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(54) Title: POWDERED FORMULATIONS OF CROMOLYN SODIUM AND IBUPROFEN

(57) Abstract: The invention is directed to a composition comprising cromolyn sodium and ibuprofen, wherein the cromolyn sodium is micronized and the cromolyn sodium and ibuprofen are present in a weight ratio of 1:1-2. In one embodiment, the ibuprofen is passed through a sieve, such as a 300 µm sieve and to methods of making the same.

POWDERED FORMULATIONS OF CROMOLYN SODIUM AND IBUPROFEN

BACKGROUND OF THE INVENTION

[001] Therapies to prevent Alzheimer's Disease (AD) progression remain a high-unmet medical need. US Food and Drug Administration (FDA) approved acetylcholinesterase (AChE) inhibitor drugs, such as donepezil, rivastigamine and galantamine are indicated for symptomatic relief in persons with mild to moderate AD (Cummings JL, "Alzheimer's disease," *N Engl J Med* (2004) 351, 56-67; Knowles J, "Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes," *Core Evidence* (2006) 1, 195-219). These drugs increase levels of available acetylcholine during synaptic transmission and thus compensate for the diminished function of cholinergic neurons. However, none of the drugs approved for AD are disease-modifying treatments that affect the underlying pathophysiology of the disease, so the duration of their benefit is short-term (Knowles, 2006). The development of successful disease-modifying treatments, in contrast, would have a long-term beneficial outcome on the course of AD progression.

[002] The treatment of AD will require addressing the multiple triggers of pathogenesis. There are two primary neuropathologies in the brains of AD patients: i) extracellular protein plaques principally composed of A β peptides, also known as amyloid plaques; and ii) intracellular tangles of fibrils composed of tau protein found inside of neurons, also known as tau tangles. The advent and spread of neurotoxic oligomeric aggregates of A β is widely regarded as the key trigger leading to neuronal damage, which then leads to the accumulation of intracellular tau tangles, and finally to neuronal cell death in AD pathogenesis.

[003] Beta-amyloid peptides (37 to 43 amino acids in length) are formed by sequential cleavage of the native amyloid precursor protein (APP) (Karran *et al.*, "The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics," *Nature Reviews* (2011) 10, 698-712). Aberrant A β peptide isoforms that are 40 or 42 amino acids in length (A β 40 and 42) misfold into aggregates of oligomers that grow into fibrils that accumulate in the brain as amyloid plaques. More importantly for AD pathogenesis, the alternate fate of A β oligomers is to become trapped in neuronal synapses where they hamper synaptic transmission, which eventually results in neuronal degeneration and death (Haass *et al.*, "Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β -peptide," *Nature Reviews Mol. Cell Biol.* (2007) 8:101-112;

Hashimoto *et al.*, “Apolipoprotein E, especially apolipoprotein E4, increases the oligomerization of amyloid beta Peptide,” *J. Neurosci.* (2012) 32, 15181-15192).

[004] The cascade of A β oligomer-mediated neuronal intoxication is exacerbated by another AD trigger: chronic local inflammatory responses in the brain (Krstic *et al.*, “Deciphering the mechanism underlying late-onset Alzheimer disease,” *Nature Reviews Neurology* (2013), Jan, 9 (1): 25-34). Alzheimer’s disease has a chronic neuro-inflammatory component that is characterized by the presence of abundant microglial cells associated with amyloid plaque. (Heneka *et al.*, “Acute treatment with the PPAR γ agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV717I transgenic mice,” *Brain* (2005) 128, 1442-1453; Imbimbo *et al.*, “Are NSAIDs useful to treat Alzheimer’s disease or mild cognitive impairment,” *Front. Aging Neurosci* (2010) 2 (article 19), 1-14). These cyclooxygenase (COX1/COX2)-expressing microglia, which phagocytose amyloid oligomers, become activated to secrete pro-inflammatory cytokines. (Hoozemans *et al.*, “Soothing the inflamed brain: effect of non-steroidal anti-inflammatory drugs on Alzheimer’s disease pathology,” *CNS & Neurological Disorders – Drug Targets* (2011) 10, 57-67; Griffin TS., “What causes Alzheimer’s?” *The Scientist* (2011) 25, 36-40; Krstic 2013). This neuro-inflammatory response, besides promoting local vascular leakage through the blood brain barrier (BBB). Zlokovic (Zlokovic B., “Neurovascular pathways to neurodegeneration in Alzheimer’s disease and other disorders,” *Nature Reviews Neurosci.* (2011) 12, 723-738) has been implicated in driving further production of aberrant A β peptides 40 and 42 via modulation of gamma-secretase activity (Yan *et al.*, “Anti-inflammatory drug therapy alters β -amyloid processing and deposition in an animal model of Alzheimer’s disease,” *J. Neurosci.* (2003) 23, 7504-7509; Karan 2011) and to be detrimental to hippocampal neurogenesis in the adult brain (Gaparini *et al.*, “Non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer’s disease: old and new mechanisms of action,” *J. Neurochem* (2004) 91, 521-536). Thus, neuro-inflammation, in combination with amyloid oligomer-mediated neuronal intoxication, creates a cycle that results in progressive neural dysfunction and neuronal cell death spreading throughout the brain in subjects with AD.

[005] Compelling evidence from multiple epidemiology studies revealed that long-term dosing with non-steroidal anti-inflammatory drugs (NSAIDs) dramatically reduced AD risk in the elderly, including delayed disease onset, reduced symptomatic severity and slowed

cognitive decline. (Veld *et al.*, “Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer’s disease,” *N. Engl. J. Med.* (2001) 345, 1515-1521; Etminan *et al.*, “Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer’s disease: systematic review and meta-analysis of observational studies,” *Brit. Med. Journal* (2003) 327, 1-5; Imbimbo, 2010). Three mechanisms have been proposed for how NSAIDs inhibit the processes that contribute to AD progression: i) by inhibiting COX activity to reduce or prevent microglial activation and cytokine production in the brain (Mackenzie, *et al.*, “Nonsteroidal anti-inflammatory drug use and Alzheimer-type pathology in aging,” *Neurology* (1998) 50, 986-990; Alafuzoff *et al.*, “Lower counts of astroglia and activated microglia in patients with Alzheimer’s disease with regular use of non-steroidal anti-inflammatory drugs,” *J. Alz. Dis.* (2000) 2, 37-46; Yan, 2003; Gasparini, 2004; Imbimbo, 2010); ii) by reducing amyloid deposition (Weggen *et al.*, “A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity,” *Nature* (2001) 414, 212-216; Yan, 2003; Imbimbo, 2010); or iii) by blocking COX-mediated prostaglandin E2 responses in synapses (Kotilinek *et al.*, “Cyclooxygenase-2 inhibition improves amyloid- β -mediated suppression of memory and synaptic plasticity,” *Brain* (2008) 131, 651-664).

[006] Therefore, NSAIDs are predicted to dampen the neuro-inflammatory response and impact AD progression via several mechanisms. When administered together with drugs that inhibit A β oligomerization, the combination treatment paradigm is proposed to attenuate the multiple triggers leading to neurodegeneration and neuronal death. The decline in cognitive performance may be reversed, due to neuronal plasticity and neurogenesis in the hippocampus (Kohman *et al.*, “Neurogenesis, inflammation and behavior,” *Brain, Behavior, and Immunity* (2013) 27, 22-32), if AD progression is arrested at a very early stage.

SUMMARY OF THE INVENTION

[007] The invention encompasses a composition comprising cromolyn sodium and ibuprofen, wherein the cromolyn sodium is micronized and the cromolyn sodium and ibuprofen are present in a weight ratio of 1:1-2. In one embodiment, the ibuprofen is passed through a sieve, such as a 300 μ m sieve.

[008] The invention also encompasses methods of making a composition of cromolyn sodium and ibuprofen comprising micronizing cromolyn sodium; separately sieving cromolyn sodium and ibuprofen; blending sieved cromolyn sodium and ibuprofen; and blend co-milling the blended cromolyn sodium and ibuprofen. In one embodiment, the sieve

is about 250 μm to 500 μm sieve. In another embodiment, the micronizing step is performed at a feed gas pressure of about 45 psi and a grinding pressure of about 45 psi.

BRIEF DESCRIPTION OF THE DRAWINGS

[009] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0010] Fig. 1 illustrates an HPLC chromatogram of a sample containing cromolyn sodium and ibuprofen, where cromolyn sodium has a peak at 3.99 and ibuprofen has a peak at 10.83.

[0011] Fig. 2 illustrates an HPLC chromatogram of a sample containing cromolyn sodium and ibuprofen, where cromolyn sodium has a peak at 2.42 and ibuprofen has a peak at 3.98.

[0012] Fig. 3 illustrates a calibration plot for cromolyn sodium over the range of 0.05 to 50 $\mu\text{g/mL}$.

[0013] Fig. 4 illustrates a calibration plot of ibuprofen over the range of 0.05 to 50 $\mu\text{g/mL}$.

[0014] Fig. 5 illustrates a particle size distribution plot of coarse ibuprofen.

[0015] Fig. 6 illustrates a powdered x-ray diffraction pattern for coarse ibuprofen.

[0016] Fig. 7 illustrates a GVS plot of coarse ibuprofen.

[0017] Fig. 8A illustrates an SEM image for Batch 1 after a single pass at a 10 μm scale.

Fig. 8B illustrates an SEM image for Batch 2 after a double pass at a 10 μm scale.

[0018] Fig. 9A illustrates an SEM image for Batch 1 after a single pass at a 2 μm scale. Fig. 8B illustrates an SEM image for Batch 2 after a double pass at a 2 μm scale.

[0019] Fig. 10A illustrates a powdered x-ray diffraction pattern for Batch 1. Fig. 10B illustrates a powdered x-ray diffraction pattern for Batch 2.

[0020] Fig. 11A illustrates a GVS pattern of coarse ibuprofen. Fig. 11B illustrates a GVS pattern for Batch 1. Fig. 11C illustrates a GVS pattern for Batch 2.

[0021] Fig. 12 illustrates a Raman spectra overlay of coarse ibuprofen, Batch 1, and Batch 2.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0022] The invention encompasses compositions for a dosage form via inhalation. Basically, the invention combines at least two pharmaceutically active ingredients, both in powdered form, for administration via inhalation. The compositions can be used in formulations to enable easy dosing for patients, in contrast to dosing each API separately such as where one is inhaled and the other taken orally. An advantage of the simultaneous dosing of two APIs via inhalation is greater patient compliance with drug administration.

[0023] In particular, the invention is applicable for patients with diseases that impair mental performance, such as Alzheimer's disease, where the patient may have difficulty remembering to administer their medications. The invention is also applicable when the disease impacts physical activity, such as difficulty grasping pills or even the act of swallowing. The inability to correctly administer a dosage form can diminish the effect of the medication. These difficulties can exacerbate the disease because drug(s) administration is difficult, inconsistent, and/or under-dosed. To address these problems and increase patient compliance and ease administration, the present invention provides a combined dosage form suitable for administration via inhalation to treat Alzheimer's disease and other neurological diseases. Because of its versatility, the composition and formulation may also be used to treat other diseases including, but not limited to, stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and asthma.

[0024] One application of the present invention is a composition of cromolyn sodium and ibuprofen each in powdered form suitable for inhalation as a combination dosage form. In this case, each ingredient is in powdered form to facilitate administration via inhalation and to enable easy and accurate dosing. The invention is based in part upon the discovery that when cromolyn sodium and ibuprofen are both in powdered form, ibuprofen improves the aerodynamic flow of cromolyn. One advantage of this improvement allows for a higher concentration of cromolyn to reach deeper within the patient's lungs thereby achieving a therapeutic effect with less drug. Another advantage is that a perfect dosage via inhalation may not be necessary to achieve adequate therapeutic effect. In patients with impaired physical abilities (which may be due to a disease such as Alzheimer's disease) a perfect inhalation (a perfect "puff") may not always be possible; with the present invention, even impaired inhalation (an imperfect "puff") will deliver sufficient drug dosage to treat the desired disease. The advantages of the present composition can be applied to other diseases

with similar problems and expand the list of indications where the improved dosage form may be applicable.

[0025] In one application, the co-administration of the composition of cromolyn sodium and ibuprofen can be used for the treatment of certain neurological diseases. The neurological diseases include, but are not limited to, AD, ALS, Parkinson's disease, and the effects from stroke.

[0026] The invention relied on a methods to analytically discriminate between two APIs in a single sample to evaluate the characteristics of ibuprofen to understand the influences ibuprofen can have on the formulation. The analytical methods to discriminate between the two APIs in a sample also allowed investigation of the effect of micronization of ibuprofen for inhalation. These methods allowed determination of the feasibility of cromolyn sodium and ibuprofen as a combined single dosed product. Further methods allowed determination of the compatibility of the combined APIs in the combination dosage form. We discuss each in turn.

[0027] To determine the appropriate combination dosage, an analytical method was developed to distinguish between cromolyn sodium and ibuprofen within the same sample. The method included an assay to identify and quantify each API and measure the performance of each compound by testing the emitted dose and aerodynamic particle size.

[0028] The method comprises submitting a sample having cromolyn and ibuprofen through two chromatographic columns in sequence having a first and a second mobile phase, wherein the first mobile phase has sodium acetate with a buffer pH of about 5.5 and methanol, and the second mobile phase perchloric acid and acetonitrile, and detecting the cromolyn and ibuprofen. The sequence of columns and mobile phases are interchangeable. For instance, regarding mobile phases the terms first and second are used to demonstrate different mobile phases, not their sequence. The chromatographic columns include, but are not limited to, Agilent Poroshell 120 SB-C18 100x3mm, 2.7 μ . The mobile phases are present in an elution gradient of about 70:30 to 3:97 by volume, preferably from about 75:25 to 5:95, and more preferably from about 80:20 to 10:90 by volume. Any known method of detection may be used in the method including, but not limited to, UV, preferably the detection is carried out by UV.

[0029] In one embodiment of the analytical method, the HPLC analytical method used two columns: (1) Phenomenex Hyperclone BDS C18 130A 250x4.6mm, 5 μ and (2) Zorbax SB

C18 150x4.6mm, 3.5 μ . The mobile phases included a sodium acetate or potassium phosphate and methanol mixture for cromolyn sodium and a perchloric acid: acetonitrile mixture for ibuprofen. For instance, in one example 23nM sodium acetate buffer (pH 5.5): methanol was used for cromolyn sodium and 0.2% perchloric acid: acetonitrile for ibuprofen. The mobile phase for cromolyn can have a pH of about 4 to about 7.5, preferably from about 4.5 to about 7, and more preferably from about 5.5 to 6.8.

[0030] The analytical method used a gradient system of 85:15 to 10:90 (v/v) to assess the elution of both APIs. The wavelength of detection (both used for the detection of each API) was as follows: cromolyn sodium – 254nm and ibuprofen – 214nm.

[0031] The injection volume was changed from 100 μ L to 10 μ L; the run time was changed from 20 to 5 minutes; and the gradient was changed from 85:15 – 10:90 (v/v) to 80:20 – 10:90.

[0032] The analytical method is exemplified in Example 1 and Example 2. Cromolyn sodium and ibuprofen separated well, as illustrated in Figure 1 and Figure 2. Cromolyn sodium was detected at 3.99 minutes and ibuprofen was detected at 10.83 minutes. After achieving distinct signals, the method was optimized resulting in a shortened retention time of 2.418 minutes for Cromolyn and 3.978 minutes for Ibuprofen.

[0033] The ibuprofen used in the composition for the formulation may be in coarse or micronized form or any other form, as long as that form is suitable for inhalation. Another prerequisite is that the ibuprofen combines well with cromolyn sodium in order to enhance the delivery of cromolyn sodium via inhalation. In particular, the combination should deliver cromolyn sodium to the deep parts of the lung, *e.g.*, DPI 4moc (stage 4 to MOC, representing the area of the lung consisting of the secondary bronchi to the alveoli).

[0034] Ibuprofen was characterized to determine the parameters necessary to administer a therapeutically effective amount using an inhalation delivery system. The methodology included particle size determination (PSD); powdered x-ray crystallization diffraction (PXRD); and gravimetric vapor sorption (GVS). The methods determined that coarse ibuprofen was crystalline and non-hygroscopic. The results are summarized in Example 3. Ibuprofen adsorption-desorption isotherm showed <0.2% weight gain upon exposure to moisture suggesting that ibuprofen is non-hydroscopic.

[0035] The invention also encompasses a composition having micronized ibuprofen, where the ibuprofen has a size parameter of about \leq 10 μ m; however, particle size may also include

$\leq 5 \mu\text{m}$. The micronization may be performed on coarse ibuprofen using an air-jet mill or similar apparatus, such as a grinder or a mill. Other methods to micronize the ibuprofen include milling, bashing, cutting, or crushing. For example, two batches were micronized with an air-jet mill using a feed gas pressure of about 45 psi and a grinding pressure of about 45 psi. One batch was micronized a second time under the same conditions. Optionally, the ibuprofen may be micronized more than once. After micronization, particle size distribution was performed on the micronized ibuprofen by wet dispersion. The micronized ibuprofen was highly soluble in organic solvents; not dispersible in water (formed agglomerates); and soluble in different surfactants containing aqueous media even at low concentrations of the surfactant. Example 3 illustrates the process and results of ibuprofen micronization.

[0036] Micronized ibuprofen adsorbed higher moisture of ~3% by weight on the surface compared to <0.2% adsorption by coarse ibuprofen. The adsorption increase was due to the increased surface area upon micronization and generation of surface amorphous material. See Figures 11A, 11B, and 11C. A diluent and a stabilizer may be necessary for product performance and stability purposes. A cromolyn stabilizer is magnesium stearate and the use of a diluent such as lactose, which optionally may be used in the composition of the formulation.

[0037] Cromolyn used in the composition formulation may primarily be manufactured for inhalation. Generally, the cromolyn is micronized. The cromolyn micronization produces an ultra-fine powder ($d < 10 \mu\text{m}$) of small particle size. Micronized Cromolyn typically has a specification of $d(90\%) \leq 5 \mu\text{m}$.

[0038] The invention also encompasses a composition of cromolyn sodium and ibuprofen for delivery via inhalation. This composition comprises micronized cromolyn sodium and ibuprofen, wherein the ibuprofen may or may not be micronized, *i.e.*, the ibuprofen may be coarse or micronized. The composition improves the delivery of cromolyn, from cromolyn only compositions or where cromolyn is delivered in sequence (not simultaneously) with ibuprofen. For instance, the inhaled formulation of cromolyn only can deliver a therapeutically effective amount of cromolyn to the deep lung of about 23% to about 29% of the dosed amount. In contrast, it was found that the composition of the present invention delivered a therapeutically effective amount of cromolyn in a range of about 34% to about 53% and preferably 35% to about 44% of the dosed amount

[0039] One composition of the invention comprises 17.1 mg of cromolyn and 10 mg of ibuprofen. This is in alignment with current study drug concentrations being utilized in clinical studies. As used herein, unless otherwise indicated, the term “cromolyn” includes cromolyn, cromolyn sodium, and other forms of pharmaceutically acceptable salts of cromolyn.

Formulation 1A

Component	Function	%w/w	mg/capsule
Cromolyn sodium	Active Ingredient	58.0	17.1 (± 1.7)
Lactose Monohydrate	Diluent	40.0	12.8(± 0.64)
Magnesium stearate (micronized)	Stabilizer	2.0	0.6(± 0.03)
		100	32.0 (± 2.4)

Formulation 2A – Cromolyn with coarse Ibuprofen

Component	Function	%w/w	mg/capsule
Cromolyn sodium	Active Ingredient	~62	17.1 (± 1.7)
Ibuprofen (coarse)	Active Ingredient	~36	10.0 (± 1.0)
Magnesium stearate (micronized)	Stabilizer	2	0.54(± 0.027)
			27.64(± 1.9)

Formulation 2B – Cromolyn with micronized Ibuprofen

Component	Function	w/Diluent		w/o Diluent	
		%w/w	mg/capsule	%w/w	mg/capsule
Cromolyn sodium	Active Ingredient	~36.6	17.1 ((± 1.7))	~62	17.1 ((± 1.7))
Ibuprofen (micronized)	Active Ingredient	~21.4	10.0 (± 1.0)	~36	10.0 (± 1.0)
Lactose Monohydrate	Diluent	~40.0	18.7(± 0.9)	-	-
Magnesium stearate (micronized)	Stabilizer	2.0	0.9	2.0	0.54(± 0.027)
		100	46.7(± 3.5)		27.64(± 1.9)

[0040] In one formulation, both cromolyn sodium and ibuprofen are passed through a sieve. The sieve size may be from about 600 μm to about 200 μm , preferably from about 500 μm

to about 250 μm , and more preferably from about 300 μm to 400 μm . Typically, the weight ratio of cromolyn sodium to ibuprofen is about 1:1 to about 1:2.5, preferably, from about 1:1.1 to about 1:2, and more preferably from about 1.1:1.7. Optionally, the formulation includes pharmaceutically acceptable excipients, such as magnesium stearate and lactose monohydrate.

[0041] The stability of the composition of cromolyn sodium and ibuprofen is exemplified in Example 5. The formulations using either micronized ibuprofen or coarse ibuprofen provided sufficient performance of an inhaled substance when compared to the specifications of the cromolyn only product. The formulation enhanced the aerodynamic performance of cromolyn sodium during inhalation by comparison to a formulation of cromolyn sodium, lactose, and magnesium stearate. The combination product batches had a comparable emitted dose as the six clinical batches produced of the cromolyn only product. The six batch formulations manufactured with cromolyn and excipients only had a mean of 34.97% of the product reaching the deep lung area based on the NGI test results summation of Stage 3-MOC whereas with combination of cromolyn using either coarse or micronized ibuprofen had a mean result of 46% of the inhaled cromolyn reaching the deep lung area. Therefore, the compositions of the invention include cromolyn and ibuprofen compositions having a mean result of 36% to 56%, preferably from about 41% to about 51%, and more preferably from about 43% to about 48% of the inhaled cromolyn reaching the deep lung area. As used herein, unless otherwise defined, the term “lung area” refers to Stage 3 – MOC. The stability study performed under accelerated conditions showed no effect of the APIs towards each other.

[0042] Table 1 NGI comparison of Ibuprofen - Cromolyn/Ibuprofen_{micronized} vs Cromolyn/Ibuprofen_{coarse}

Location	Feasibility Batches (Cromolyn w/Ibuprofen) % of Ibuprofen Dose ¹			
	AFC05 Ibuprofen _{Micronized} w/MgSt ²	AFC06 Ibuprofen _{Micronized} w/o MgSt ²	AFC09 Ibuprofen _{coarse} w/MgSt ²	AFC10 Ibuprofen _{coarse} w/o MgSt ²
Stage 1 -Mouth	6.5	6.4	59.9	64.5
Stage 2- Pharynx	18.9	20.7	11.1	5.9
Stage 3 – Trachea/Primary Branch	18.2	18.5	1.7	1.7

Stage 4 – Secondary Bronchi	12.4	11.4	0.9	0.8
Stage 5 – Terminal Branch	3.6	2.8	0	0
Stage 6&7 - Alveoli	1.5	0.7	0	0

1 – All batches used micronized Cromolyn sodium API

2 – MgSt – Magnesium Stearate

3 – Cromolyn with Lactose monohydrate and Magnesium stearate

Table 2 NGI comparison of Cromolyn - Cromolyn/Ibuprofen_{micronized} vs Cromolyn/Ibuprofen_{coarse} vs. Cromolyn Only³

Location	Feasibility Batches (Cromolyn w/Ibuprofen vs Cromolyn Only)				
	% of Cromolyn Dose ¹				
	AFC05 Ibuprofen _{Micronized} w/MgSt ²	AFC06 Ibuprofen _{Micronized} w/o MgSt ²	AFC09 Ibuprofen _{coarse} w/MgSt ²	AFC10 Ibuprofen _{coarse} w/o MgSt ²	13PM792-PG67 Cromolyn Only ³
Stage 1 -Mouth	6.9	7.1	15.5	16.3	11.1
Stage 2- Pharynx	21.8	24.3	9.4	7.1	21.1
Stage 3 – Trachea/Primary Branch	20.5	20.6	12.7	13.0	19.4
Stage 4 – Secondary Bronchi	10.1	10.5	11.6	15.7	15.4
Stage 5 – Terminal Branch	3.4	2.9	7.2	9.2	7.8
Stage 6&7 - Alveoli	1.7 ⁴	1.7 ⁴	4.9	4.9	3.3

1 – All batches used micronized Cromolyn sodium API

2 – MgSt – Magnesium Stearate

3 – Cromolyn with Lactose monohydrate and Magnesium stearate

4 – With addition of Lactose Monohydrate this will improve the performance

[0043] Pharmaceutically acceptable excipients for dry powdered inhalers include, but are not limited to, lactose monohydrate and magnesium stearate.

[0044] The invention encompasses methods of making the described compositions comprising micronizing ibuprofen; separately sieving cromolyn sodium and ibuprofen; blending sieved cromolyn sodium and sieved ibuprofen; and blend co-milling the blended cromolyn sodium and ibuprofen to obtain the composition.

[0045] The ibuprofen micronization step can be carried out using standard equipment commonly used in the pharmaceutical arts. The feed pressure and grinding pressure are about 30 psi to about 60 psi, preferably about 35 psi to about 50 psi, and more preferably about 45 psi. The blending step comprises blending both ingredients for a time of about 5

minutes to about 20 minutes and preferably about 10 minutes to about 15 minutes, and more preferably for about 10 minutes. The blending rate is about 35 rpm to about 60 rpm, preferably about 40 rpm to about 50 rpm, and more preferably about 49 rpm. The blend co-milling step may be blended in a single pass. The feed pressure and grinding pressure for the co-milling step are about 30 psi to about 60 psi, preferably about 35 psi to about 50 psi, and more preferably about 45 psi. Examples 4 and 5 demonstrate the method of making the formulation.

[0046] While certain features of the invention were illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

EXAMPLES

[0047] Example 1: Detection of Cromolyn Sodium and Ibuprofen in Same Sample

[0048] Two columns were used in the method: (1) Phenomenex Hyperclone BDS C18 130A 250x4.6mm, 5 μ and (2) Zorbax SB C18 150x4.6mm, 3.5 μ . The mobile phases were as follows: cromolyn sodium: 23nM sodium acetate buffer pH 5.5: methanol and ibuprofen: 0.2% perchloric acid : acetonitrile. The mobile phases used a gradient system from 85:15 to 10:90 to assess the elution of both APIs. The wavelength used to detect each API was 254nm for cromolyn sodium and 214nm for ibuprofen. Table 1 summarizes the method parameters and Figure 1 illustrates the results.

[0049] Table 3 - Method Parameters

Parameter	Value
Column	Agilent Poroshell 120 SB-C18 100x3mm, 2.7 μ
Column temperature	40°C
Injection Volume	10 μ L
Flow	0.7mL/min.
Wavelength	214nm
Run time	20 minutes
Diluent	25mM Potassium phosphate pH 6.8 : Methanol (1:1)

[0050] Example 2: Detection of Cromolyn Sodium and Ibuprofen in Sample

[0051] The method described in Example 1 was repeated using the method parameters described in Table 4. The results are illustrated in Figure 2.

[0052] Table 4 - Method Parameters

Parameter	Value
Column	Agilent Poroshell 120 SB-C18 100x3mm, 2.7 μ
Column temperature	40°C
Injection Volume	100 μ L
Mobile Phase	0.2% perchloric acid :acetonitrile Gradient run 0 – 2 min. 80:20 – 10:90 2 – 2.1 min. 10:90 – 80:20 2.1 – 5 min. 80:20
Flow	0.7mL/min.
Wavelength	214nm
Run time	5 minutes
Diluent	25mM Potassium phosphate pH 6.8 : Methanol (1:1)

[0053] Using the method described in Table 4, the analysis was repeated using a 50 μ g/mL standard. Table 5 summarizes the results.

Table 3. System Repeatability

Injection #	Area (μ V.sec)	
	Cromolyn	Ibuprofen
1	1988124	1775569
2	1992850	1777595
3	1992853	1775814
4	1993644	1777975
5	1994323	1775675
6	1996294	1773172
mean	1993015	1775967
%RSD	0.1	0.1

[0054] Based on the data of Table 3, the linearity was calculated for cromolyn sodium and ibuprofen over the range of 0.05 – 50 g/mL. Figures 3 and 4 illustrate the data for cromolyn sodium and ibuprofen calibration plot, respectively.

[0055] Example 3: Physical Characterization of Ibuprofen

[0056] Coarse ibuprofen was characterized using PSD, PXRD, and GVS. The tests demonstrated that coarse ibuprofen was crystalline and non-hydroscopic. Table 6 illustrates the effect of the dispersant.

Table 6. Effect of Dispersant

T (Day)	D10 (μ m)	D50 (μ m)	D90 (μ m)
0	22.586	57.693	108.743
1	22.401	57.611	108.724

[0057] The average particle size determinations are illustrated in Figure 5. The parameters and results were as follows: concentration 0.0406 %Vol; span 1.493; uniformity 0.459; specific surface area 0.239 m²/g; surface weighted mean D[2,3] 25.136 μm; and vol. weighted mean D[4,3] 62.020 μm.

[0057] Figure 6 illustrates the PXRD and Figure 7 illustrates the GVS of coarse ibuprofen. The ibuprofen adsorption-desorption isotherm showed <0.2% weight gain upon exposure to moisture, suggesting that the ibuprofen was non-hygroscopic.

[0058] Subsequently, two batches of coarse ibuprofen were micronized using an air-jet mill at feed gas pressure of 45 psi and a grinding pressure of 45 psi. Batch 1 was micronized by a single pass and Batch 2 was passed twice.

[0059] Following micronization, Particle Size Distribution (PSD) analysis was performed by wet dispersion. It was observed that micronized ibuprofen did not disperse well in either aqueous or organic dispersing media as micronized ibuprofen, it was highly soluble in organic solvents, was not dispersible in water and formed agglomerates, and was soluble in different surfactant containing aqueous media even at low surfactant concentrations, as observed with reducing % obscuration in the PSD analyzer instrument. Due to the limitations of PSD analysis by wet dispersion, SEM imagery was performed to infer PSD. Figures 8A and 8B illustrate the SEM imagery of micronized ibuprofen at a 10 μm scale for Batch 1 and Batch 2, respectively. Figures 9A and 9B illustrate the SEM imagery of micronized ibuprofen at a 2 μm scale for Batch 1 and Batch 2, respectively. Figures 10A and 10B illustrate the PXRD of micronized ibuprofen for Batch 1 and Batch 2, respectively. Table 7 contains the data for moisture content of micronized ibuprofen as determined by simultaneous thermal analyzer (STA), which tests both by DTA (Differential Temperature Analysis) and TG (Thermogravimetry). Figures 11A, 11B, and 11C illustrate the hygroscopicity as determined GVS for coarse ibuprofen (Figure 11A), Batch 1 (Figure 11B), and Batch 2 (Figure 11C).

Table 7. Moisture Content of Micronized Ibuprofen by STA

	Coarse	Batch 1	Batch 2
% Moisture content	0.20	1.19	1.14
Enthalpy change (J/g)	131.0	120.5	94.4
Inference	Crystalline	Partly amorphous exhibited by reducing enthalpy change	

[0060] Micronize ibuprofen adsorbed greater moisture of ~3% on the surface compared to <0.2% adsorption on coarse ibuprofen. This increase in adsorption was due to increase surface area upon micronization and generation of surface amorphous material. Figure 12 illustrates the Raman spectra overlay of coarse ibuprofen and micronized ibuprofen. The bottom spectra is coarse ibuprofen, followed by Batch 1, and the topmost spectra is Batch 2.

[0061] Example 4: Formulation of Cromolyn Sodium and Ibuprofen

[0062] A series of blend combinations of cromolyn sodium and coarse or micronized ibuprofen were evaluated for blend uniformity, emitted dose, and aerodynamic particulate (NGI). Ten samples were taken from geometric locations within the blend. Batch 3 consisted of cromolyn sodium and coarse ibuprofen at a weight ratio of 1.7:1 and passed through a 300 μm sieve. The blend parameters for the turbula mixer were as follows: mixing speed: 49 rpm and mix time: 10 minutes. Table 8 illustrates the results of Batch 3 that showed uniformity for cromolyn sodium and an acceptable %RSD for ibuprofen.

Table 8. Batch 3 Uniformity

Sample #	% Label Claim	
	Cromolyn	Ibuprofen _{course}
1	102.07	101.29
2	104.94	99.94
3	102.28	106.17
4	102.57	105.8
5	100.42	114.83
6	93.05	124.66
7	103.71	107.54
8	106.23	102.88
9	107.15	110.57
10	102.34	101.23
mean	102.5	107.5
%RSD	3.8	7.1

[0063] Subsequently, the Batch 3 blend was then filled into HPMC size 3 clear capsules to a fill weight of 30 mg per capsule. The capsules were allowed to relax overnight to dissipate any static charge and then emitted dose testing was performed for five capsules. The test parameters were as follows: device: low resistance and the flowrate: 80L/min for 3 seconds. Table 9 has the results of the emitted dose test for Batch 3.

Table 9. Batch 3 Emitted Dose

Sample #	Emitted Dose (mg)	
	Cromolyn	Ibuprofen _{course}
1	13.487	5.122
2	13.601	4.594
3	14.186	5.557
4	12.013	4.116

5	14.258	5.635
mean	13.509	5.005
%RSD	6.7	12.9
Observed ED from benchmark	15	10

[0064] Batch 4 includes Batch 3 and magnesium stearate (2% w/w). Table 10 contains the results of blend uniformity testing for Batch 4. The test parameters as the same as those for Batch 3.

[0065]

Table 10. Batch 4 Blend Uniformity		
	% Label Claim	
Sample #	Cromolyn	Ibuprofen _{course}
1	98.52	103.65
2	98.94	99.16
3	95.31	94.96
4	95.27	99.36
5	100.09	98.6
6	100.48	95.41
7	97.23	101.53
8	101.88	101.61
9	97.68	104.06
10	100.04	105.46
mean	98.5	100.4
%RSD	2.2	3.5

[0066] Subsequently, the Batch 4 blend was then filled into HPMC size 3 clear capsules to a fill weight of 30 mg per capsule. The capsules were allowed to relax overnight to dissipate any static charge and then emitted dose testing was performed for five capsules. The test parameters were as follows: device: low resistance and the flowrate: 80L/min for 3 seconds.

Table 11 has the results of the emitted dose test for Batch 4.

[0067]

Table 11. Batch 4 emitted dose		
	Emitted Dose (mg)	
Sample #	Cromolyn	Ibuprofen _{course}
1	15.668	5.615
2	15.059	5.686
3	15.955	5.456
4	15.973	5.585
5	17.969	5.130
mean	16.125	5.495
%RSD	6.8	4.0
Observed ED from benchmark	15	10

[0068] The concentration of coarse ibuprofen was increased to determine the effect on emitted dose performance. Three batches were made adding magnesium stearate: Batch 5 (weight ratio cromolyn sodium: ibuprofen 1.7:1.1); Batch 6 (weight ratio cromolyn sodium: ibuprofen 1.7:1.5); and Batch 7 (weight ratio cromolyn sodium: ibuprofen 1.7:2.0). Table 12 illustrates the blend uniformity for batches 4, 5, 6, and 7. The blends were homogeneous.

[0069]

Table 12. Blend uniformity for Batches 4, 5, 6, and 7.

Sample #	Batch 4		Batch 5		Batch 6		Batch 7	
	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn
1	98.52	103.65	104.66	95.01	99.42	87.21	111.17	93.72
2	98.94	99.16	100.29	100.72	93.10	98.52	102.58	83.07
3	95.31	94.96	96.77	104.56	97.05	98.46	105.13	85.56
4	95.27	99.36	101.94	97.85	94.35	96.46	101.07	86.49
5	100.09	98.6	99.26	99.19	93.74	94.66	96.4	84.65
6	100.48	95.41	103.43	98.3	96.33	99.77	105.64	83.45
7	97.23	101.53	99.35	101.56	94.37	100.2	104.58	86.6
8	101.88	101.61	105.96	97.13	95.09	96.29	94.88	79.87
9	97.68	104.06	98.66	95.81	93.27	100.86	103.45	84.96
10	100.04	105.46	103.76	97.84	97.62	98.25	101.35	85.51
mean	98.5	100.4	101.4	98.8	95.4	97.1	102.6	85.4
%RSD	2.2	3.5	2.9	2.9	2.2	4.1	4.5	4.1

[0070] Using the same parameters as before, the emitted dose testing results are summarized in Table 13.

Table 13. Emitted Dose Testing for Batched 4, 5, 6, and 7.

Fill weight	Batch 4		Batch 5		Batch 6		Batch 7	
	30mg		32mg		35mg		40mg	
Sample #	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn	Crmlyn	Ibuprfn
1	13.487	5.122	14.49	10.651	13.536	16.057	14.29	18.668
2	13.601	4.594	13.331	10.451	14.618	14.417	14.656	17.882
3	14.186	5.557	13.851	10.004	14.006	15.378	15.564	18.916
4	12.013	4.116	13.42	9.635	15.235	15.161	14.32	17.093
5	14.258	5.635	12.922	10.148	14.478	15.072	13.417	19.011
mean	13.509	5.005	13.603	10.178	14.375	15.217	14.449	18.314
%RSD	6.7	12.9	4.4	3.9	4.5	3.9	5.4	4.4

[0071] The results show that by increasing the fill weight of Ibuprofen there was an increase in the emitted dose. Cromolyn sodium maintained consistent performance for the emitted dose regardless of the Ibuprofen concentration.

[0072] Magnesium stearate was removed from the formulation of Batch 5 to obtain Batch 8. Table 14 illustrates the blend uniformity testing for Batch 8, which was a homogeneous powder blend. Table 15 contains the data for emitted dose testing of Batch 5 and Batch 8.

[0073]

Table 14. Blend Uniformity for Batch 8

Sample #	Batch 8	
	Cromolyn	Ibuprofen _{course}
1	84.98	88.33
2	86.67	87.98
3	87.57	87.69
4	91.89	90.43
5	94.21	91.35
6	88.82	92.93
7	90.61	92.7
8	90.64	90.96
9	89.41	95.35
10	90.92	92.2
mean	89.6	91.0
%RSD	3.0	2.7

[0074]

Table 15. Emitted Dose comparison between Batch 5 and Batch 8

	Batch 5 (32mg)		Batch 8 (32mg)	
	Cromolyn	Ibuprofen	Cromolyn	Ibuprofen
1	14.49	10.651	14.929	10.547
2	13.331	10.451	15.102	10.627
3	13.851	10.004	15.271	10.078
4	13.42	9.635	16.544	10.142
5	12.922	10.148	15.996	10.349
mean	13.603	10.178	15.568	10.349
%RSD	4.4	3.9	4.4	2.3

[0075] Example 5: Formulation of Cromolyn Sodium and Ibuprofen

[0076] Two formulations were made using a blend of micronized ibuprofen and magnesium stearate and another without magnesium stearate. Batch 9 with 2% by weight magnesium stearate and Batch 10 without magnesium stearate. The blending process comprises the steps (1) micronizing ibuprofen at a feed pressure of 45psi and a grinding pressure of 45psi for one pass; (2) separately passing the micronized ibuprofen and cromolyn sodium through a 300 μ m sieve; (3) blending the two materials in a Turbula mixer for 10 minutes at 49rpm; and (4) blend co-milling by milling the blend (single pass) with a feed pressure of 45psi and grinding pressure of 45 psi. Table 14 summarizes the assay results for the two batches without magnesium stearate.

Table 16. Results – Assay without magnesium stearate

	Batch 9		Batch 10	
	Cromolyn (0.584mg)	Ibuprofen (0.344mg)	Cromolyn (0.596mg)	Ibuprofen (0.351mg)
1	107.63	89.52	106.44	87.65
2	99.93	85.83	102.83	85.03
mean	103.8	87.7	104.6	86.3
%RSD	5.2	3.0	2.4	2.1

[0077] Table 15 summarizes the assay results for the two batches with magnesium stearate.

Table 17. Results – Assay with magnesium stearate				
	Batch 9 (40mg)		Batch 10 (40mg)	
	Cromolyn	Ibuprofen	Cromolyn	Ibuprofen
1	17.889	10.961	17.262	10.649
2	16.516	10.562	18.199	10.894
3	17.568	10.667	17.71	10.618
4	17.368	10.606	18.144	10.913
5	25.334*	15.327*	17.207	10.474
mean	17.335	10.699	17.704	10.71
%RSD	3.4	1.7	2.7	1.8

[0078] The results show no difference between formulation with and without magnesium stearate in terms of emitted dose. Both batches were tested for NGI and stability.

[0079] Aerodynamic particle size distribution determined by NGI. Batch 9 was co-milled and magnesium stearate was added. Batch 10 was co-milled and had no magnesium stearate. Batch 5 was blended with coarse ibuprofen and magnesium stearate was added. Batch 8 was blended with coarse ibuprofen and had no magnesium stearate. Table 18 summarizes the conditions used in the NGI method.

Table 18.	
Type & Size of Capsules	Clear HPMC size 3 capsules
Fill weights	<ul style="list-style-type: none"> Batch 9 and Batch 10: 40mg Batch 5 and Batch 8: 32mg
Number of shots	1
Coating solution used	1mg/mL Pluronic F68 and 3% v/v PEG400 in Acetone
Volume of the coating solution used in each of the cups	Cups 1, MOC: 3mL Cups 2-7: 1.5mL
Diluents used	25mM potassium phosphate buffer pH 6.8 : Methanol (1:1)
Device used	Low resistance device
Flow rate	80L/min for 3 seconds
Dilution used	Device + capsule: 50mL Throat (induction port): 50mL Pre-separator: 100mL Stages 1 - 7, MOC: 10mL
Number of Replicates per formulation	3

[0080] Tables 19-22 summarize the data for each batch. Table 23 contains the data comparing batches 5, 8, 9, and 10.

Table 19. NGI Results of Batch 9.							
API	Cromolyn			Ibuprofen			
Shots fired	1			1			
Batch Strength	23.36mg			13.76mg			
Device Number	1	2	3	4	5	6	
Stage of Use	Mean			Mean			Mean

Device	3.90	3.93	3.93	3.9	2.20	2.19	2.23	2.2
Throat	2.22	2.17	2.22	2.2	1.02	1.02	1.01	1.0
Pre-sep	0.58	0.64	0.63	0.6	0.29	0.33	0.30	0.3
Stage 1	0.94	1.08	0.87	1.0	0.54	0.63	0.49	0.6
Stage 2	5.27	5.05	5.10	5.1	2.60	2.57	2.53	2.6
Stage 3	4.77	4.63	5.01	4.8	2.49	2.47	2.61	2.5
Stage 4	2.58	2.38	2.60	2.5	1.70	1.60	1.72	1.7
Stage 5	0.83	0.75	0.79	0.8	0.54	0.50	0.53	0.5
Stage 6	0.29	0.27	0.28	0.3	0.16	0.15	0.16	0.2
Stage 7	0.09	0.08	0.08	0.1	0.05	0.04	0.04	0.0
MOC	0.02	0.02	0.02	0.0	0.01	0.01	0.01	0.0
Total recovery	21.50	21.00	21.53	21.3	11.60	11.51	11.64	11.6
Total ex-device	17.60	17.07	17.61	17.4	9.40	9.32	9.41	9.4
FPM	8.59	8.13	8.79	8.5	4.95	4.77	5.08	4.9
FPF	48.79	47.64	49.93	48.8	52.65	51.19	53.93	52.6
%Recovery	92.04	89.88	92.18	91.4	84.27	83.66	84.61	84.2

[0081]

Table 20. NGI Results of Batch 10								
API	Cromolyn			Ibuprofen				
Shots fired	1			1				
Batch Strength	23.84mg			14.04mg				
Device Number	1	2	3		4	5	6	
Stage of Use				Mean				Mean
Device	3.49	3.88	4.42	3.9	1.87	2.09	2.55	2.2
Throat	1.73	2.32	2.06	2.0	0.90	1.08	1.00	1.0
Pre-sep	0.50	0.64	0.73	0.6	0.26	0.32	0.38	0.3
Stage 1	0.90	1.01	1.37	1.1	0.51	0.59	0.82	0.6
Stage 2	5.69	5.82	5.75	5.8	2.80	2.91	2.87	2.9
Stage 3	5.49	4.92	4.33	4.9	2.79	2.59	2.33	2.6
Stage 4	2.72	2.38	2.32	2.5	1.75	1.57	1.51	1.6
Stage 5	0.78	0.71	0.65	0.7	0.49	0.44	0.39	0.4
Stage 6	0.27	0.25	0.24	0.3	0.12	0.11	0.10	0.1
Stage 7	0.07	0.06	0.07	0.1	0.03	0.03	0.03	0.0
MOC	0.00	0.00	0.00	0.0	0.01	0.01	0.01	0.0
Total recovery	21.64	21.98	21.94	21.9	11.53	11.71	11.97	11.7
Total ex-device	18.15	18.10	17.52	17.9	9.66	9.63	9.42	9.6
FPM	9.33	8.32	7.61	8.4	5.19	4.73	4.35	4.8
FPF	51.39	45.95	43.43	46.9	53.71	49.12	46.23	49.7
%Recovery	90.77	92.19	92.01	91.7	82.09	83.43	85.23	83.6

[0082]

Table 21. NGI Results of Batch 5.								
API	Cromolyn			Ibuprofen				
Shots fired	1			1				
Batch Strength	18.048mg			11.68mg				
Device Number	1	2	3		4	5	6	
Stage of Use				Mean				Mean
Device	2.02	2.03	2.06	2.0	0.52	0.52	0.38	0.5
Throat	3.33	3.32	3.93	3.5	1.30	1.30	1.00	1.2
Pre-sep	2.31	2.07	2.08	2.2	7.93	6.56	6.40	7.0
Stage 1	0.51	0.60	0.63	0.6	0.88	1.53	1.59	1.3

Stage 2	1.69	1.74	1.77	1.7	0.18	0.17	0.17	0.2
Stage 3	2.37	2.25	2.30	2.3	0.08	0.06	0.06	0.1
Stage 4	2.22	1.94	1.99	2.1	0.05	0.04	0.04	0.0
Stage 5	1.37	1.19	1.22	1.3	0.02	0.02	0.02	0.0
Stage 6	0.62	0.56	0.58	0.6	0.01	0.01	0.01	0.0
Stage 7	0.21	0.20	0.20	0.2	0.00	0.00	0.00	0.0
MOC	0.10	0.07	0.08	0.1	0.00	0.00	0.00	0.0
Total recovery	16.76	15.97	16.83	16.5	10.98	10.21	9.67	10.3
Total ex-device	14.73	13.94	14.77	14.5	10.46	9.69	9.29	9.8
FPM	6.89	6.22	6.37	6.5	0.17	0.13	0.13	0.1
FPF	46.77	44.58	43.12	44.8	1.58	1.30	1.38	1.4
%Recovery	92.84	88.46	93.27	91.5	94.03	87.41	82.78	88.1

Table 22. NGI Results of Batch 8.

API	Cromolyn			Ibuprofen				
Shots fired	1			1				
Batch Strength	18.432mg			11.936mg				
Device Number	1	2	3			4	5	6
Stage of Use				Mean				Mean
Device	1.82	2.13	2.21	2.1	0.30	0.43	0.62	0.4
Throat	2.88	3.09	3.14	3.0	2.05	2.04	1.67	1.9
Pre-sep	2.45	2.57	2.57	2.5	7.89	7.65	7.65	7.7
Stage 1	0.53	0.54	0.54	0.5	0.79	0.70	0.71	0.7
Stage 2	1.39	1.32	1.25	1.3	0.13	0.16	0.19	0.2
Stage 3	2.55	2.38	2.31	2.4	0.05	0.05	0.06	0.1
Stage 4	3.10	2.81	2.80	2.9	0.04	0.03	0.04	0.0
Stage 5	1.75	1.66	1.78	1.7	0.02	0.02	0.02	0.0
Stage 6	0.55	0.60	0.76	0.6	0.01	0.01	0.01	0.0
Stage 7	0.11	0.16	0.26	0.2	0.00	0.00	0.00	0.0
MOC	0.05	0.05	0.09	0.1	0.00	0.00	0.00	0.0
Total recovery	17.18	17.30	17.72	17.4	11.26	11.08	10.97	11.1
Total ex-device	15.36	15.16	15.51	15.3	10.96	10.65	10.36	10.7
FPM	8.11	7.65	8.01	7.9	0.11	0.11	0.14	0.1
FPF	52.82	50.47	51.62	51.6	1.02	1.01	1.34	1.1
%Recovery	93.19	93.84	96.11	94.4	94.35	92.82	91.94	93.0

Table 23. Data Comparison between Batches 5, 8, 9, and 10.

Formulation Code	Co-milled				Blended - coarse Ibuprofen				Feasibility Batch*	
	Batch 9		Batch 10		Batch 5		Batch 8		13PM792-PG67 Find batch XAX	
Units	mg	%	mg	%	mg	%	mg	%	mg	%
Device	3.9	18.3	3.9	17.8	2.0	12.0	2.1	12.1	1.6	9.6
Throat	2.2	10.3	2.0	9.1	3.5	21.1	3.0	17.3	2.1	12.1
Pre-sep	0.6	2.8	0.6	2.7	2.2	13.3	2.5	14.5	1.1	6.5
Stage 1	1.0	4.7	1.1	5.0	0.6	3.6	0.5	2.9	0.8	4.6
Stage 2	5.1	23.9	5.8	26.5	1.7	10.2	1.3	7.5	3.6	21.1
Stage 3	4.8	22.5	4.9	22.4	2.3	13.9	2.4	13.9	3.3	19.4
Stage 4	2.5	11.7	2.5	11.4	2.1	12.7	2.9	16.8	2.6	15.4
Stage 5	0.8	3.8	0.7	3.2	1.3	7.8	1.7	9.8	1.3	7.8
Stage 6	0.3	1.4	0.3	1.4	0.6	3.6	0.6	3.5	0.4	2.4
Stage 7	0.1	0.5	0.1	0.5	0.2	1.2	0.2	1.2	0.1	0.6
MOC	0.0	0.0	0.0	0.0	0.1	0.6	0.1	0.6	0.1	0.3
Total Recovery	21.3	100.0	21.9	100.0	16.6	100.0	17.3	100.0	17.0	100.0
Total ex-device	17.4	81.7	17.9	82.2	14.5	88.0	15.3	87.9	15.3	90.4
FPM	8.5	39.9	8.5	38.8	6.6	39.8	7.9	45.7	7.8	46.0
Stage 3 - MOC	8.5	39.9	8.5	38.8	6.6	39.8	7.9	45.7	7.8	46.0
%Recovery	91.4	100.0	91.7	100.0	91.5	100.0	94.4	100.0	99.2	100.0

[0083] In a composition for systemic delivery rather than local delivery, deposition in Stages 3 – MOC is of importance. The data demonstrated that blended formulations are superior in terms of Stages 3 – MOC deposition compared to cromolyn only formulation. Batch 5 was comparable to the current formulation used in the current clinic while Batch 8 was better than the current product in terms of Stages 3-MOC. The blended formulation has shown an increase in cromolyn reaching the deep lung thereby increasing the amount of bioavailability of cromolyn into the plasma, the ibuprofen emitted dose and NGI test results both in course and micronized form show that it can reach the lung as well.

[0084] A stability study was performed to determine the compatibility of the combined APIs under accelerated degradation conditions. Separate control samples of micronized cromolyn sodium (Sample A) and micronized ibuprofen (Sample B) were included in the study to be used as a comparator to the blend of Cromolyn/Ibuprofen (Sample C). The study was performed at 40°C and 75% relative humidity. Measurements were taken at time 0, 1 month, 2 months, and 3 months.

[0085] Tables 24A, 24B, and 24C summarize the study results for Sample A, Sample B, and Sample C, respectively.

Table 24A, related substances in Sample A, cromolyn sodium

	Related Substances	
	Individual Related Substances $\geq 0.5\%$	Total Impurities (%)
Initial T=0	0.11	0.1
1 month	0.11	0.1
2 months	0.11	0.1
3 months	0.11	0.1

[0086]

Table 24B, related substances in Sample B, micronized ibuprofen

	Individual Related Substances $\geq 0.5\%$		Total Impurities (%)
	RRT 0.93	RRT 1.11	
Initial T=0	0.07	ND	0.1
1 month	0.07	0.05	0.1
2 months	0.07	<LOQ	0.1
3 months	0.07	<LOQ	0.1

[0087]

Table 24C, related substances in Sample C, cromolyn sodium and ibuprofen

	Ibuprofen		Cromolyn sodium	
	Individual Related		Individual Related	

	Substances ≥0.5%	Total Impurities (%)	Substances ≥0.5%	Total Impurities (%)
	RRT 0.93		RRT 1.88	
Initial T=0	0.07	0.1	0.11	0.1
1 month	0.07	0.1	0.11	0.1
2 months	0.07	0.1	0.11	0.1
3 months	0.07	0.1	0.11	0.1

[0088]

[0089] The combination of cromolyn sodium and ibuprofen had no effect on the stability of the material, and therefore the APIs were compatible in the combine formulation.

[0090] The study demonstrated that the method developed for the assay of the combined cromolyn sodium and ibuprofen composition distinguished between the two APIs without interference. The formulations using either micronized ibuprofen or coarse ibuprofen provided sufficient performance of an inhaled substance to achieve a therapeutic effect. The combined formulation enhanced the performance of cromolyn sodium by comparison to the original formulation. In other words, cromolyn concentration in the deeper regions of the lung were higher than seen with a formulation of cromolyn only with lactose.

CLAIMS

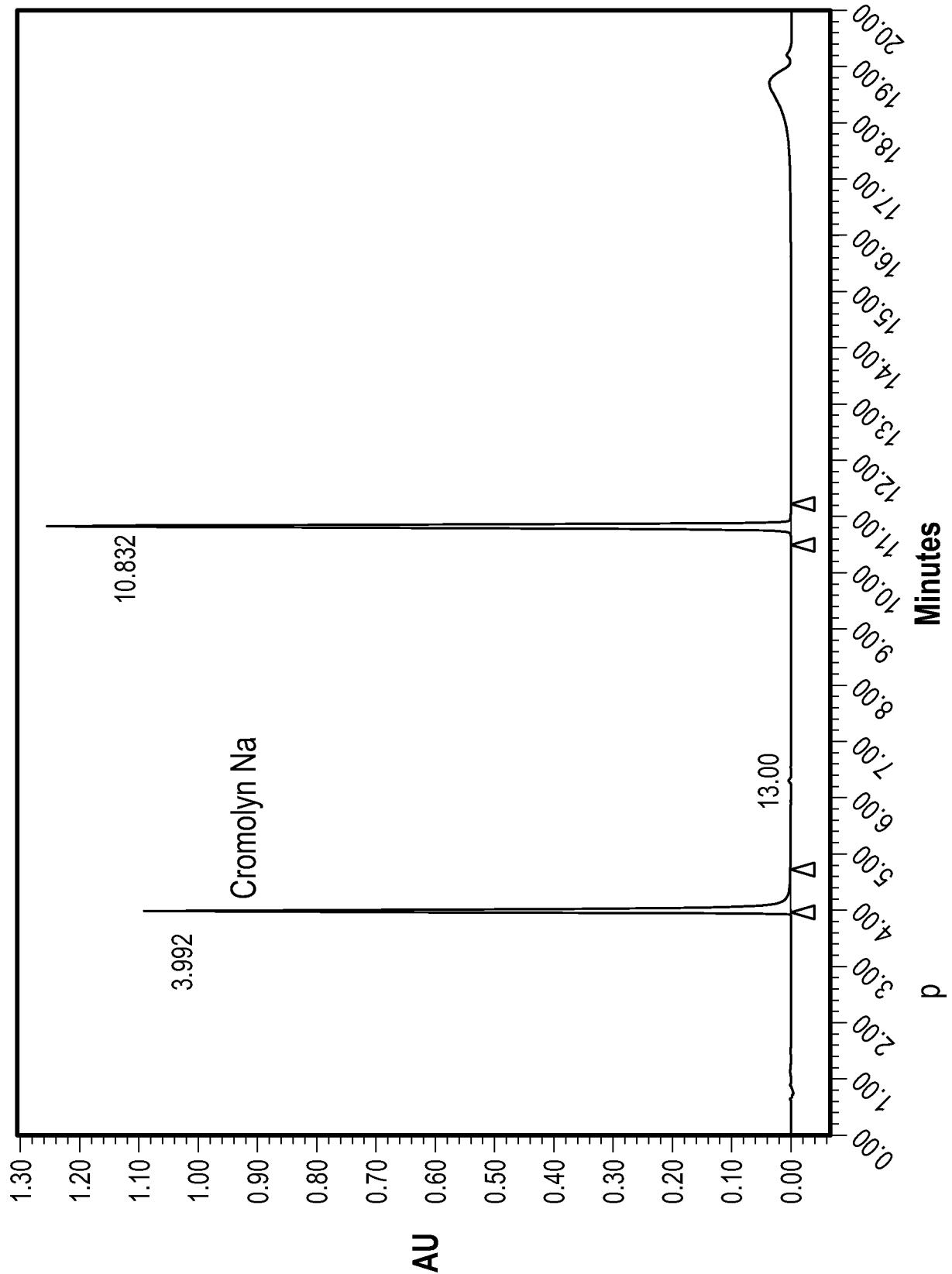
What is claimed is:

1. A composition comprising cromolyn sodium and ibuprofen, wherein the cromolyn sodium is micronized and the cromolyn sodium and ibuprofen are present in a weight ratio of 1:1-2.
2. The composition according to claim 1, wherein the ibuprofen is micronized.
3. The composition according to claim 1, wherein the ibuprofen has been passed through a sieve.
4. The composition according to claim 3, wherein the sieve is a 200 to 600 μm sieve.
5. The composition according to claim 3, wherein the sieve is a 300 to 400 μm sieve.
6. The composition according to claim 1, wherein the cromolyn sodium and ibuprofen are in powdered form.
7. The composition according to claim 6, wherein the ibuprofen has a particle size of about $\leq 3 \mu\text{m}$.
8. A method of making a composition of cromolyn sodium and ibuprofen comprising micronizing cromolyn sodium; separately sieving cromolyn sodium and ibuprofen; blending sieved cromolyn sodium and ibuprofen; and blend co-milling the blended cromolyn sodium and ibuprofen.
9. The method according to claim 8, wherein the sieve is a 200 μm to 600 μm sieve.
10. The method according to claim 8, wherein the sieve is a 300 to 400 μm sieve.
11. The method according to claim 8, wherein the micronizing is performed with an air jet mill.
12. The method according to claim 11, wherein the air jet mill has a feed gas pressure of about 45 psi and a grinding pressure of about 45 psi.
13. A method of treating Alzheimer's disease comprising administering a powdered formulation of cromolyn sodium and ibuprofen, wherein the cromolyn sodium is micronized and the cromolyn sodium and ibuprofen are present in a weight ratio of 1:1-2.

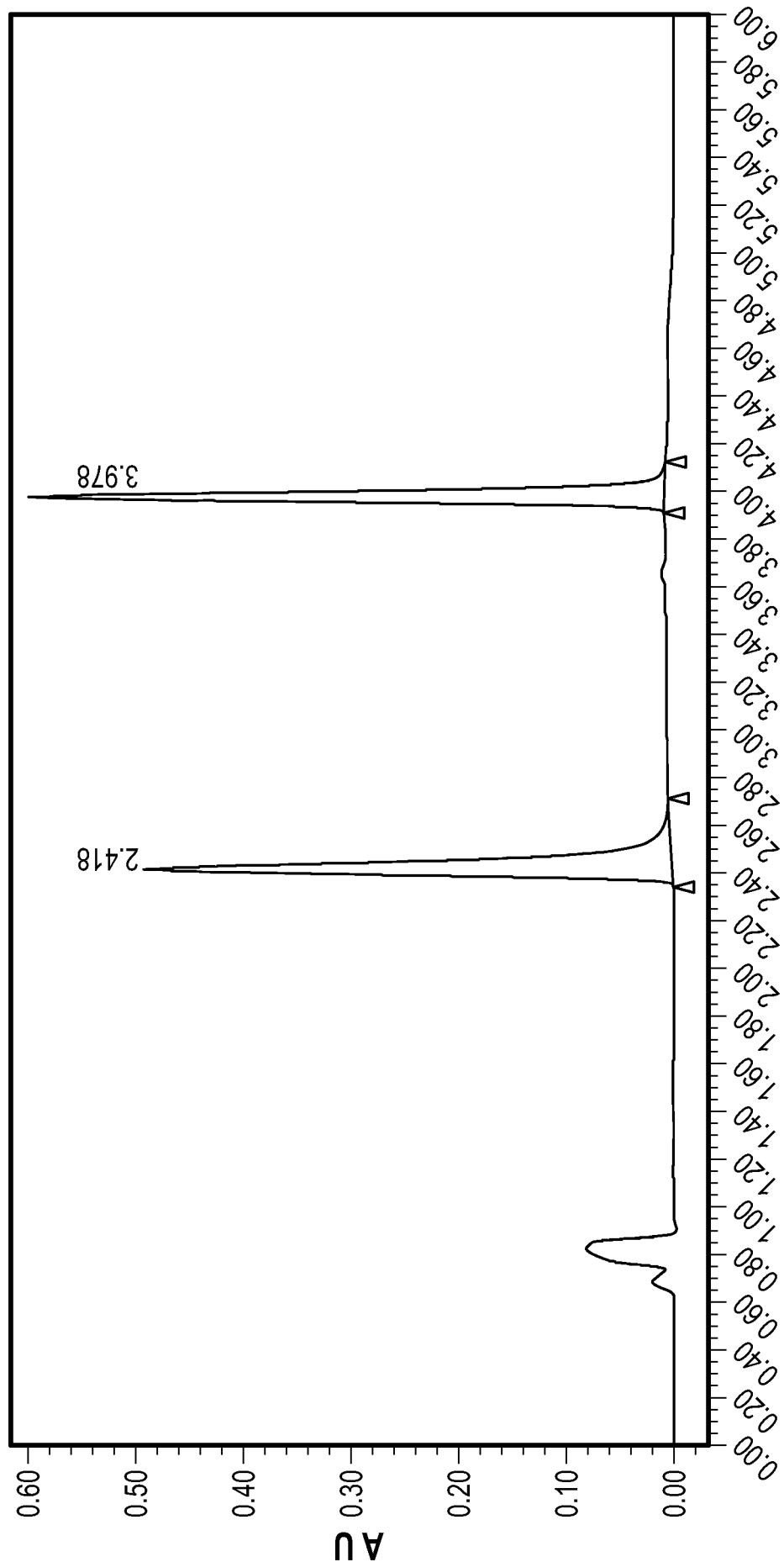
14. The method according to claim 13, wherein the ibuprofen is passed through a sieve.
15. The composition according to claim 14, wherein the sieve is a 200 to 600 μm sieve.
16. The composition according to claim 14, wherein the sieve is a 300 to 400 μm sieve.
17. The composition according to claim 13, wherein the cromolyn sodium and ibuprofen are in powdered form.
18. The composition according to claim 13, wherein the ibuprofen has a particle size of about $\leq 3 \mu\text{m}$.

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FIG. 1



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Minutes

FIG. 2

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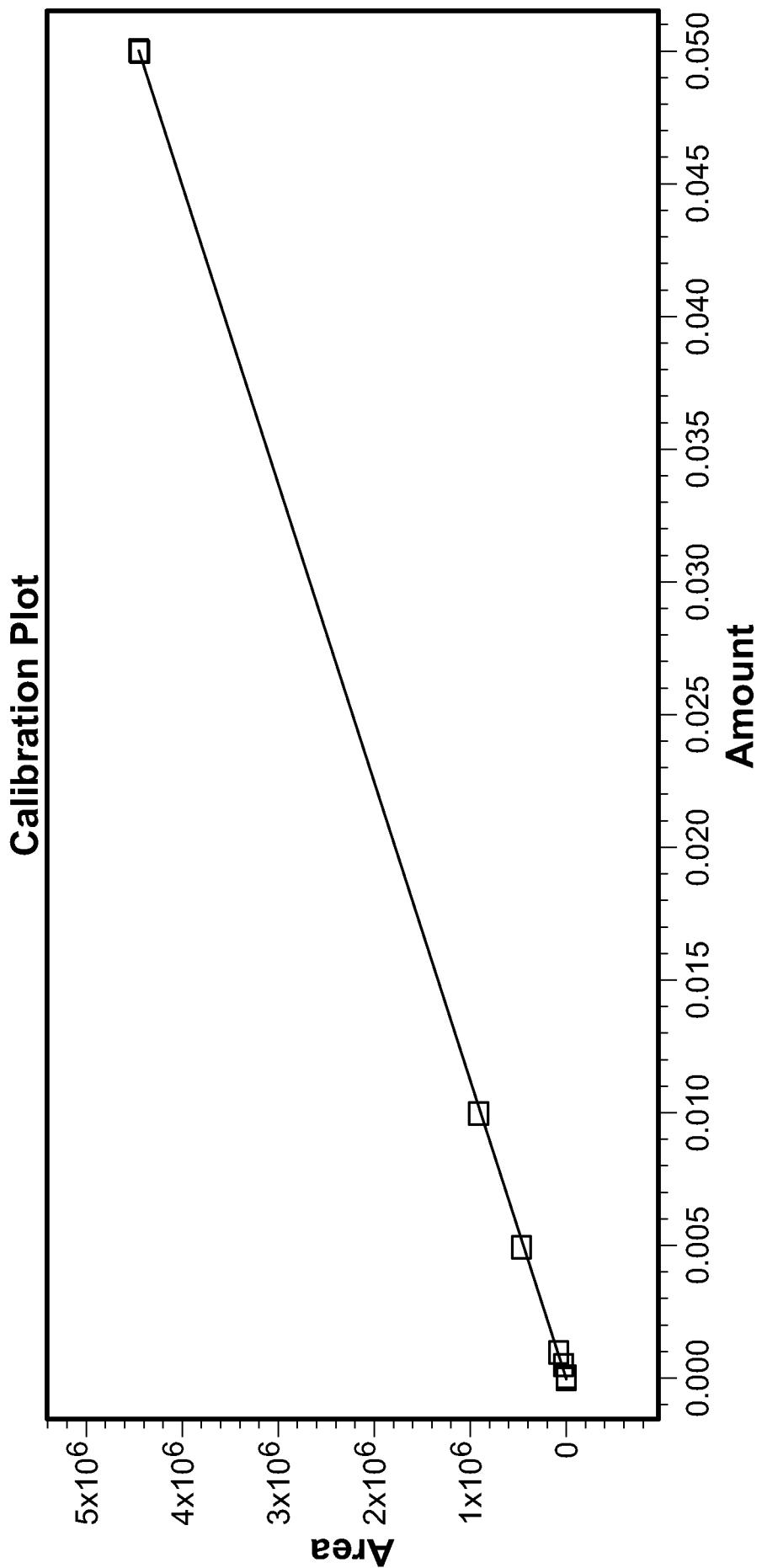


FIG. 3

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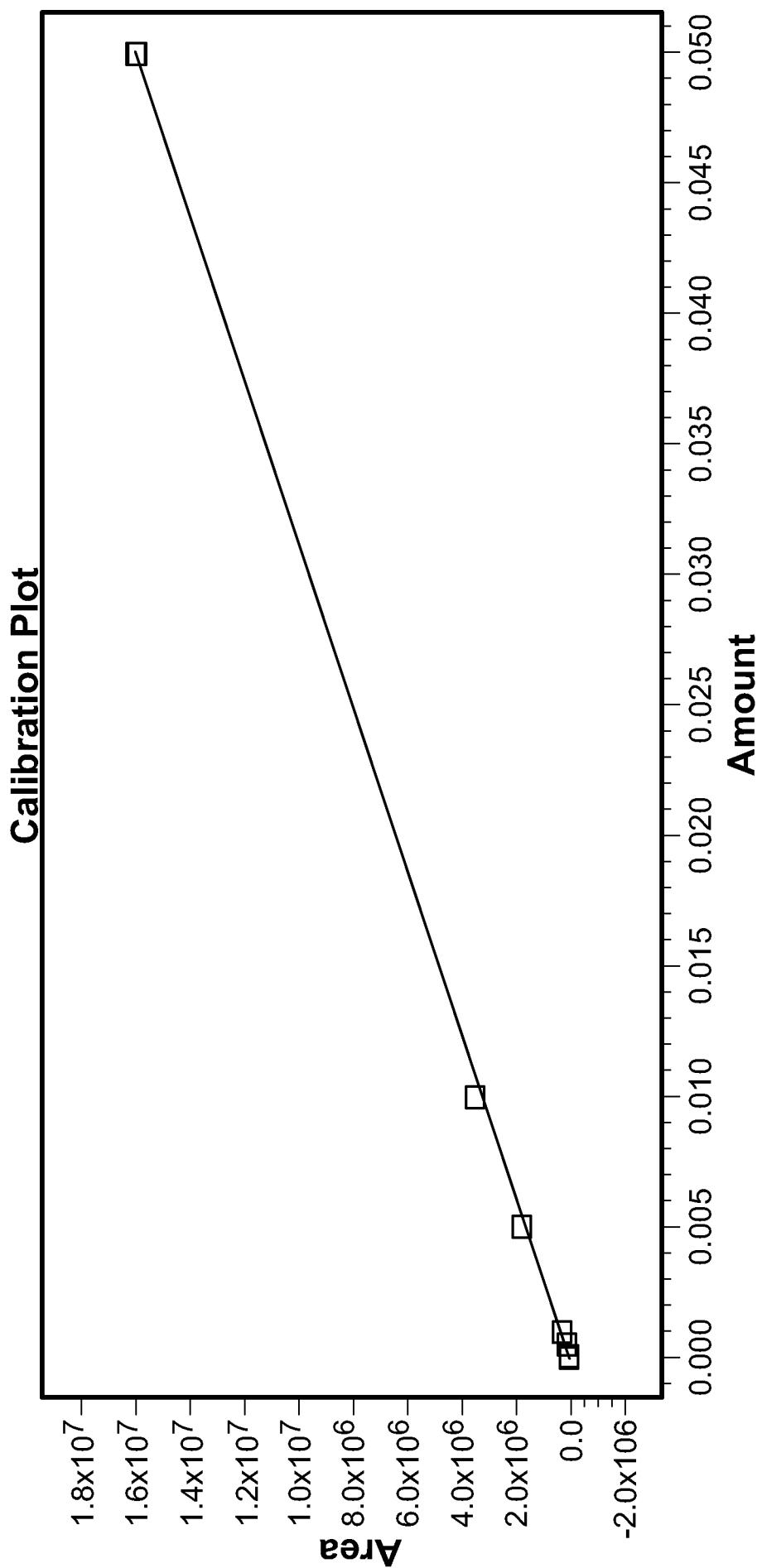


FIG. 4

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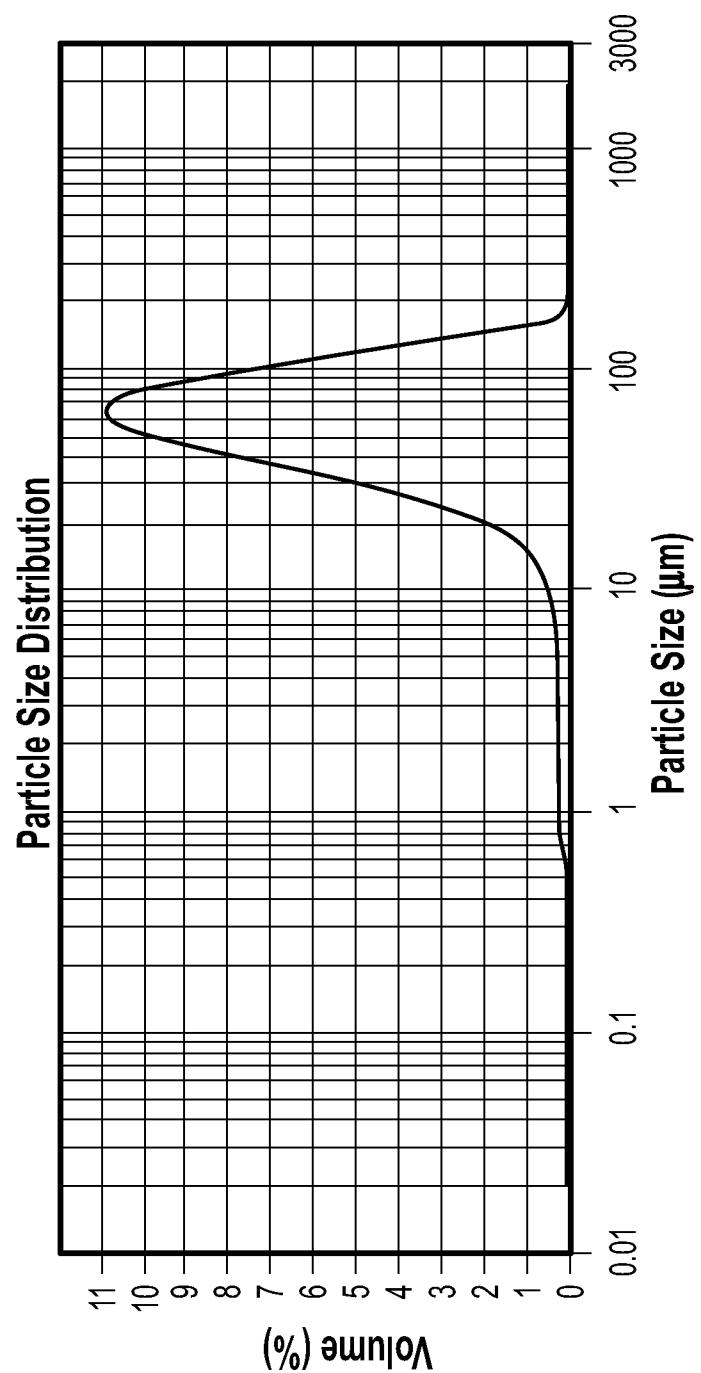
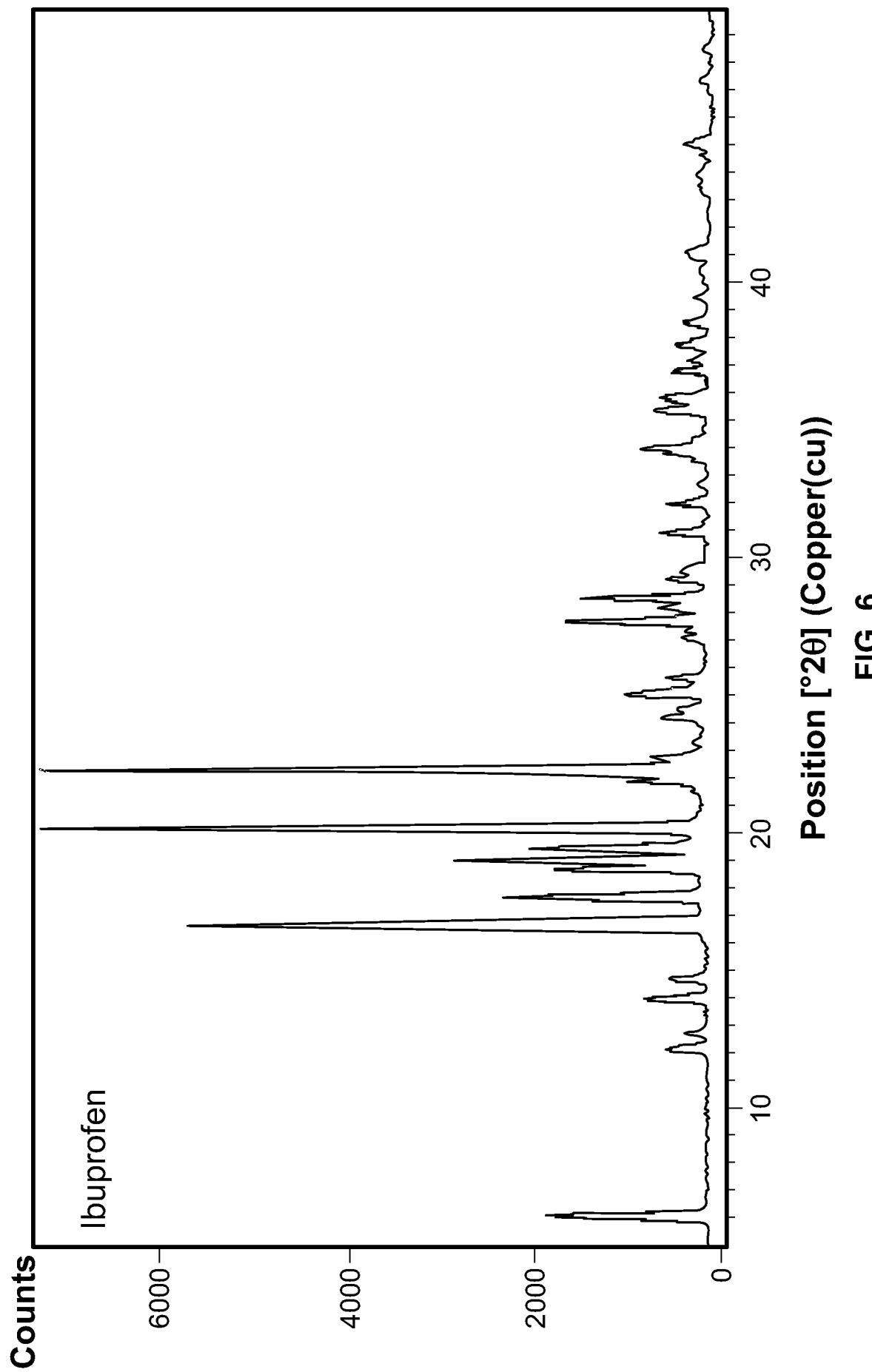


FIG. 5

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Position [°2θ] (Copper(cu))

FIG. 6

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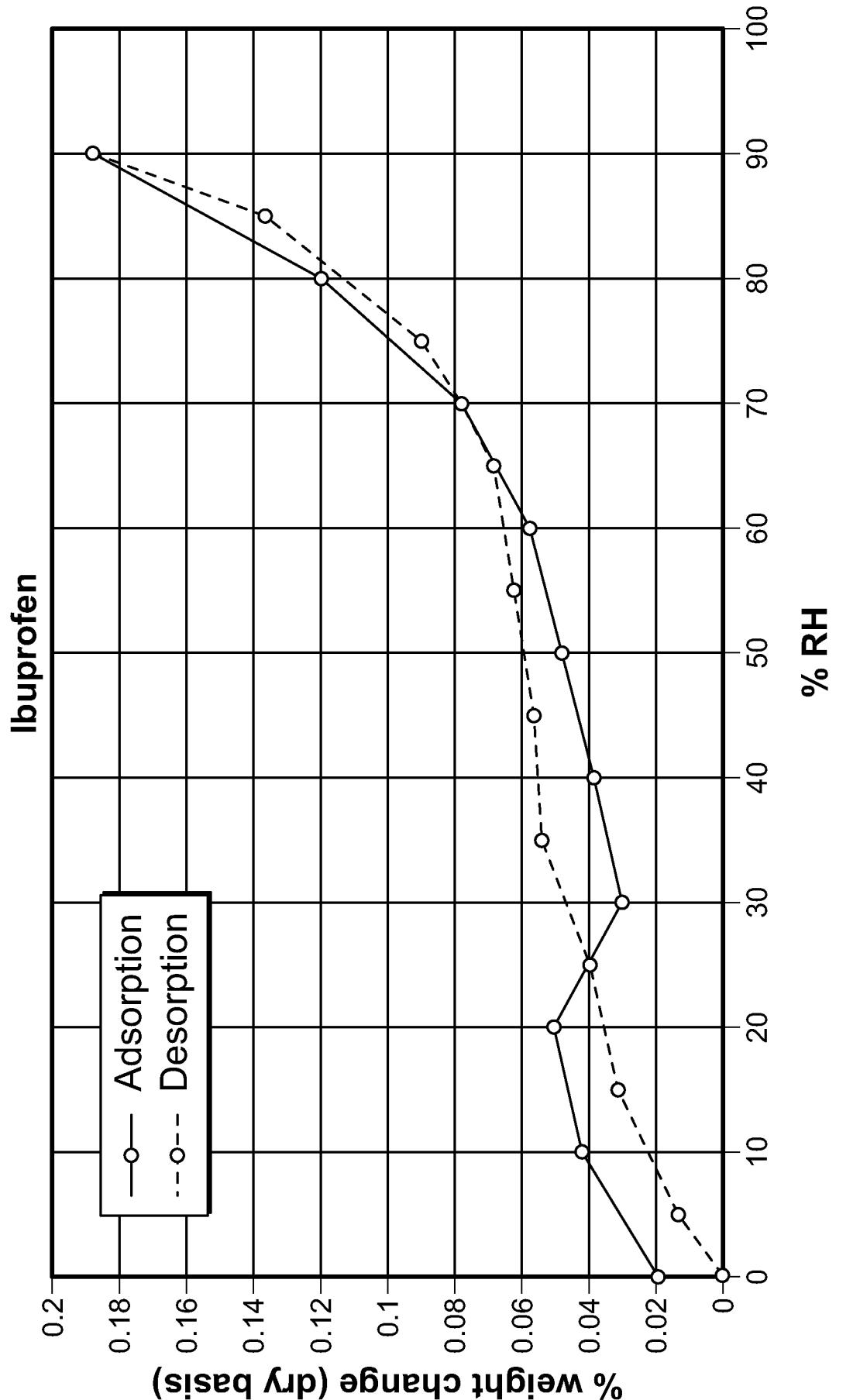


FIG. 7

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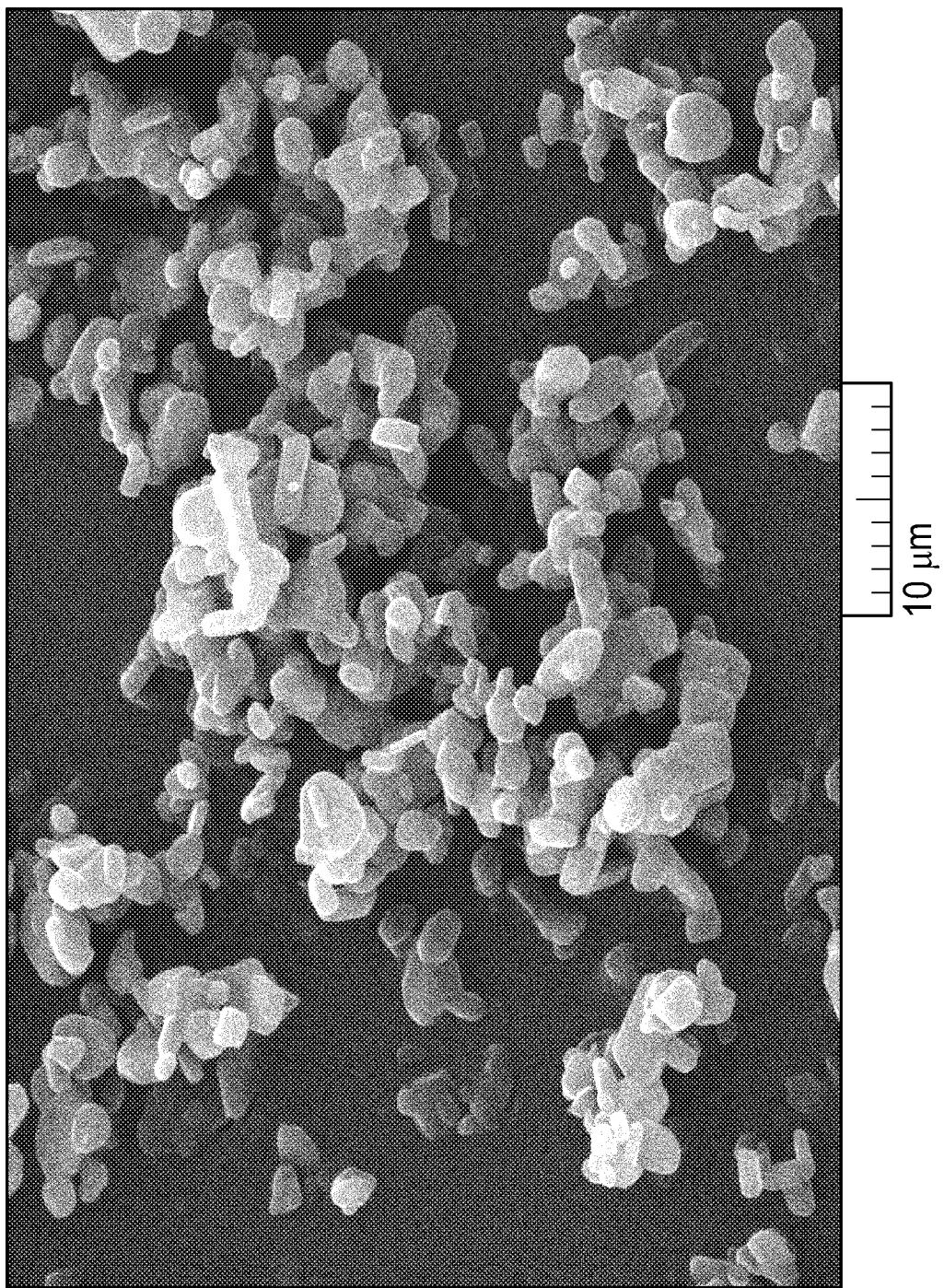


FIG. 8A

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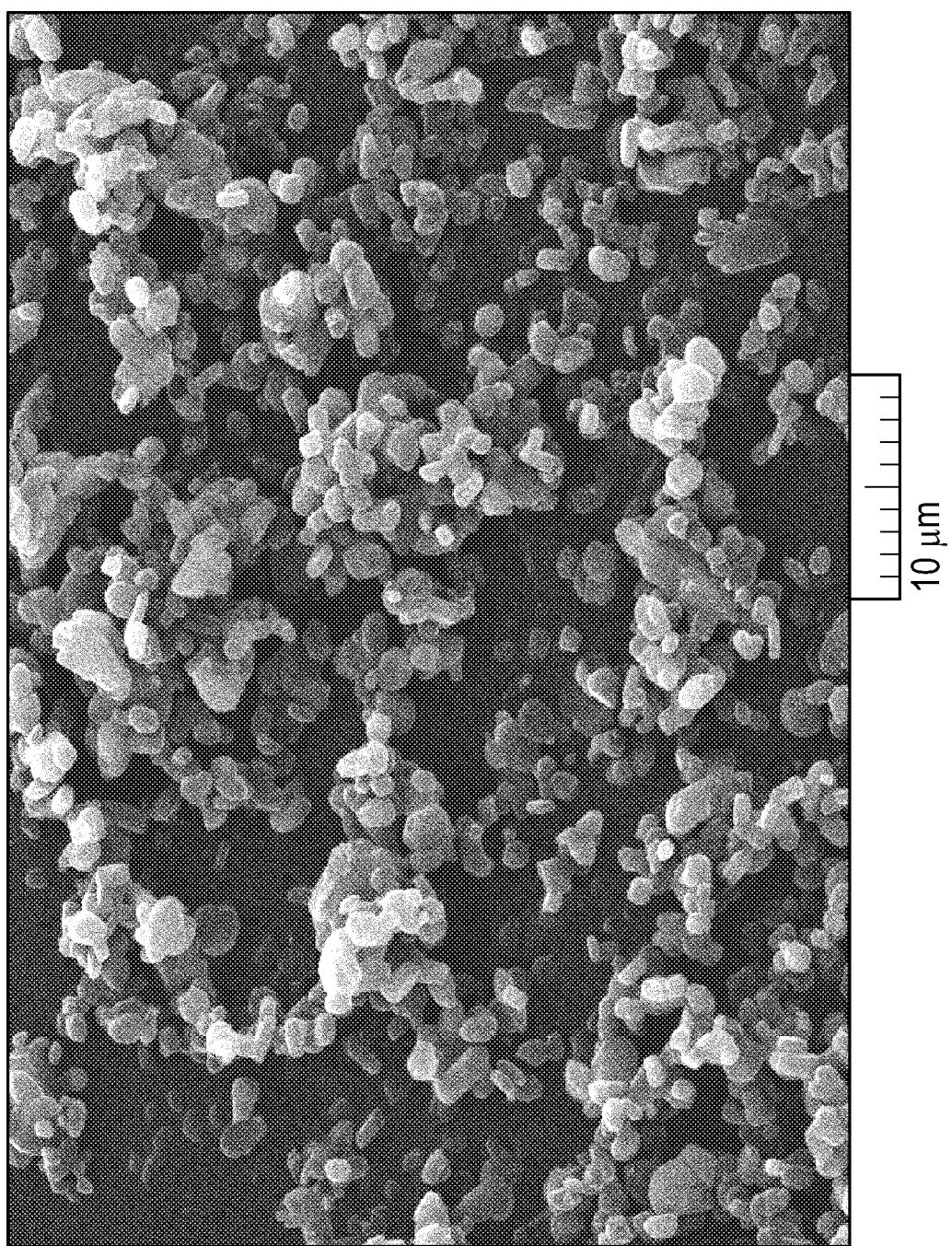


FIG. 8B

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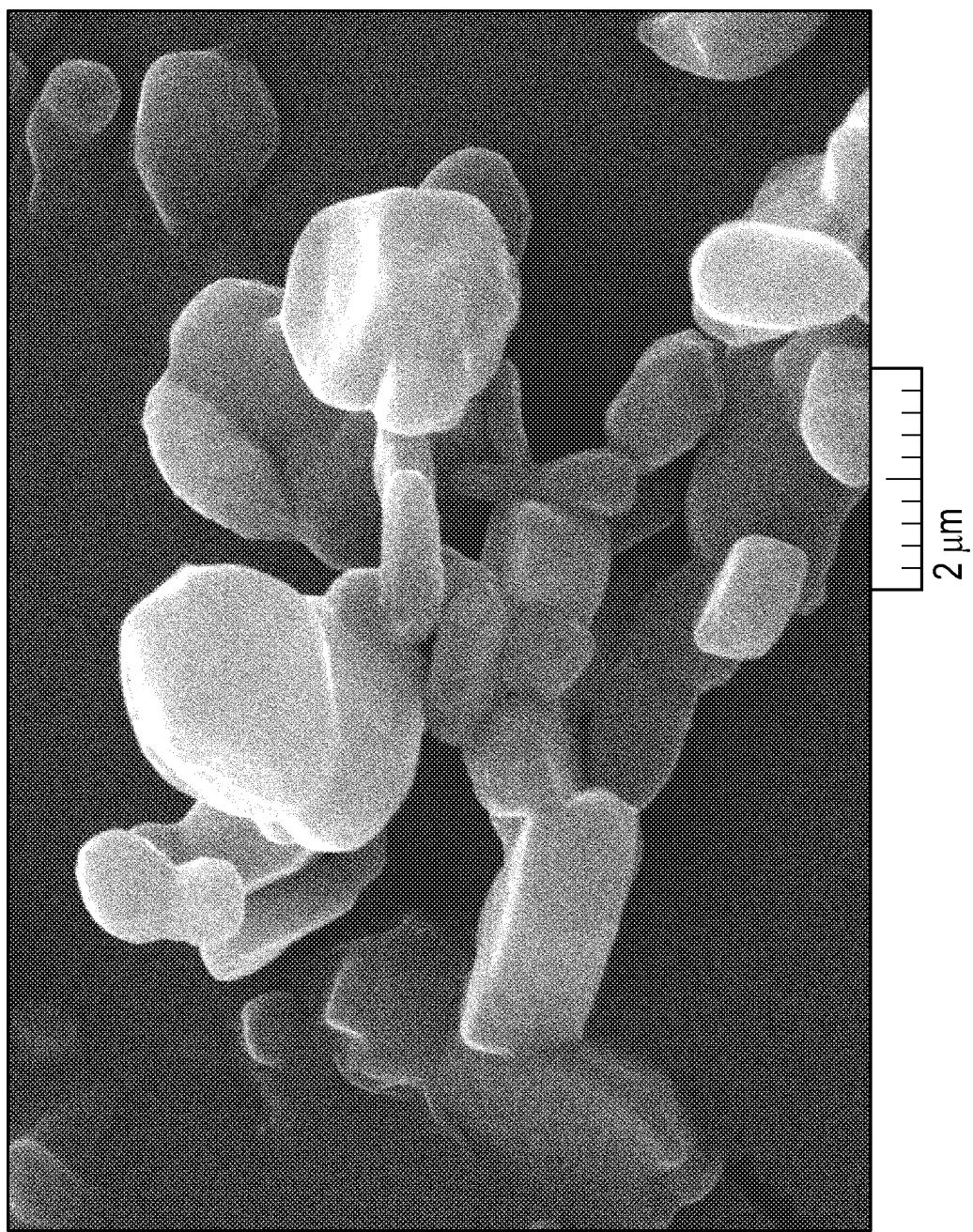


FIG. 9A

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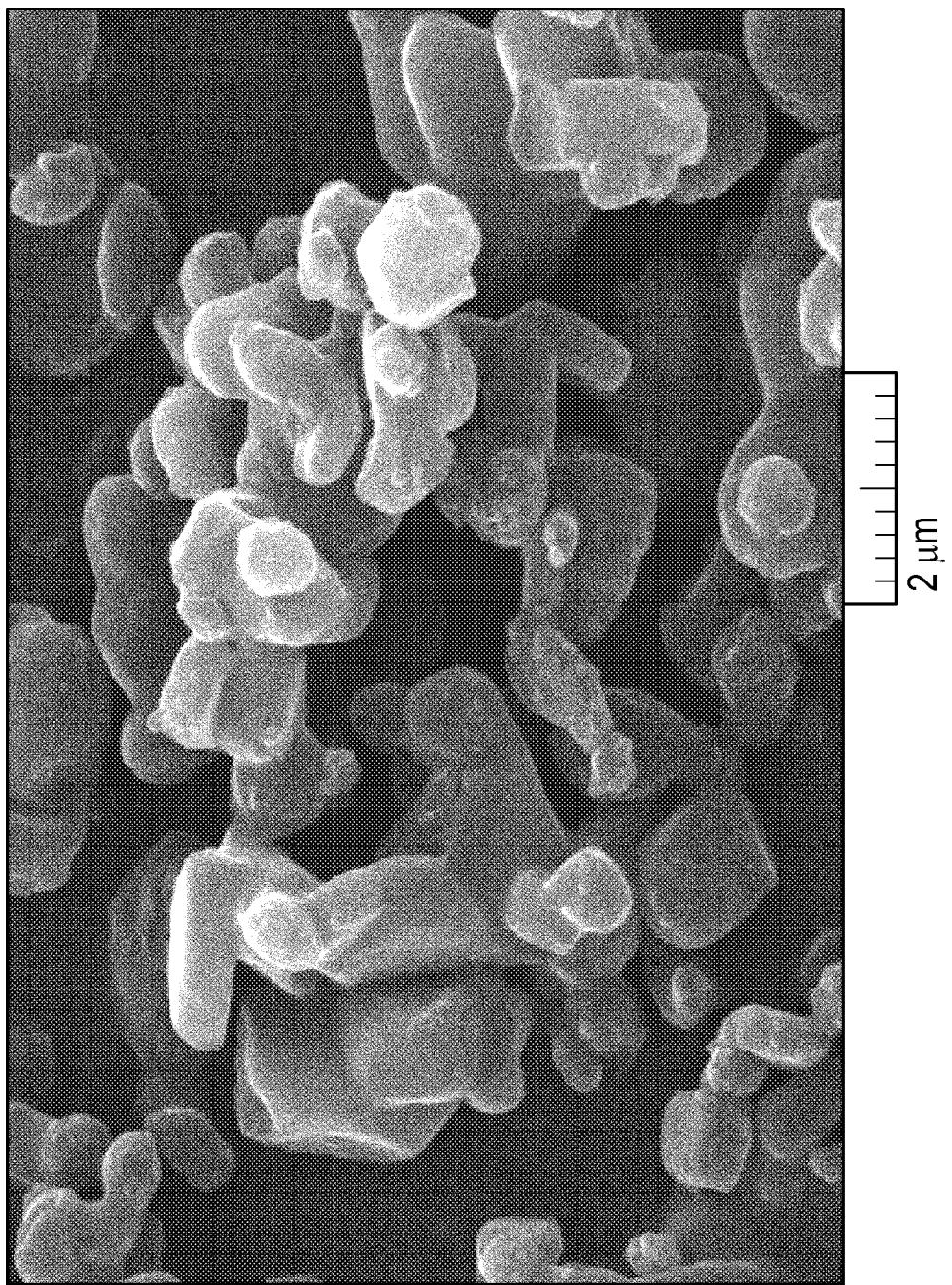


FIG. 9B

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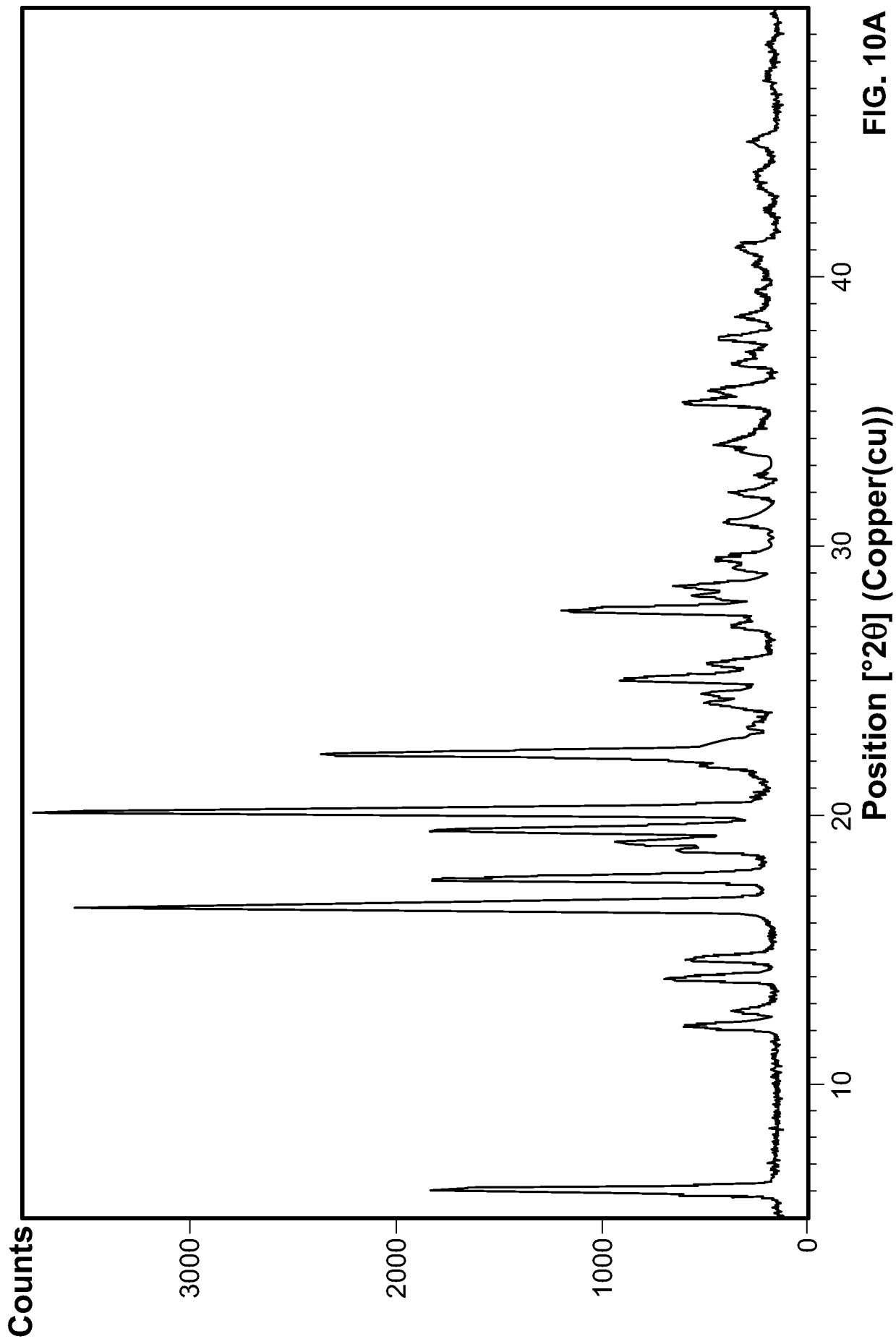
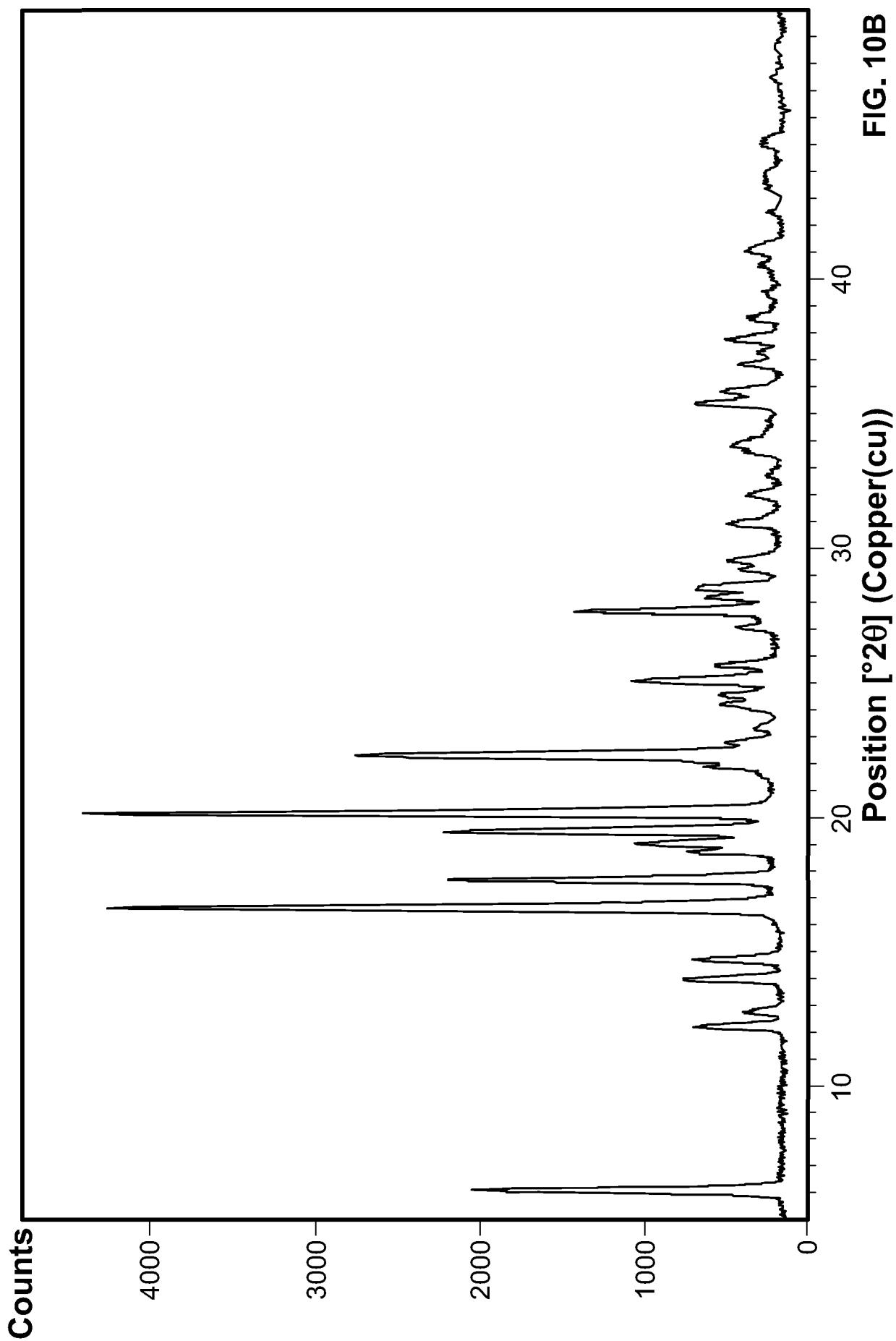
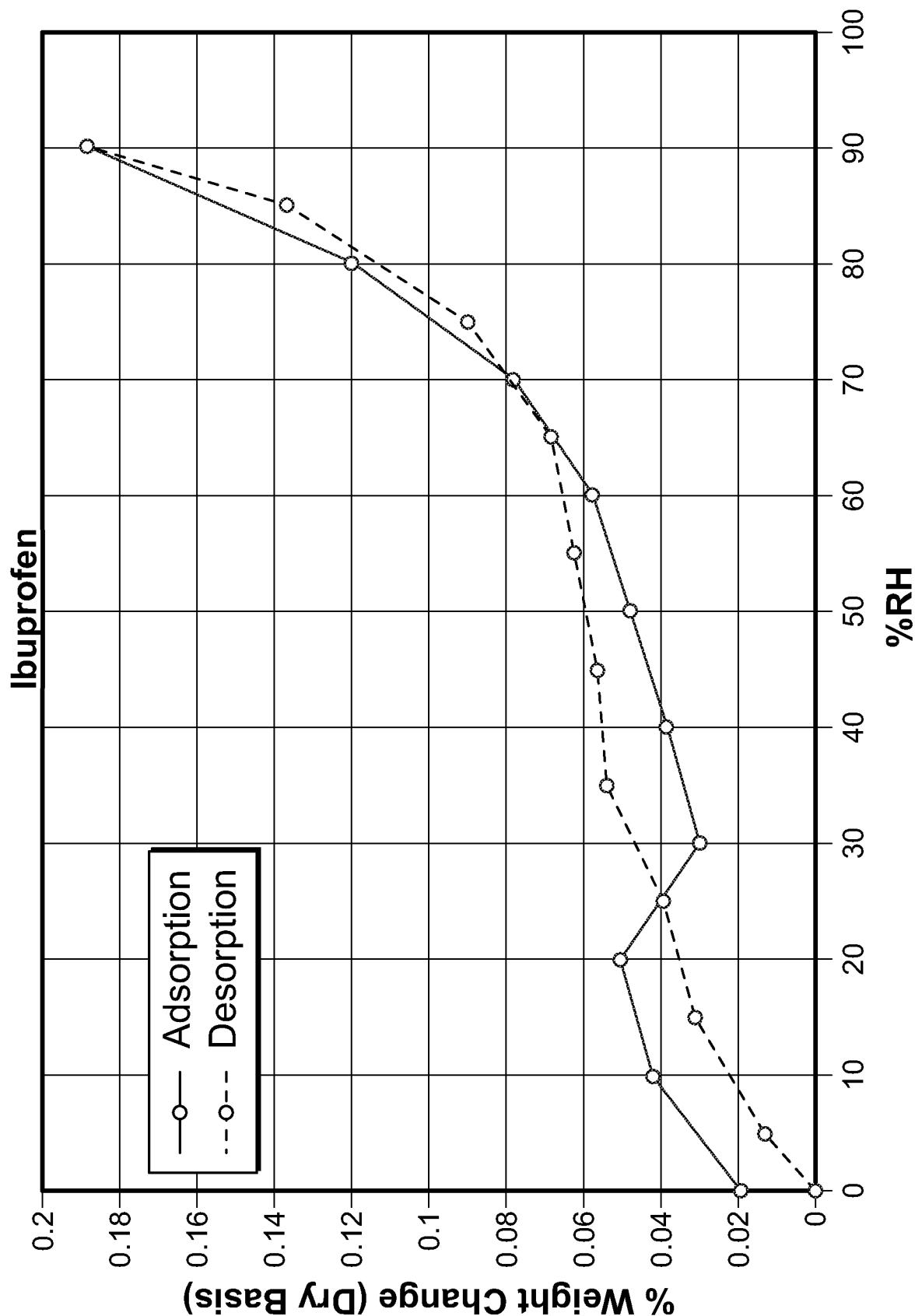


FIG. 10A

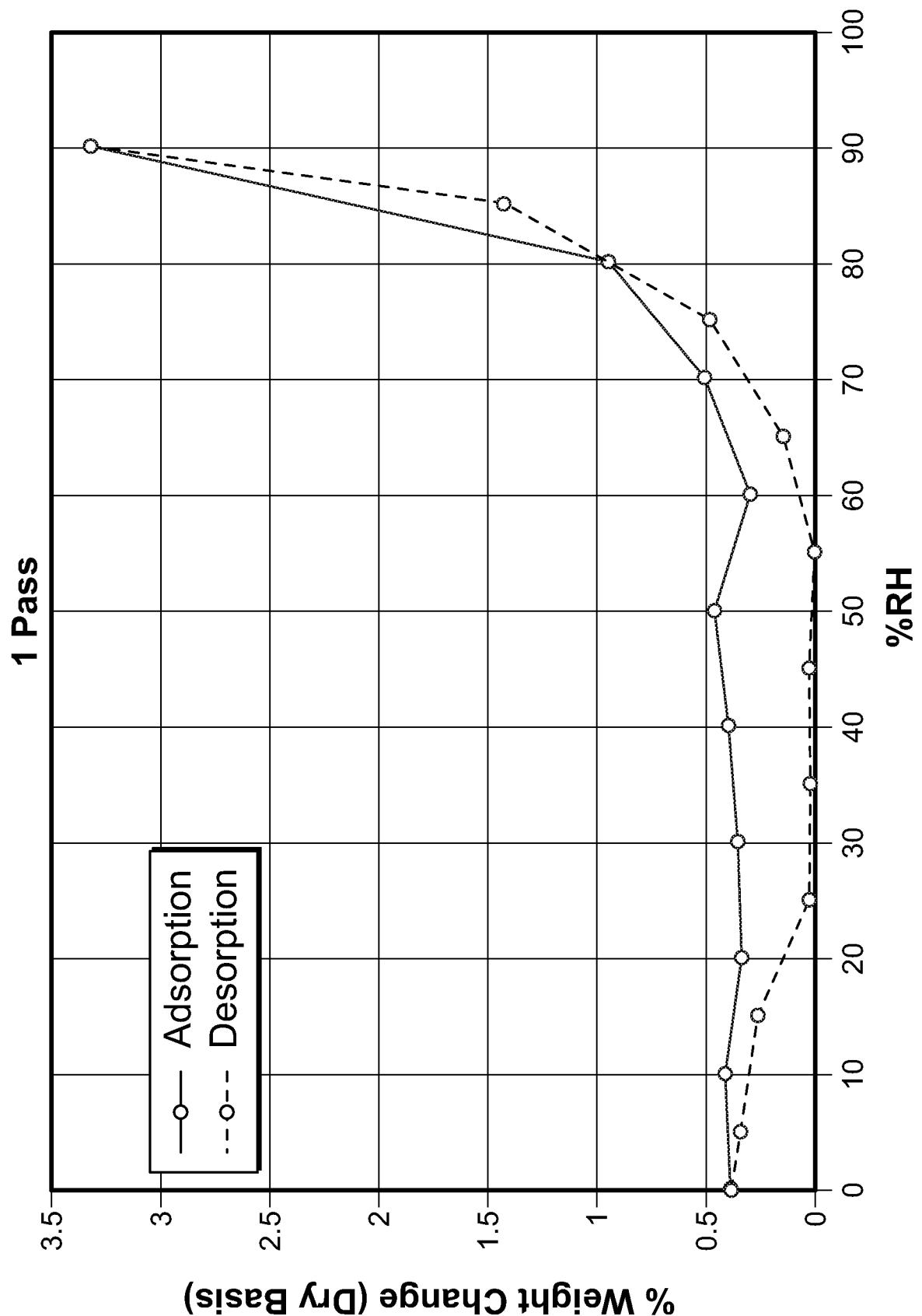
Position [°2θ] (Copper(cu))

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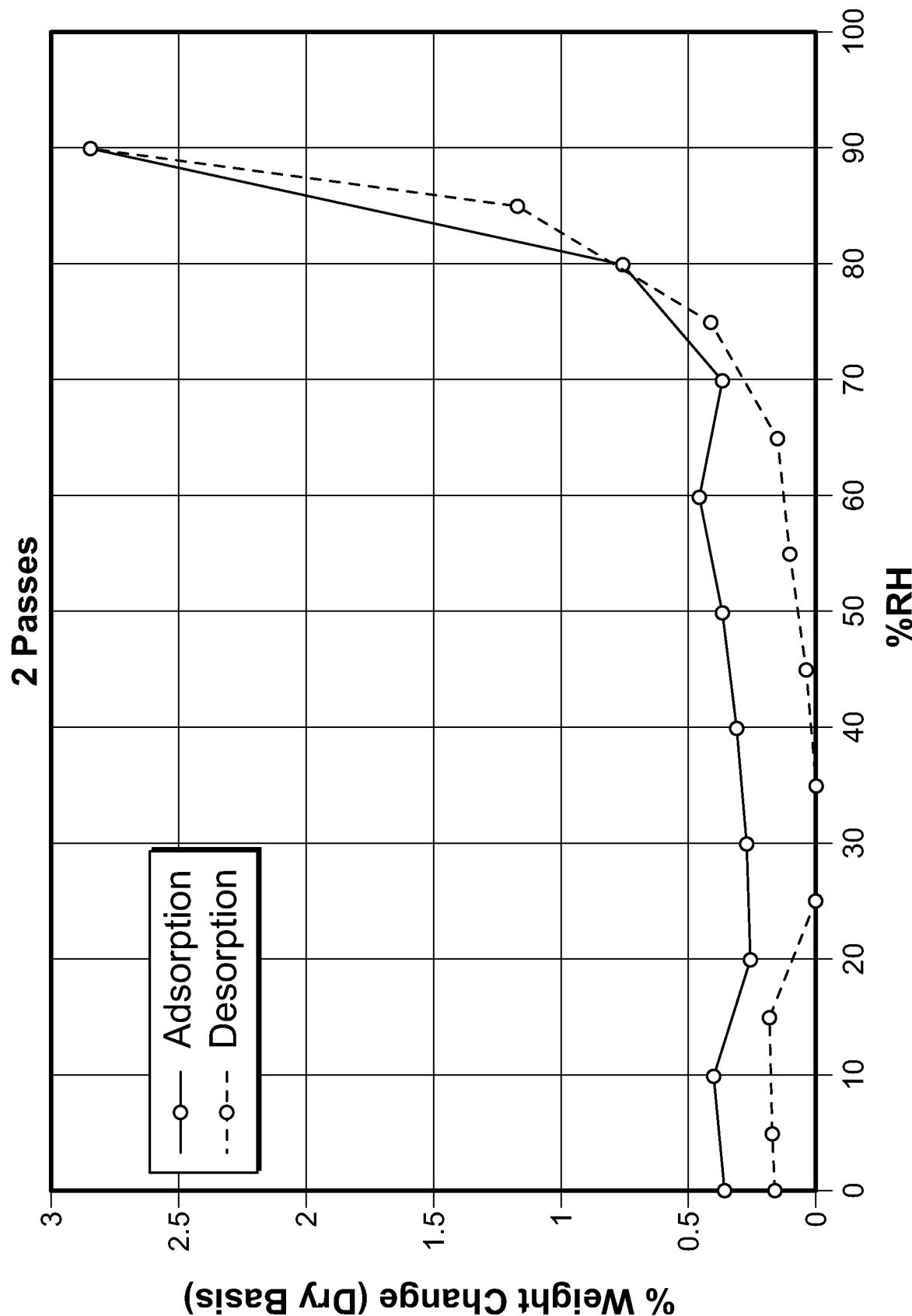


FIG. 11C

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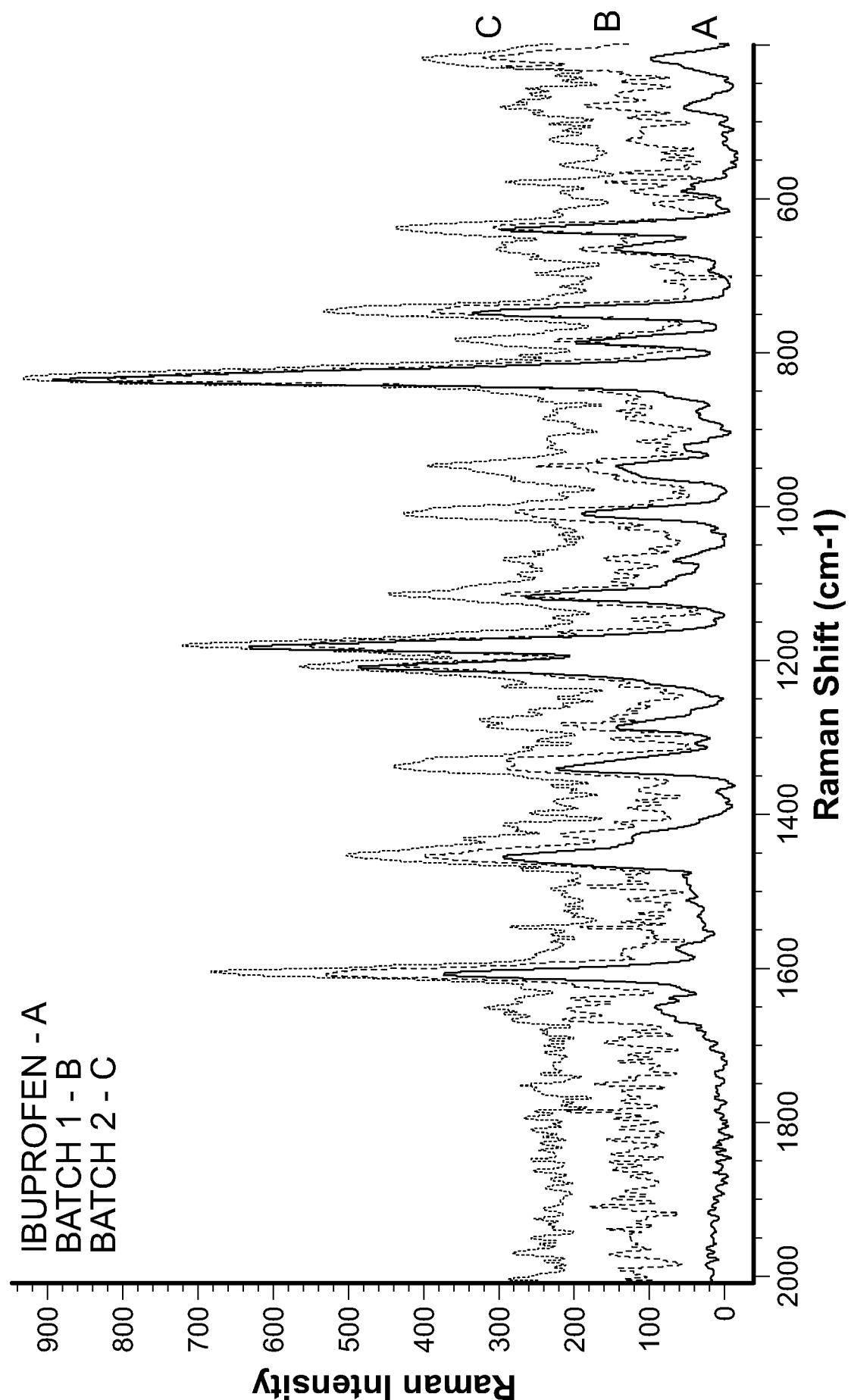


FIG. 12