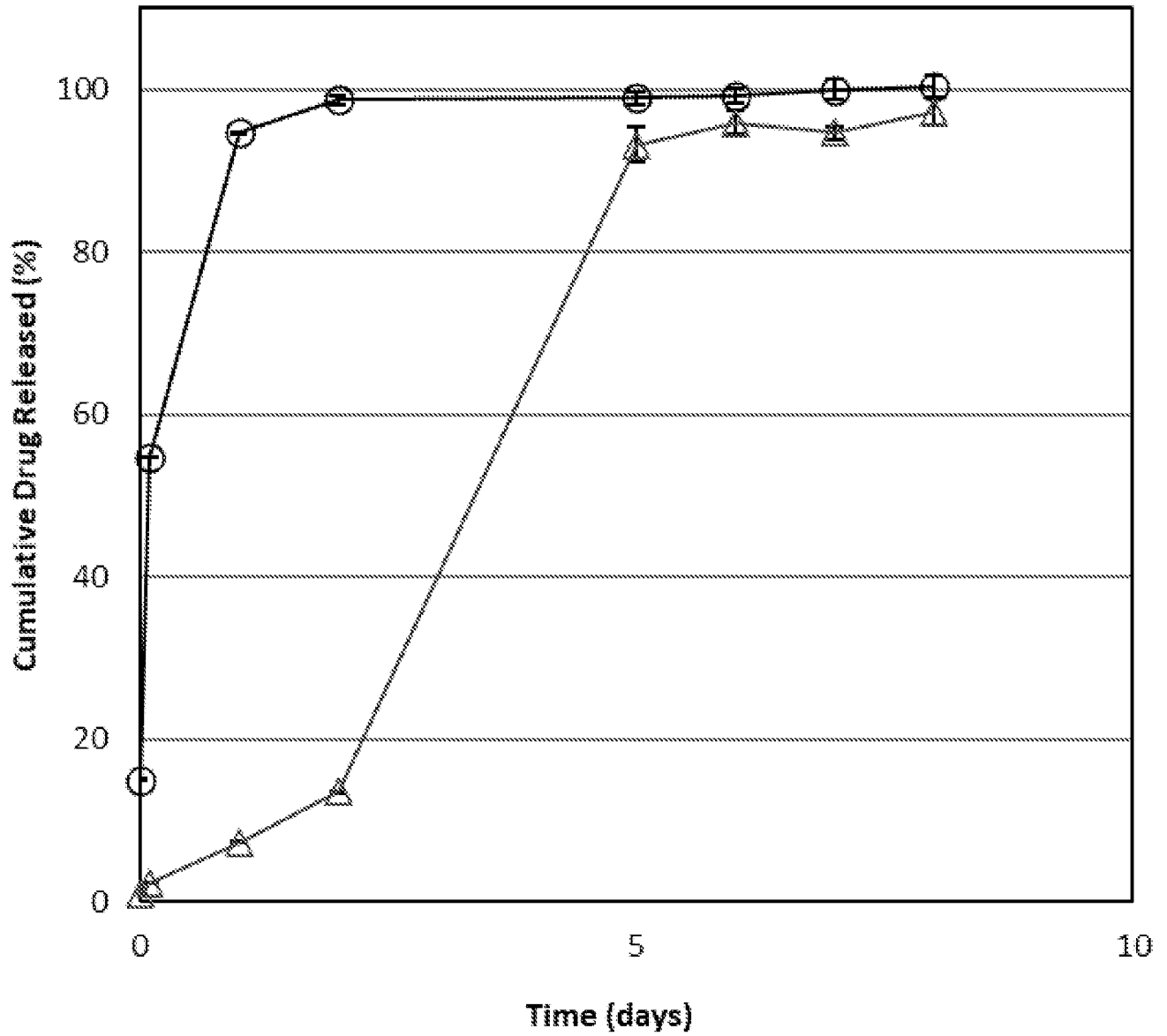
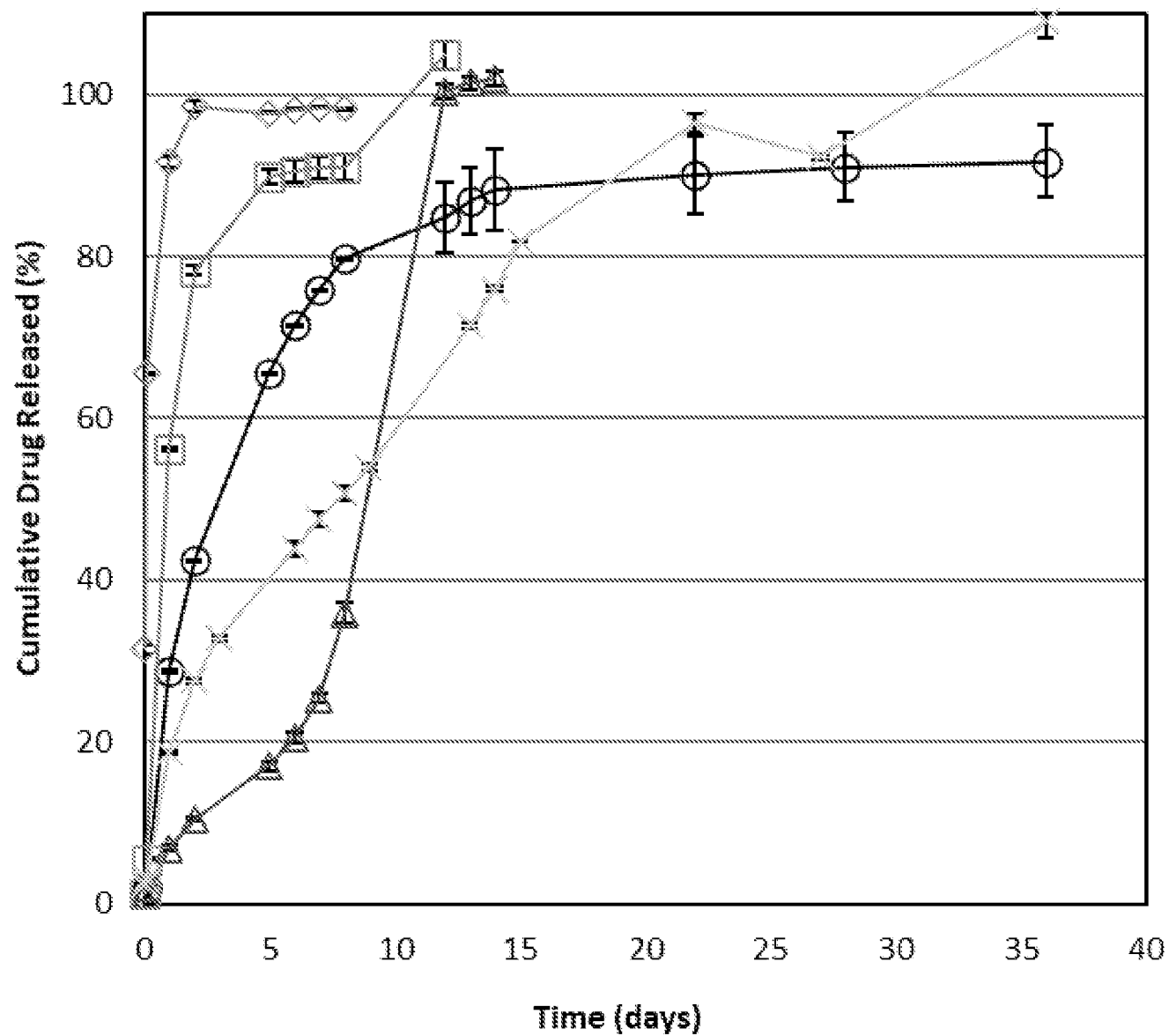


FIG. 1



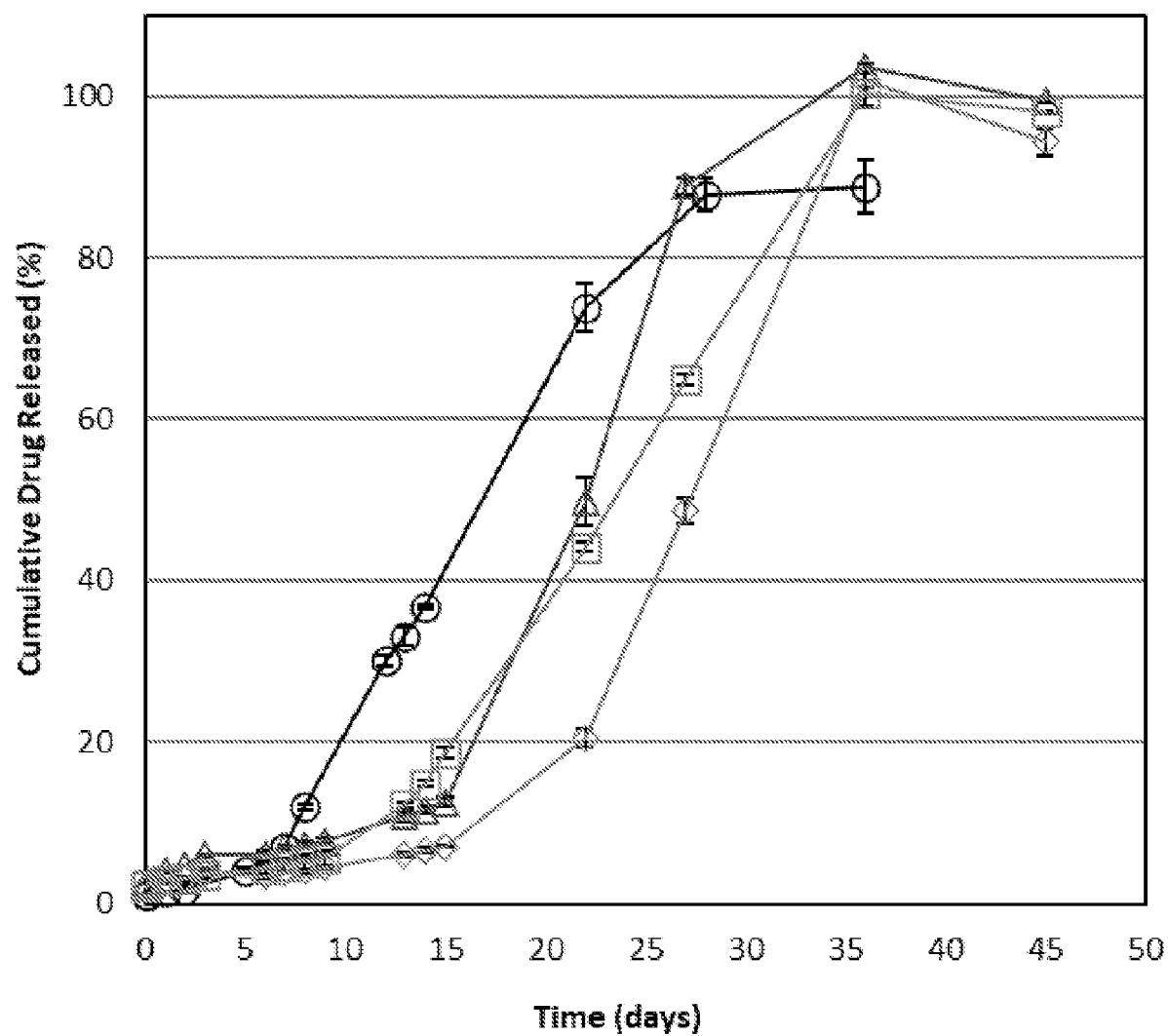
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FIG. 2



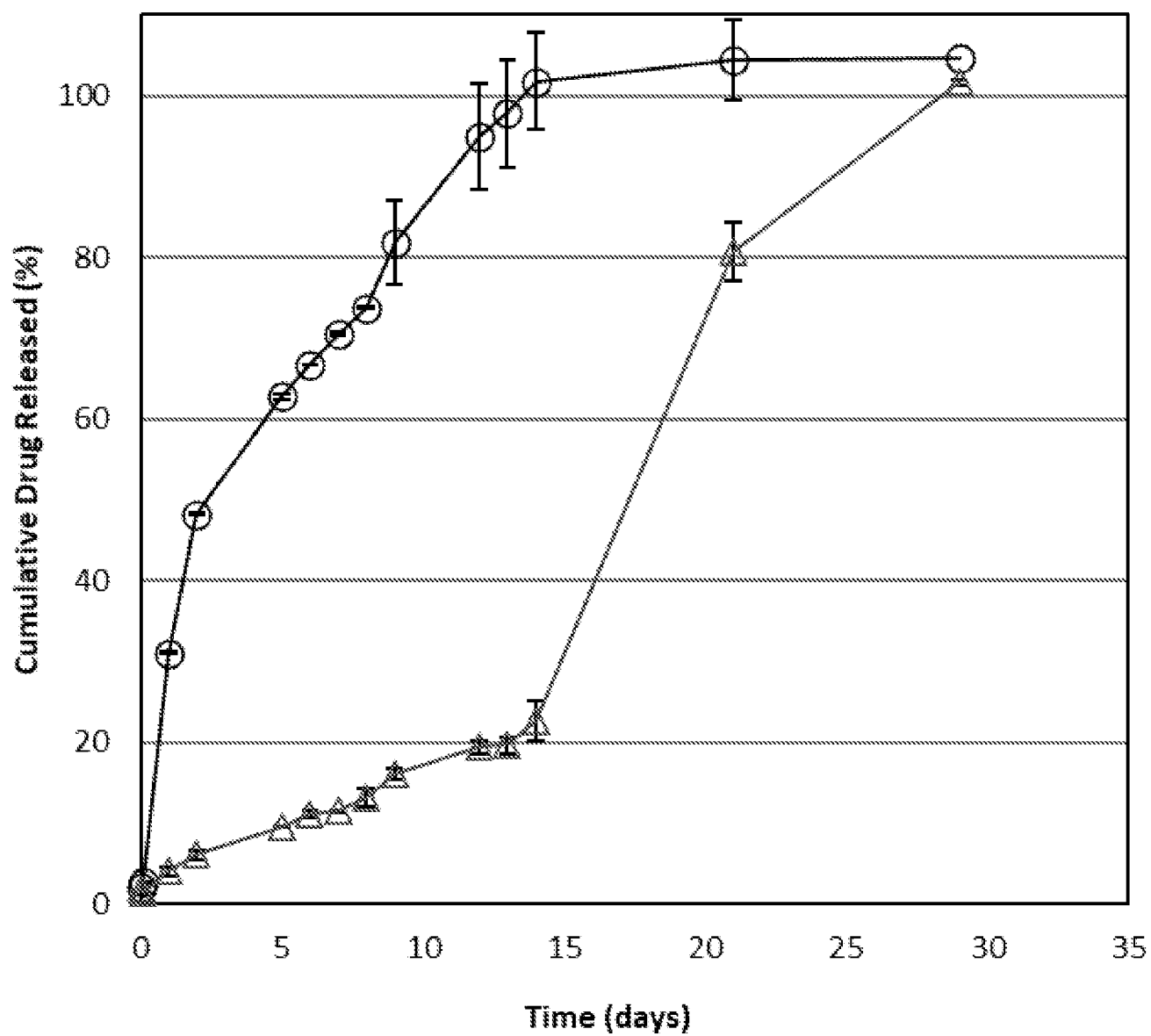
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FIG. 3



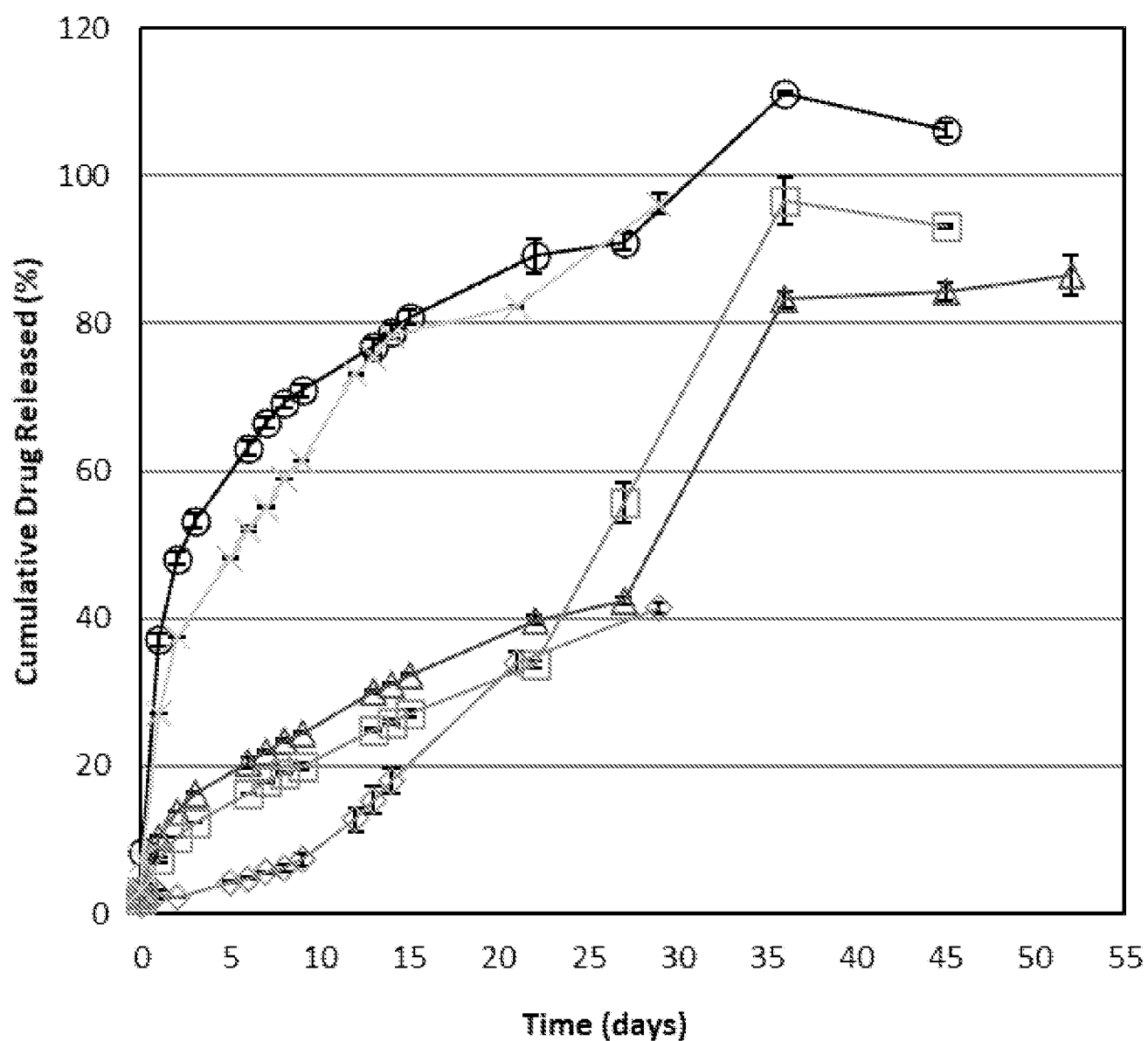
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FIG. 4



Batch No. 18 ◻	Batch No. 19 ◊
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FIG. 5



Batch No. 8 ○	Batch No. 9 Δ	Batch No. 10 □	Batch No. 16 ◇	Batch No. 17 X
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FIG. 6

