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(54) **COMPOSITE CHITOSAN-TANNIN-ACTIVE AGENT COMPOSITIONS AND METHODS OF MAKING AND USING SAME**

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(57) **ABSTRACT**

Composite composition comprising chitosan, tannin, and an active agent and methods of making and using same.

20 Claims, 35 Drawing Sheets

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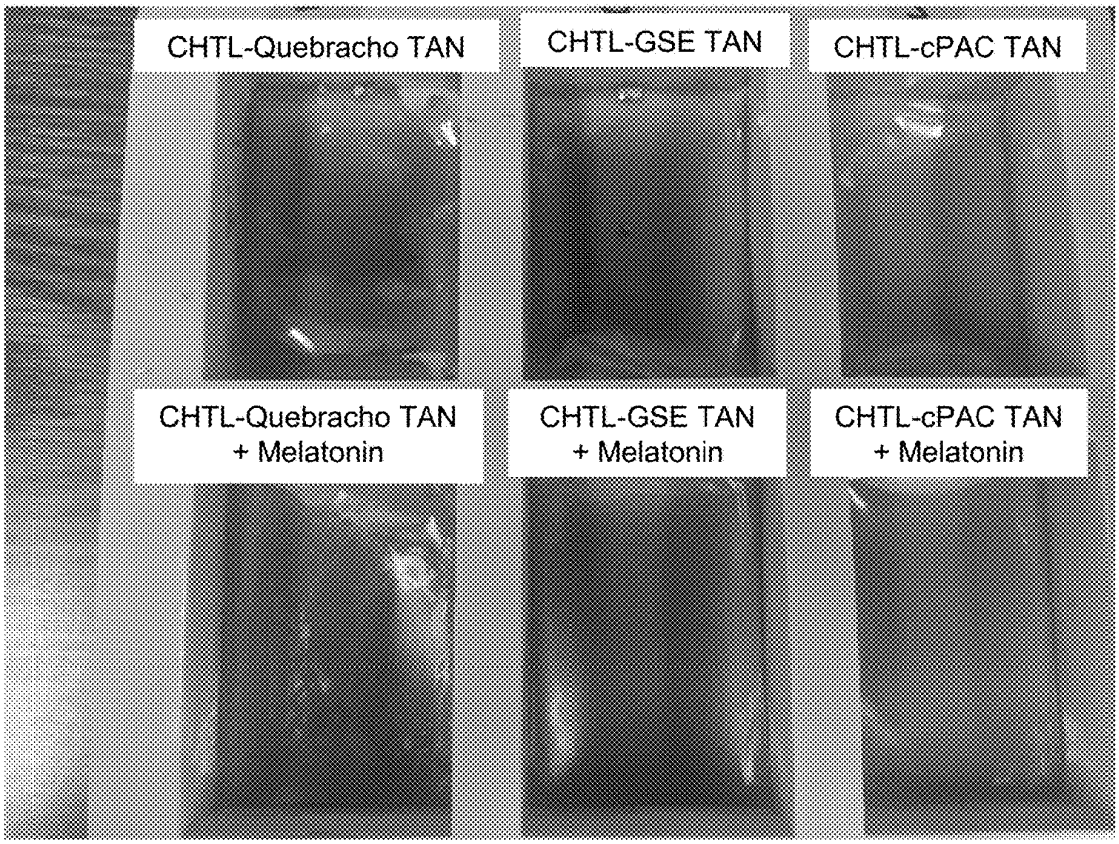

CHTL-Quebracho TAN
CHTL-GSE TAN
CHTL-cPAC TAN
CHTL-Quebracho TAN + Melatonin
CHTL-GSE TAN + Melatonin
CHTL-cPAC TAN + Melatonin

Figure 1

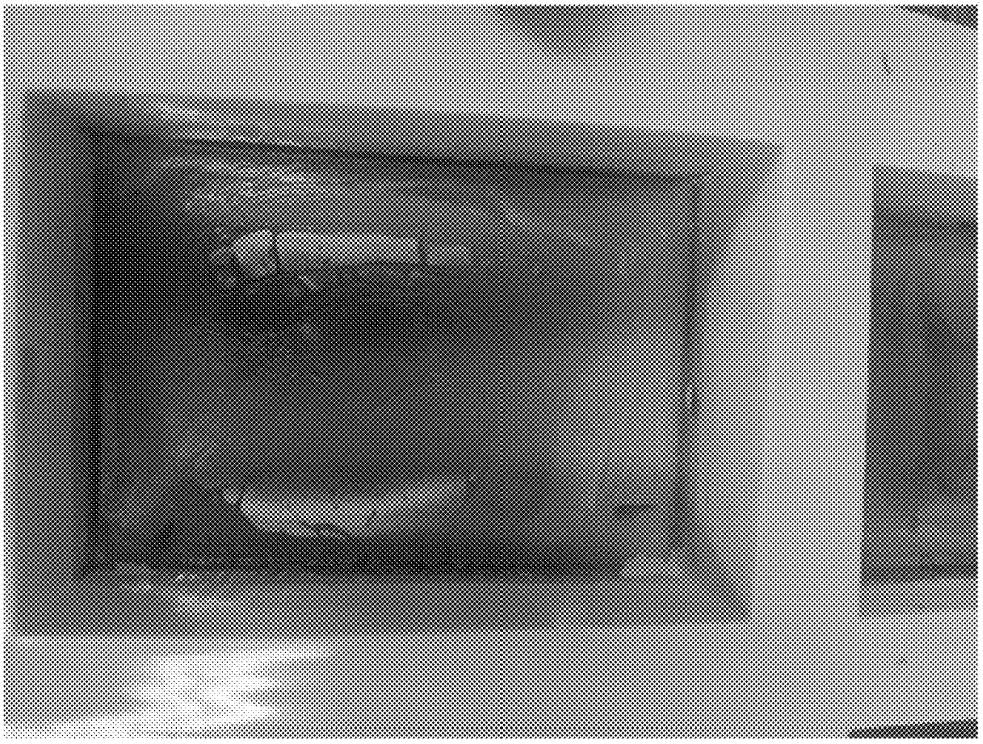


Figure 2

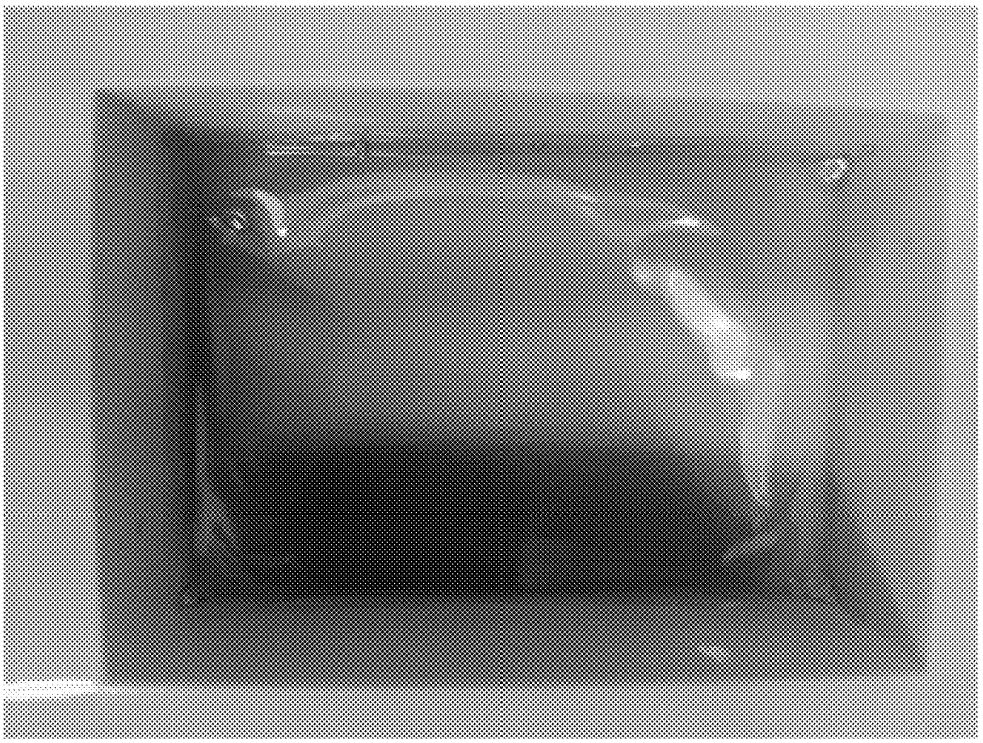


Figure 3

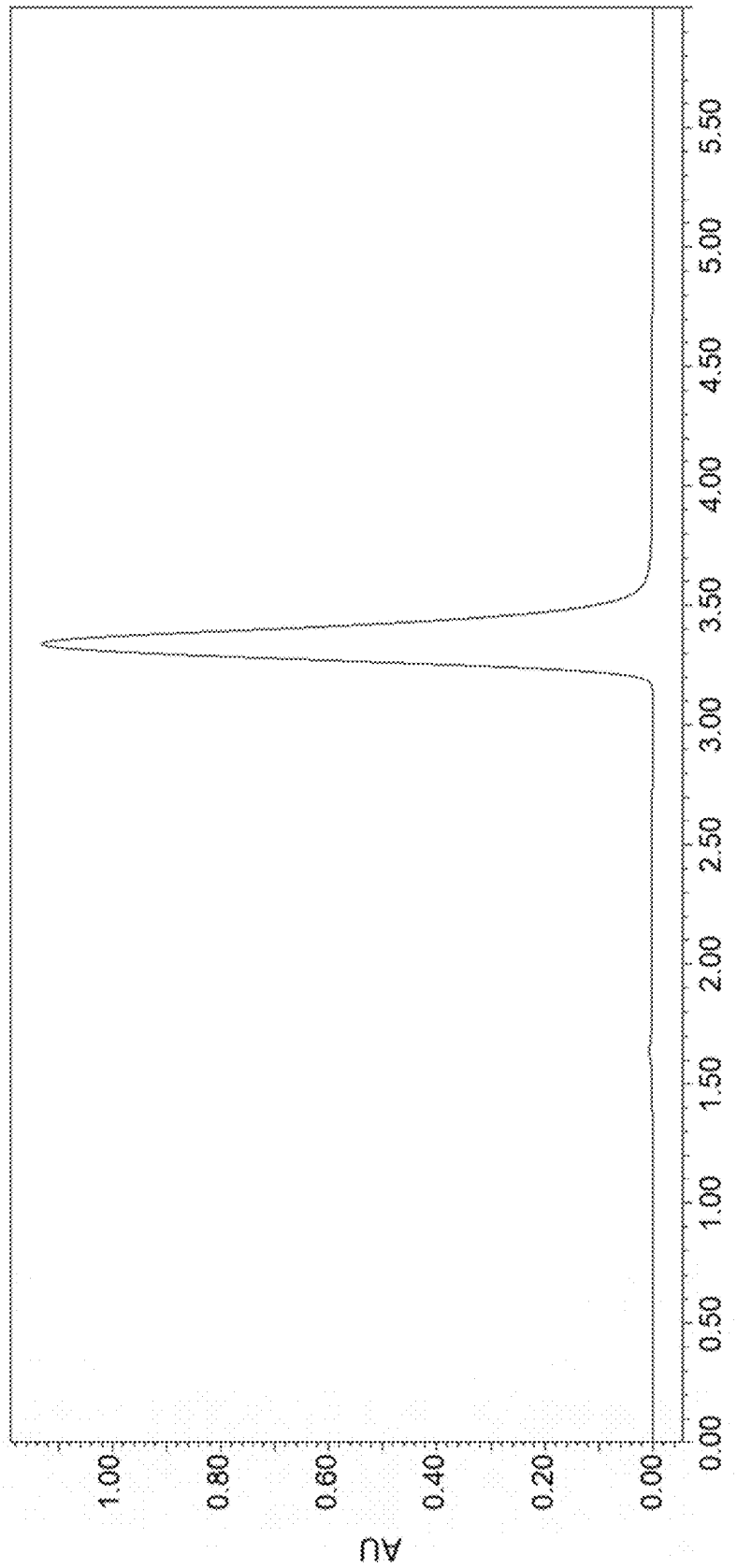

AU
1.00
0.80
0.60
0.40
0.20
0.00
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
Minutes

Figure 4

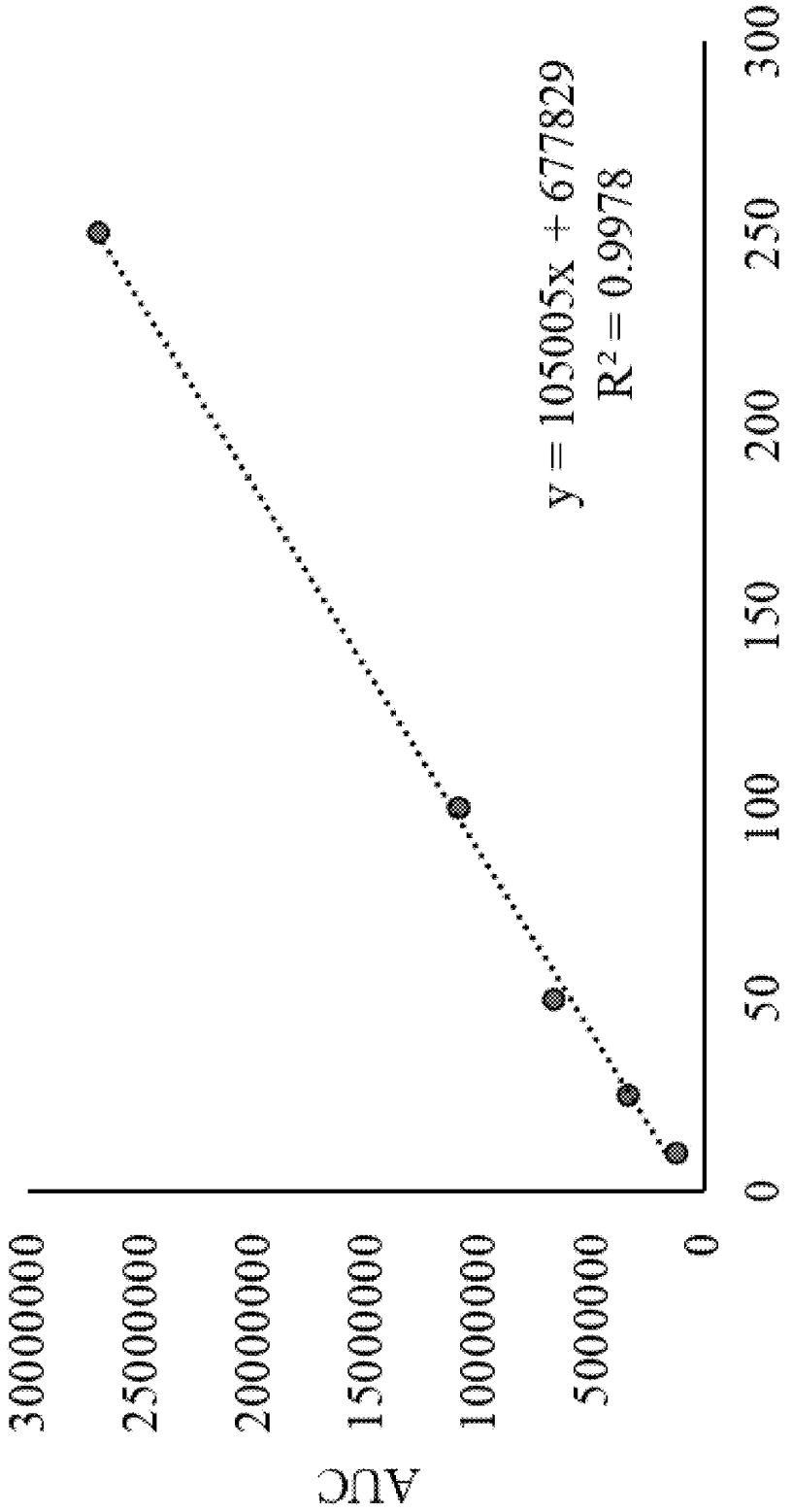

y = 105005x + 677829
R² = 0.9978
AUC
30000000
25000000
20000000
15000000
10000000
5000000
0
0
50
100
150
200
250
300
Melatonin ug/mL

Figure 5

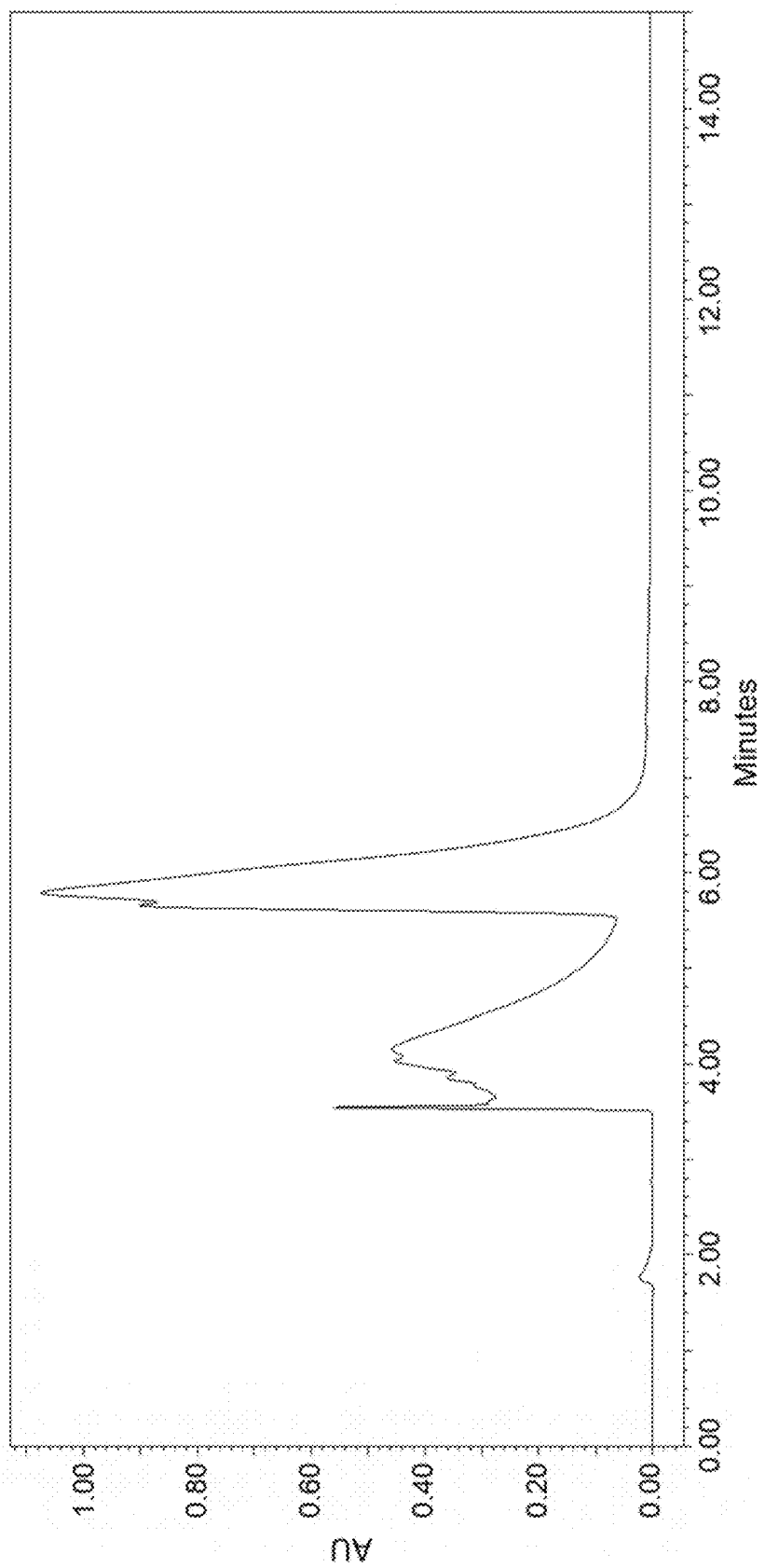

AU
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 6

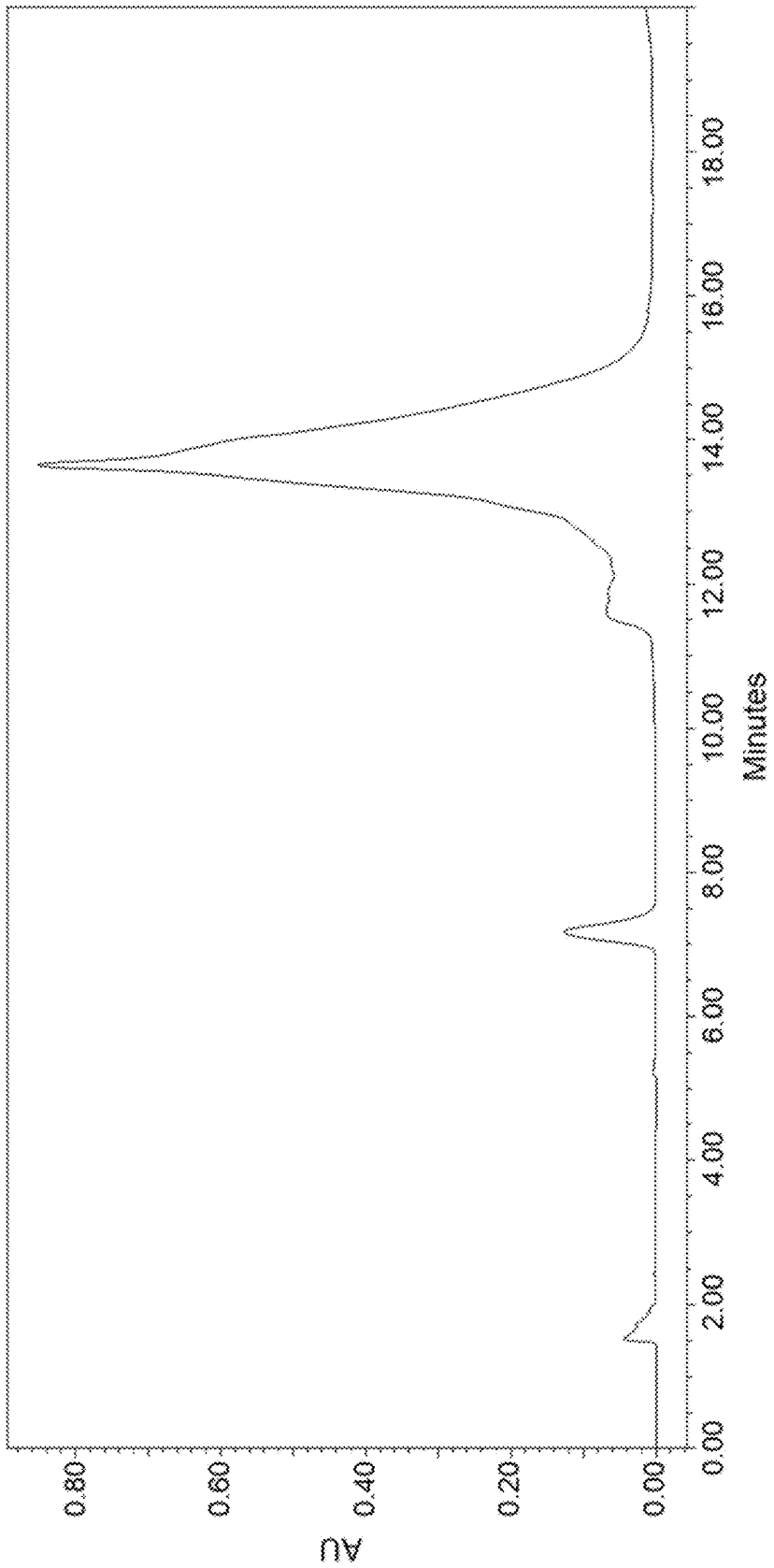

AU
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
Minutes

Figure 7

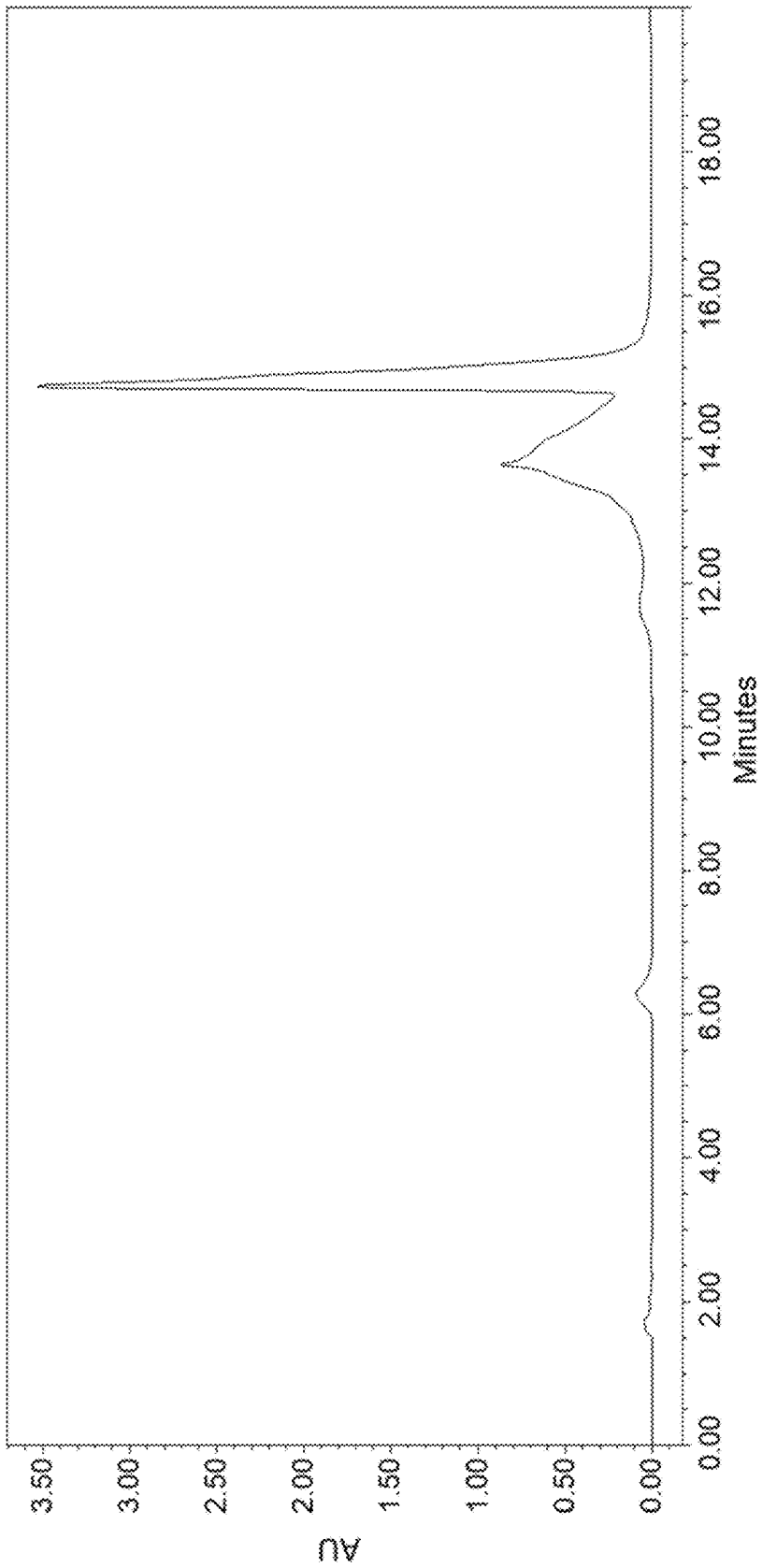

AU
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
Minutes

Figure 8

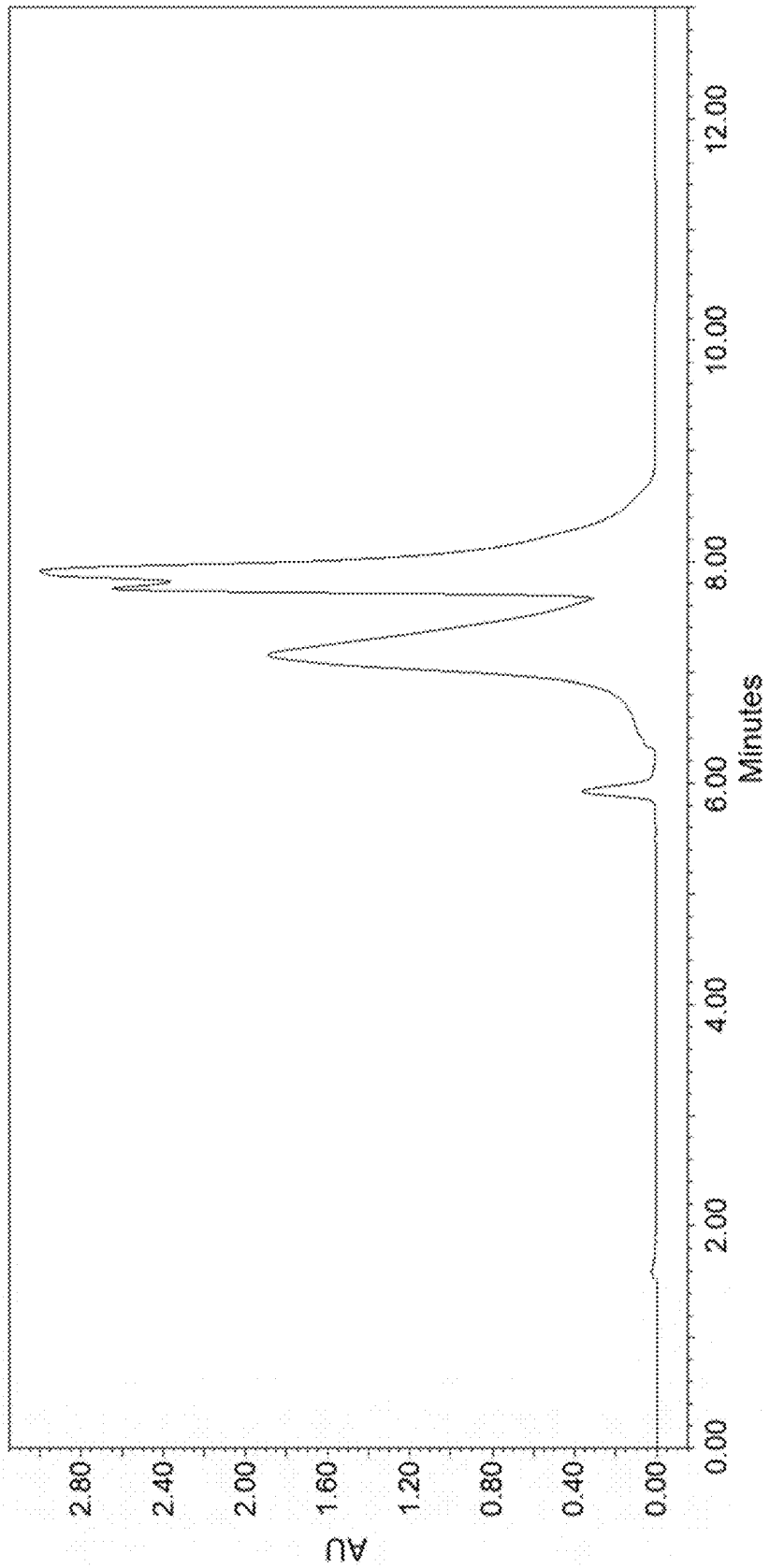

AU
2.80
2.40
2.00
1.60
1.20
0.80
0.40
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

Figure 9

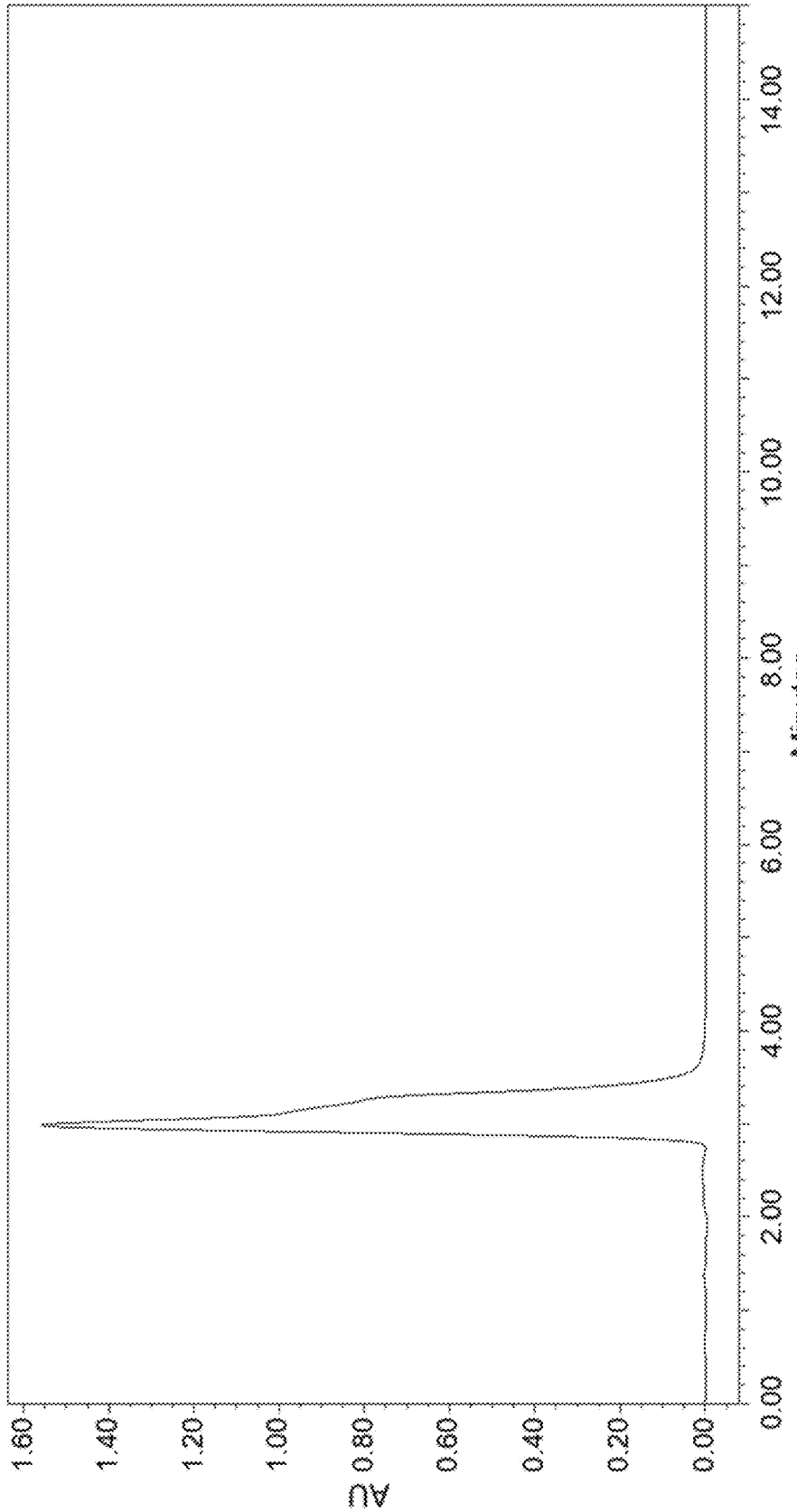

AU
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 10A

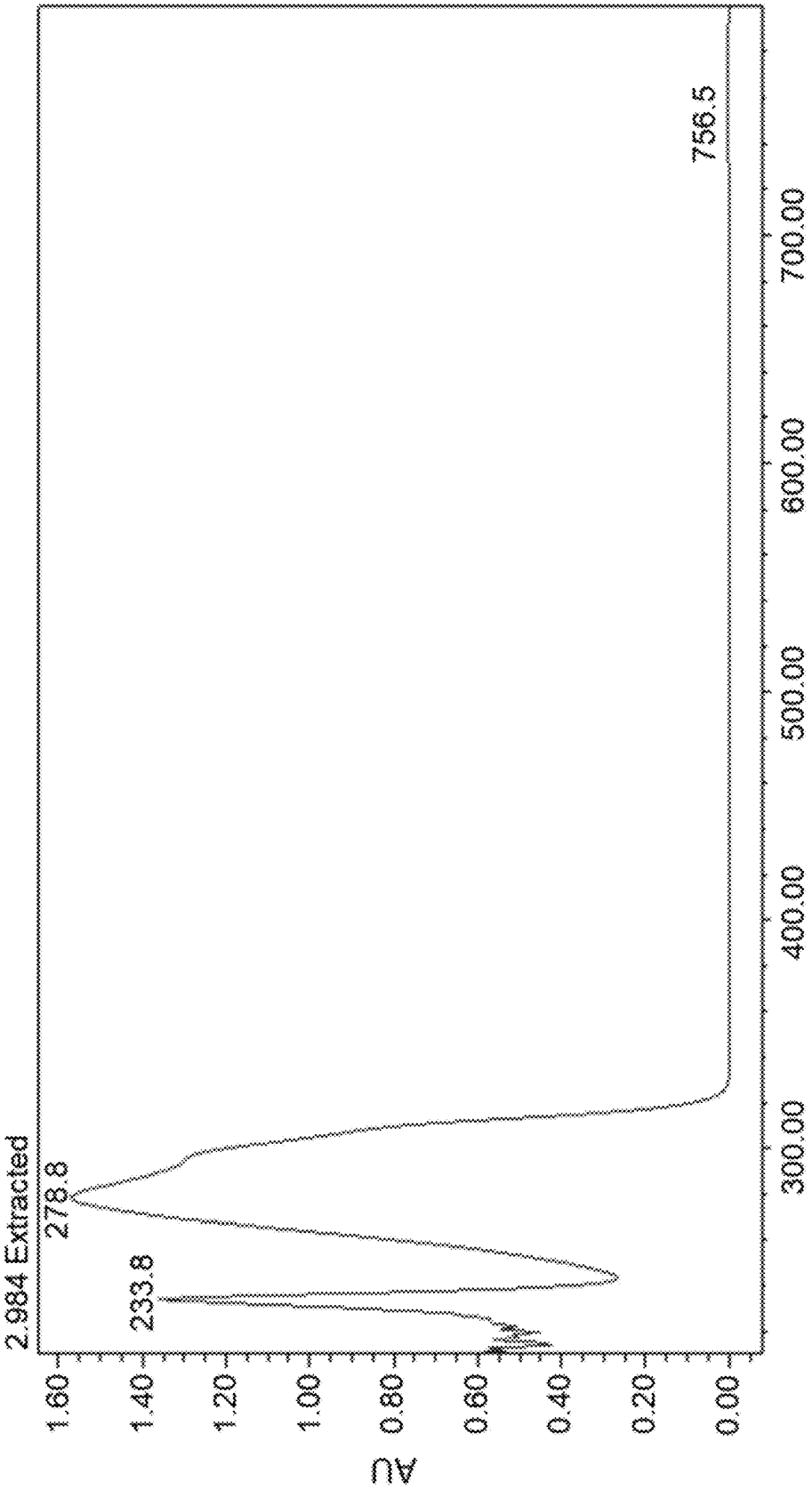

2.984 Extracted
278.8
233.8
756.5
AU
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
300.00
400.00
500.00
600.00
700.00
nm

Figure 10B

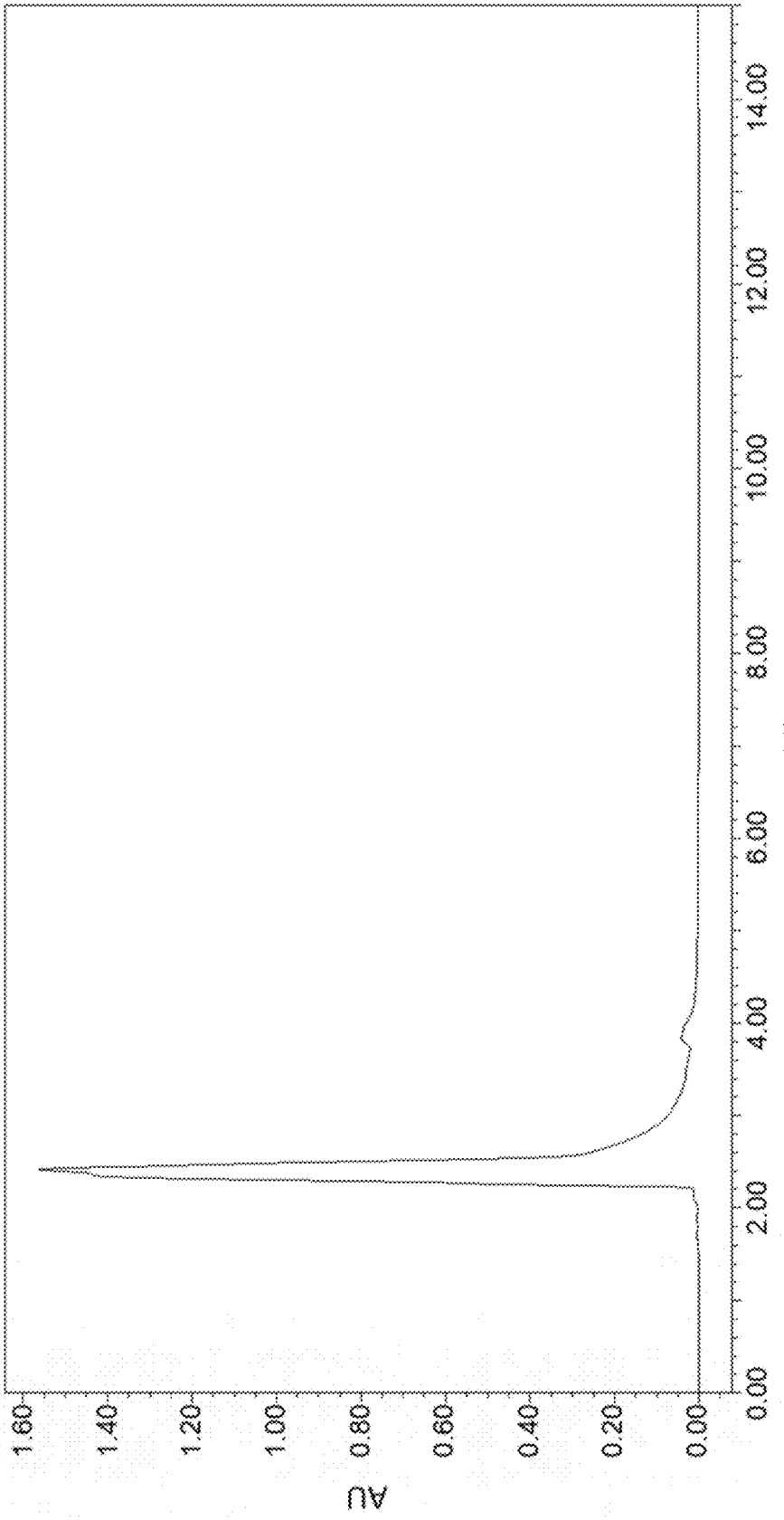

AU
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 11A

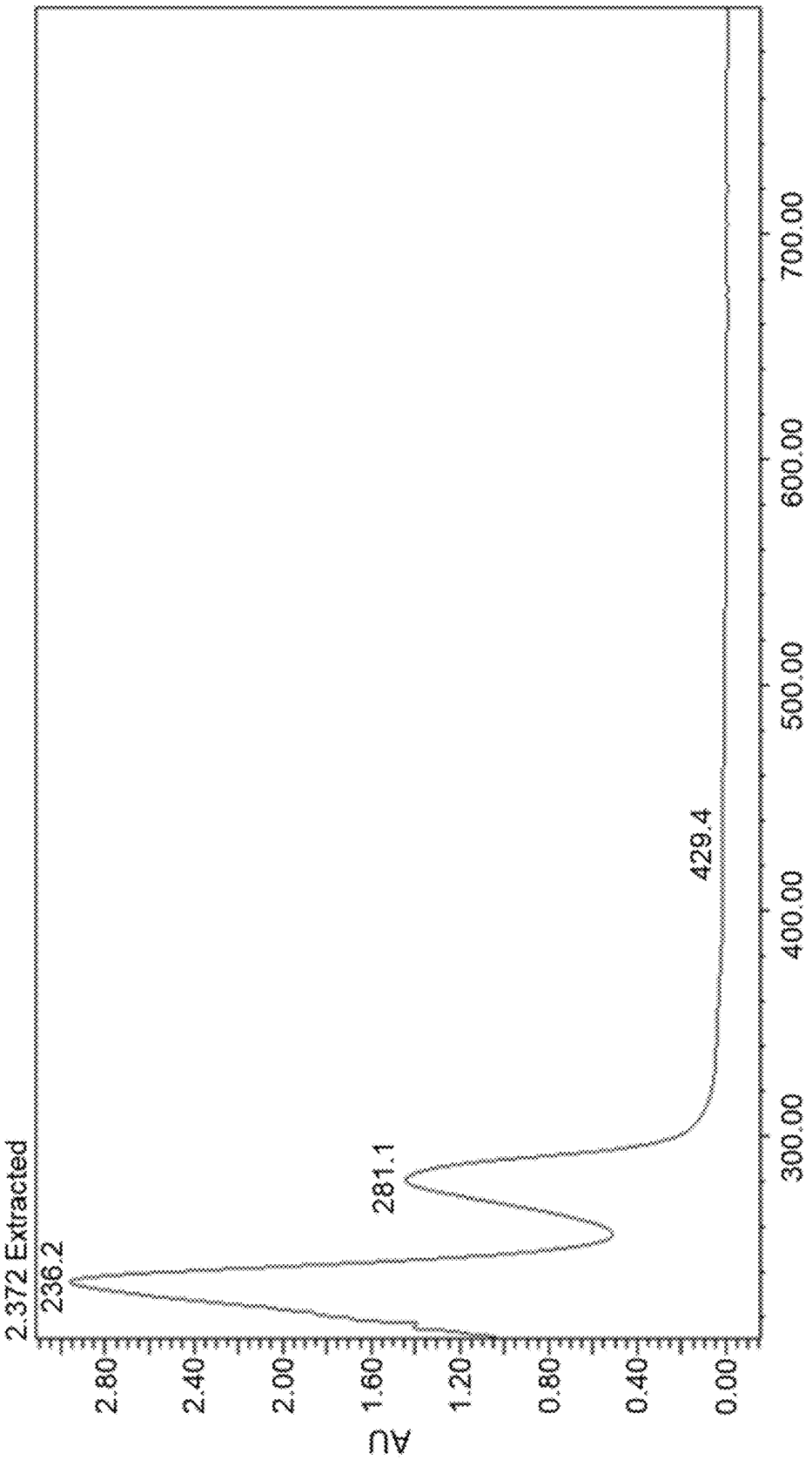

2.372 Extracted
236.2
281.1
429.4
AU
2.80
2.40
2.00
1.60
1.20
0.80
0.40
0.00
300.00
400.00
500.00
600.00
700.00
nm

Figure 11B

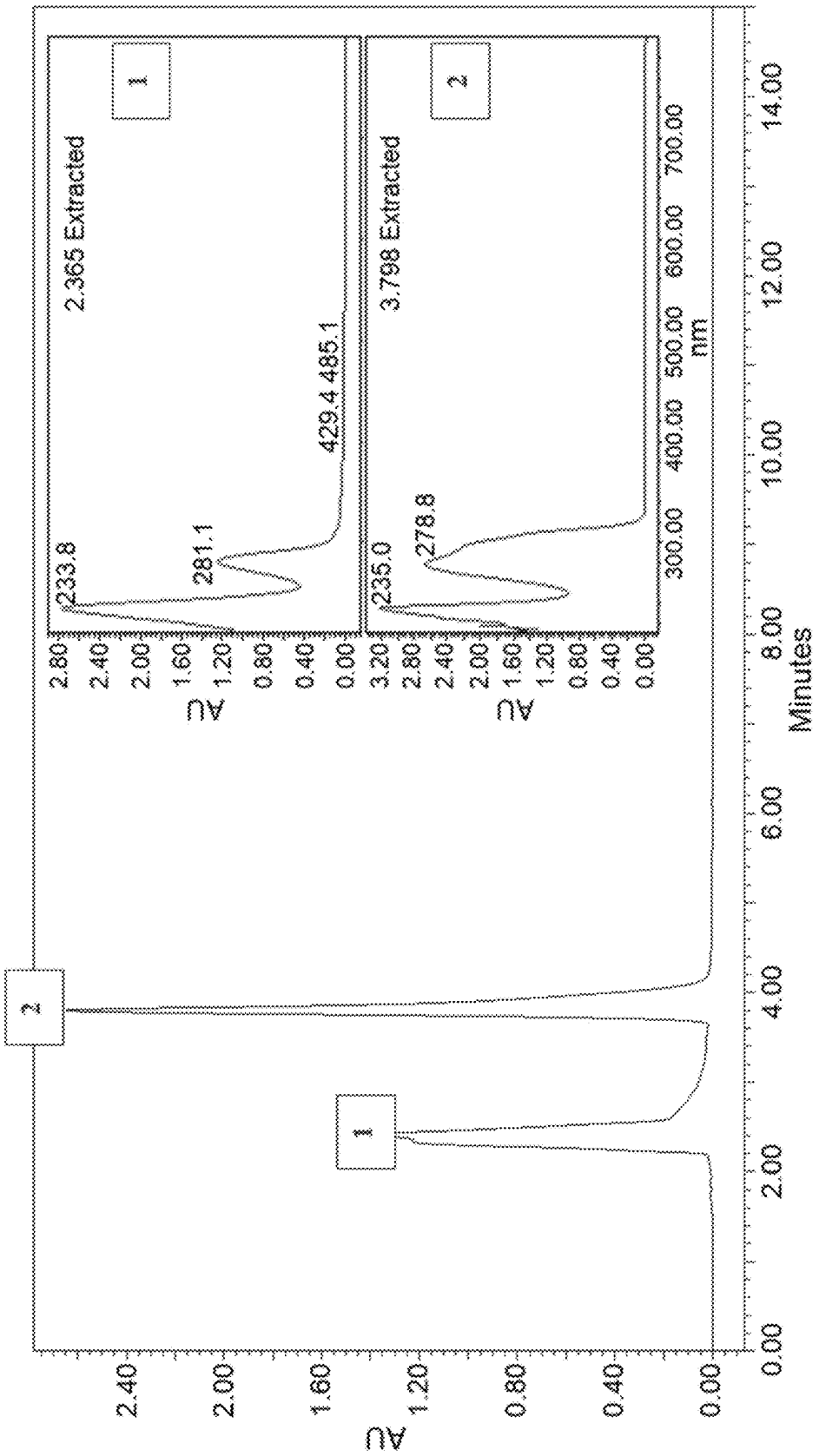

AU
Minutes
2.365 Extracted
3.798 Extracted
233.8
281.1
429.4
485.1
235.0
278.8
nm

Figure 12

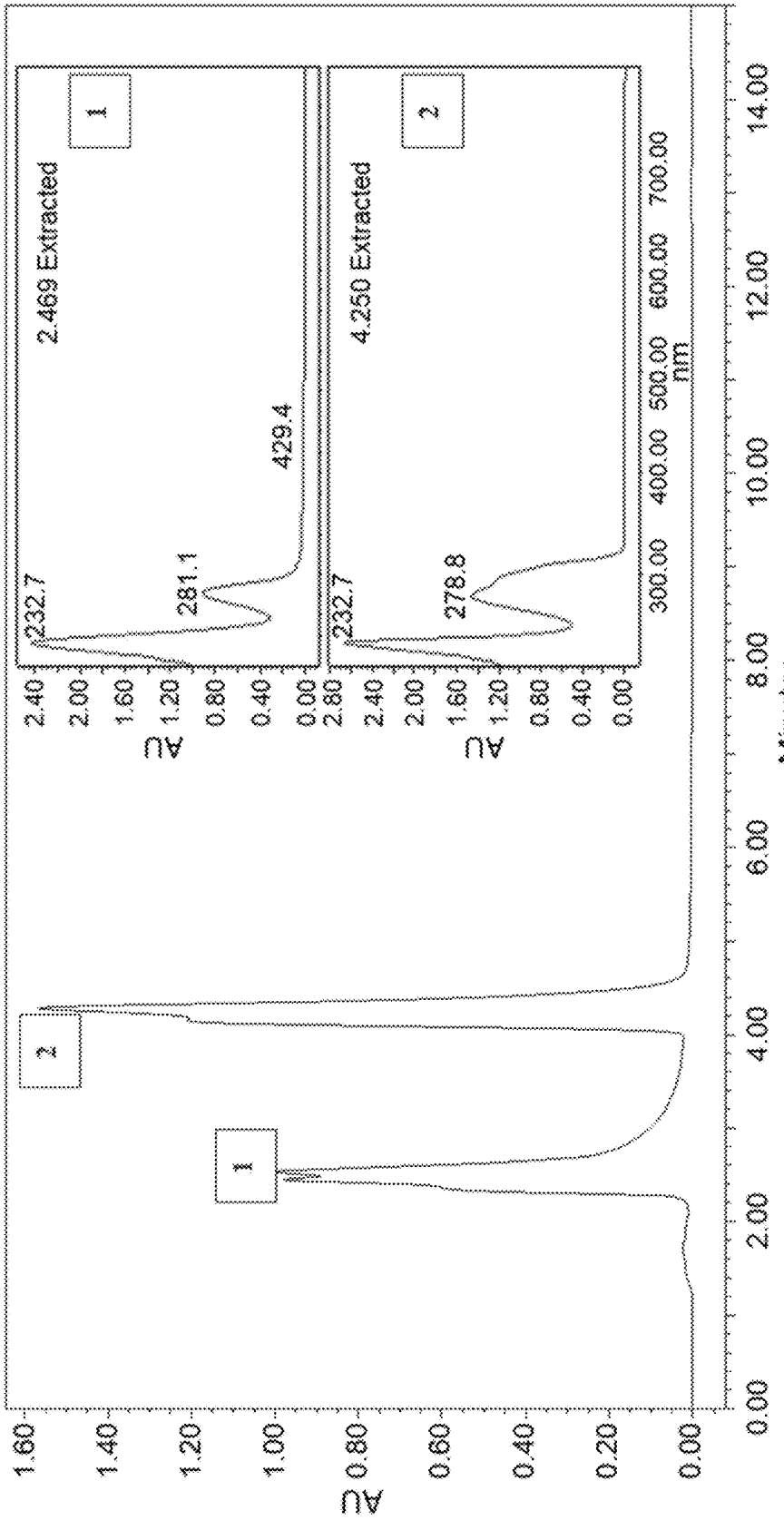

AU
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes
1
2
2.469 Extracted
232.7
281.1
429.4
4.250 Extracted
232.7
278.8
300.00
400.00
500.00
600.00
700.00
nm

Figure 13

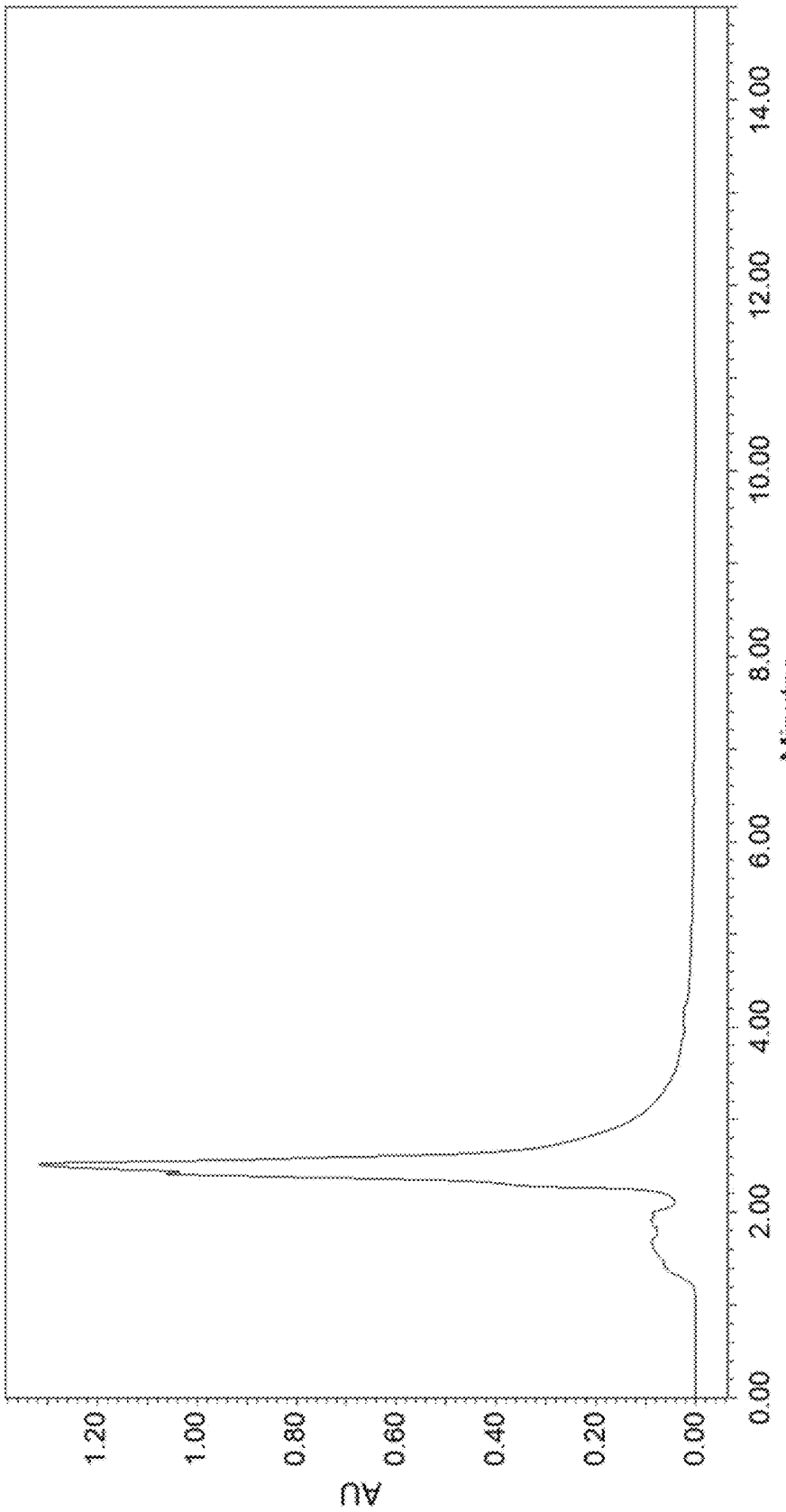

AU
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 14A

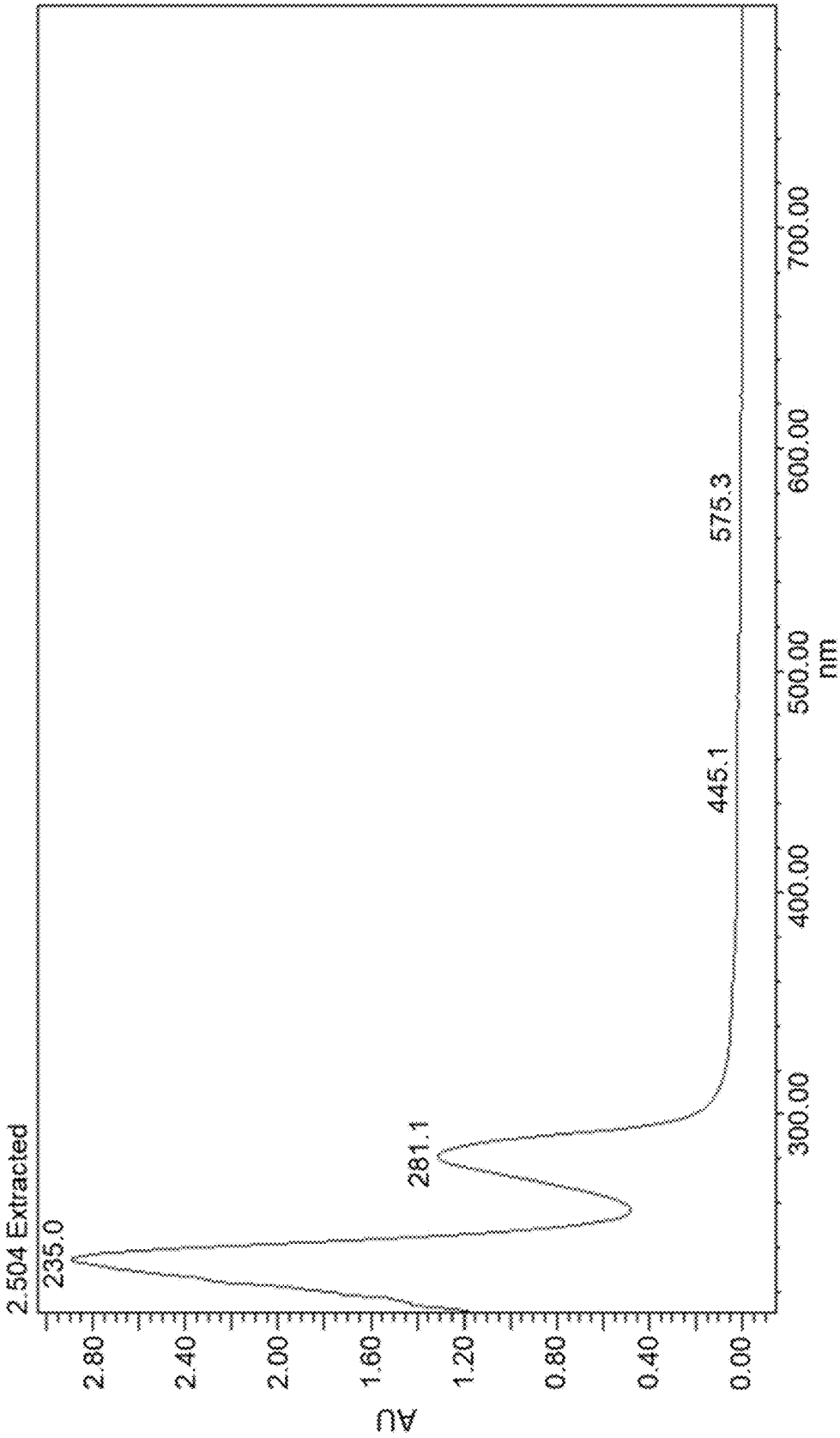

2.504 Extracted
235.0
281.1
445.1
575.3
AU
2.80
2.40
2.00
1.60
1.20
0.80
0.40
0.00
300.00
400.00
500.00
600.00
700.00
nm

Figure 14B

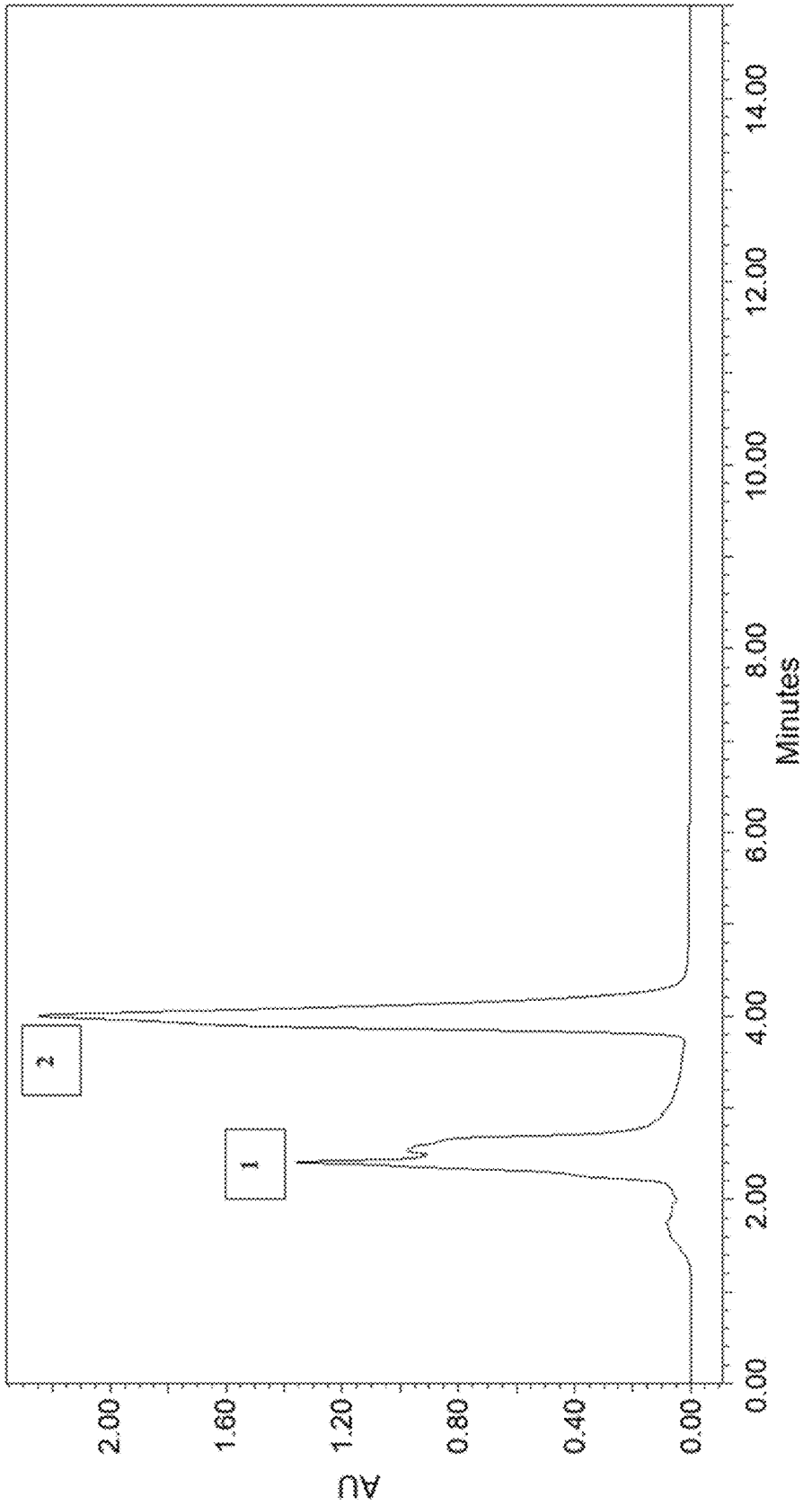

AU
2.00
1.60
1.20
0.80
0.40
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes
1
2

Figure 15A

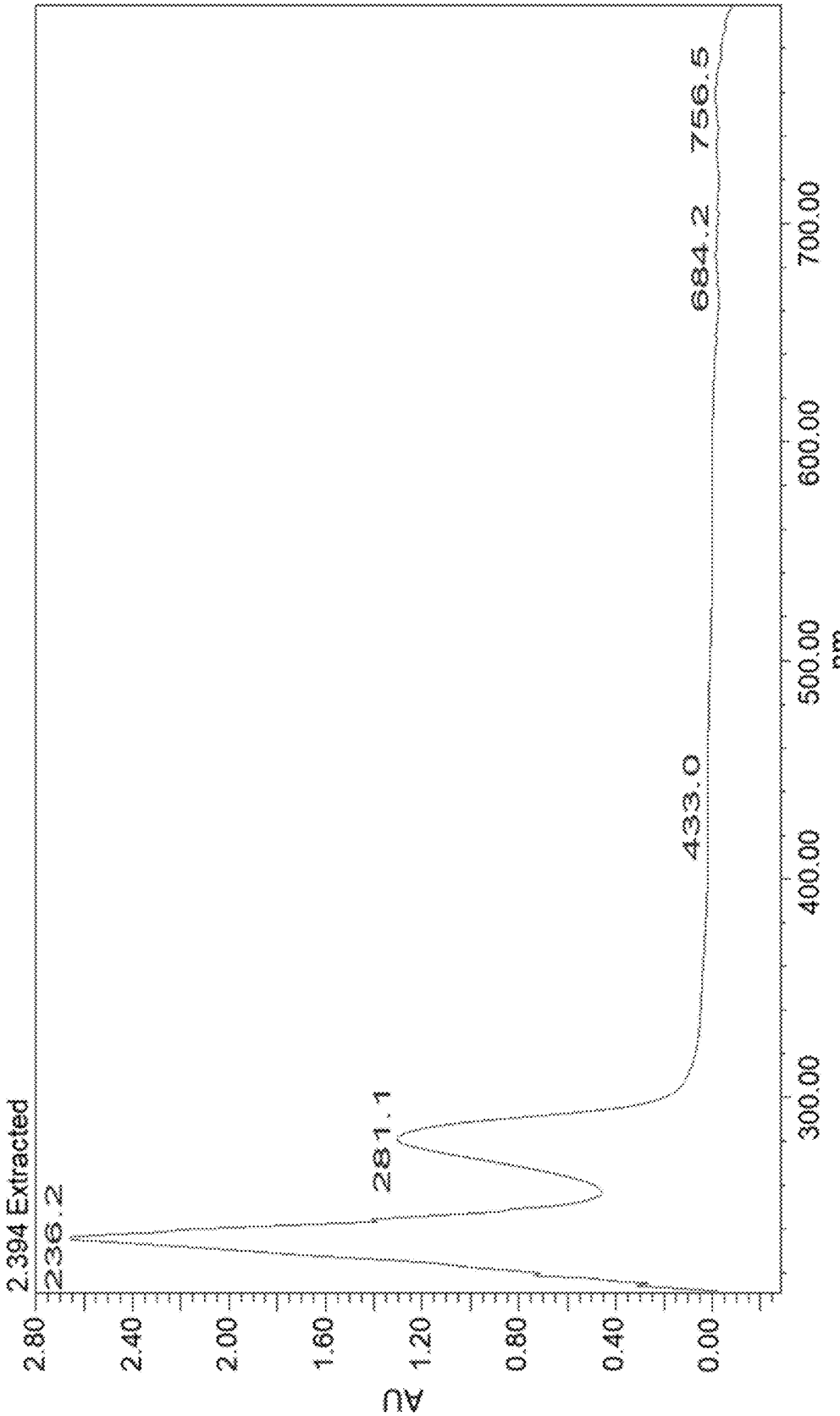

2.394 Extracted
236.2
281.1
433.0
684.2
756.5
AU
2.80
2.40
2.00
1.60
1.20
0.80
0.40
0.00
300.00
400.00
500.00
600.00
700.00
nm

Figure 15B

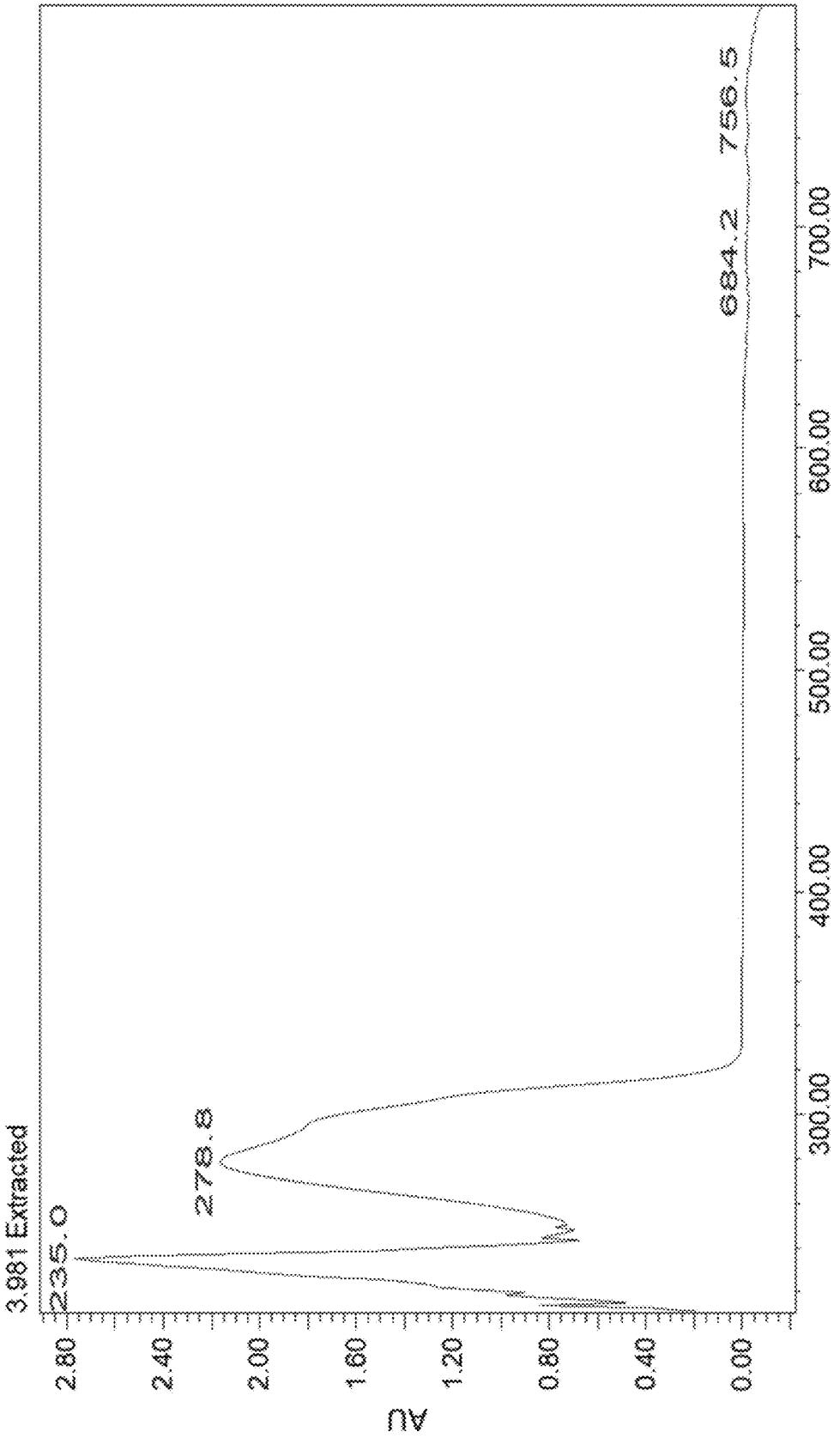

3.981 Extracted
235.0
278.8
684.2
756.5
AU
2.80
2.40
2.00
1.60
1.20
0.80
0.40
0.00
300.00
400.00
500.00
600.00
700.00
nm

Figure 15C

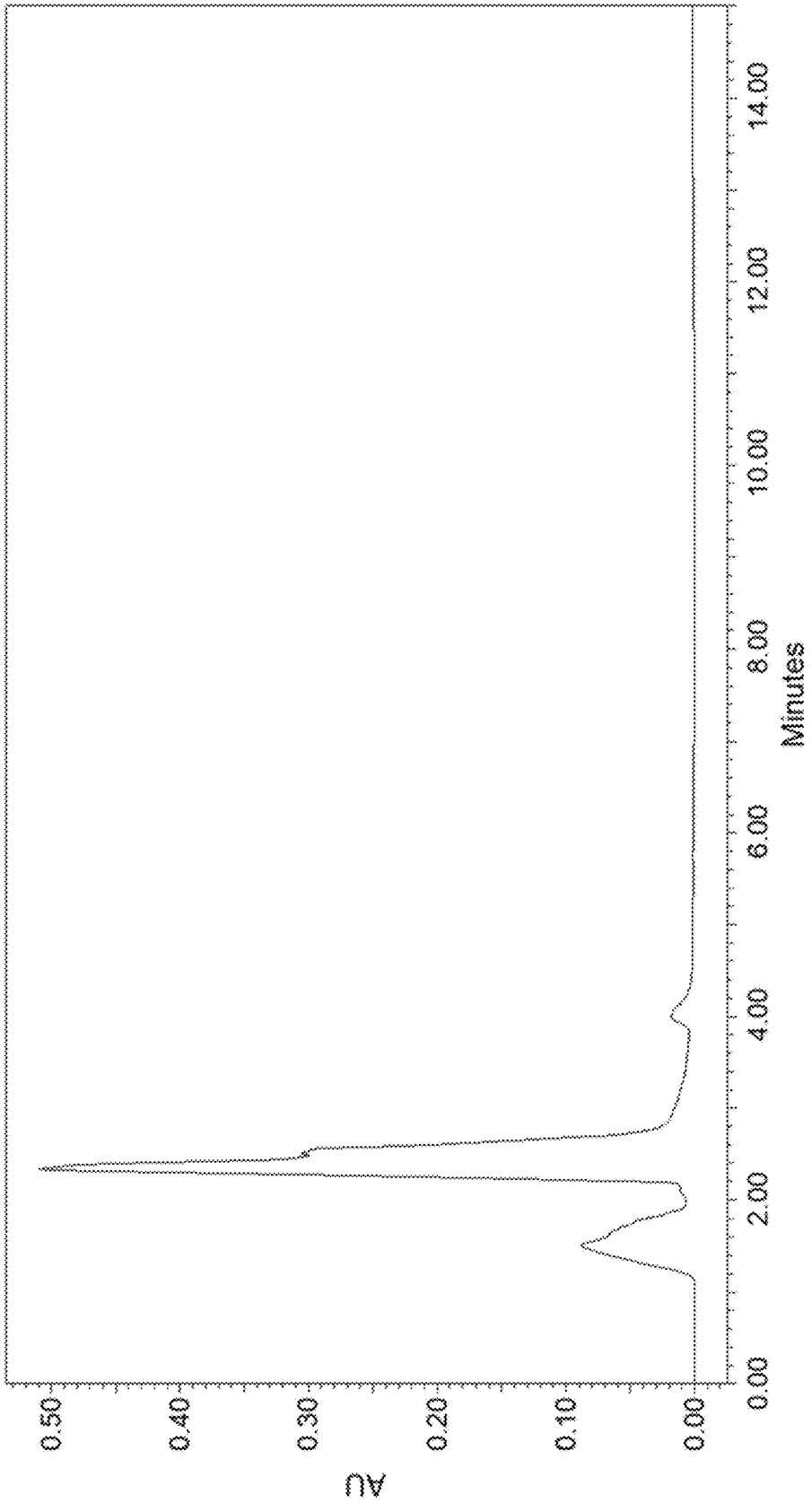

AU
0.50
0.40
0.30
0.20
0.10
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 16

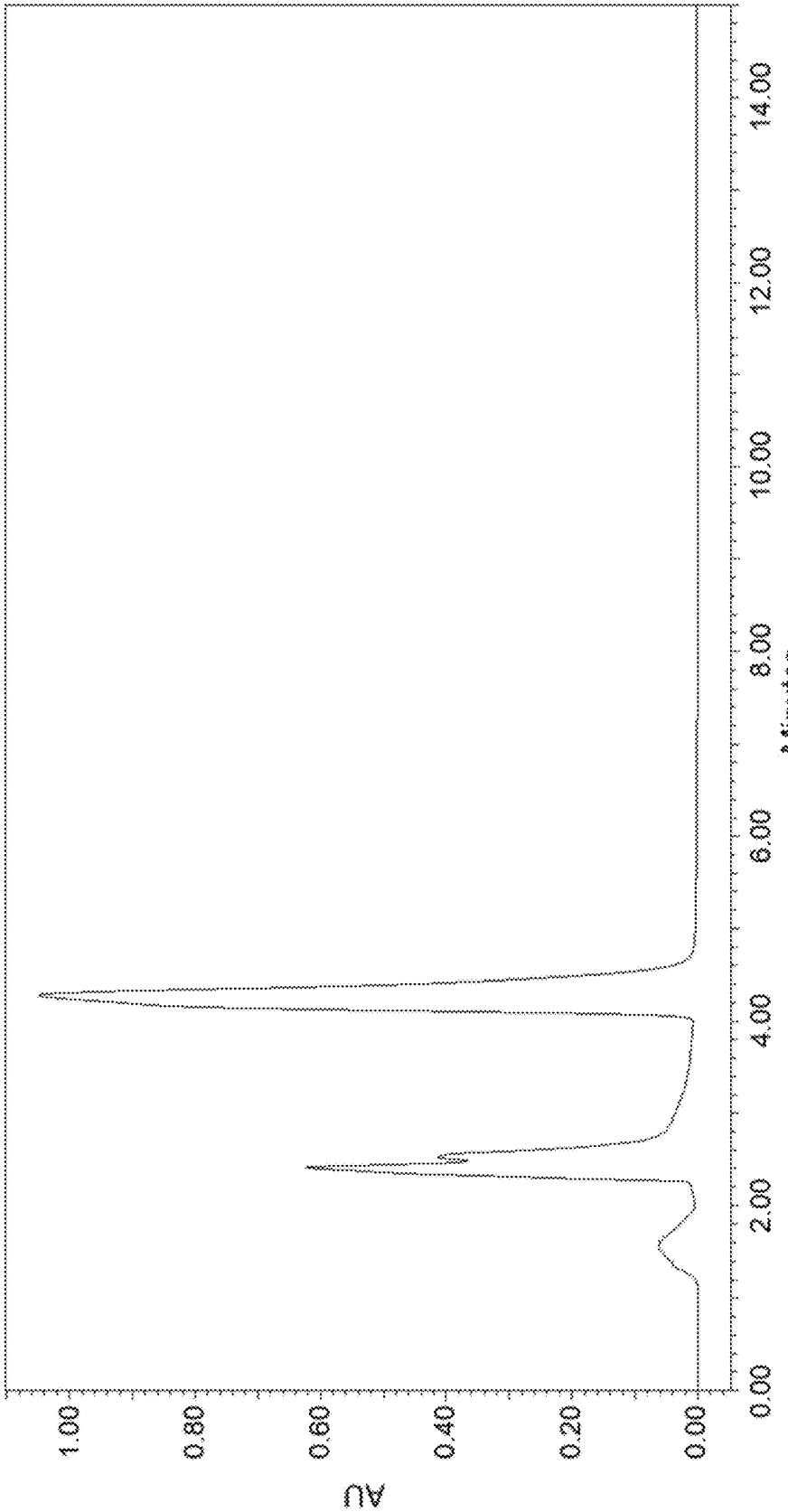

AU
1.00
0.80
0.60
0.40
0.20
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 17

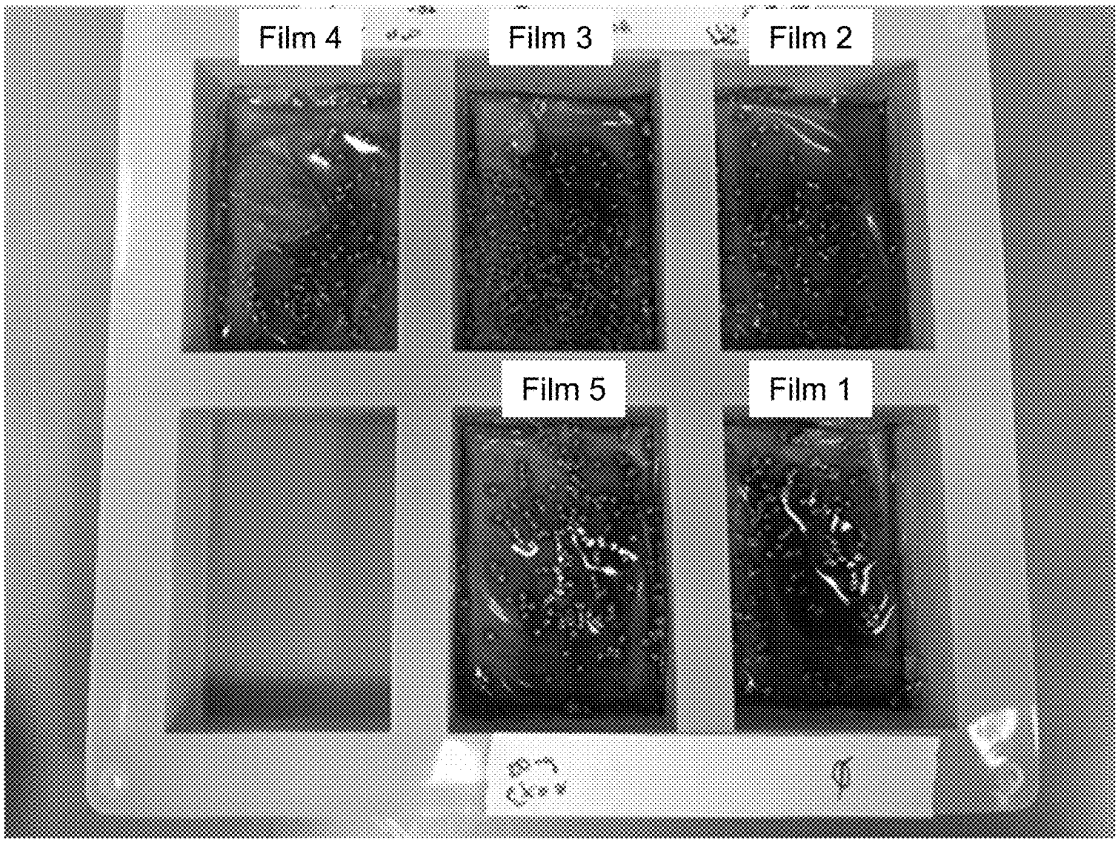


Figure 18

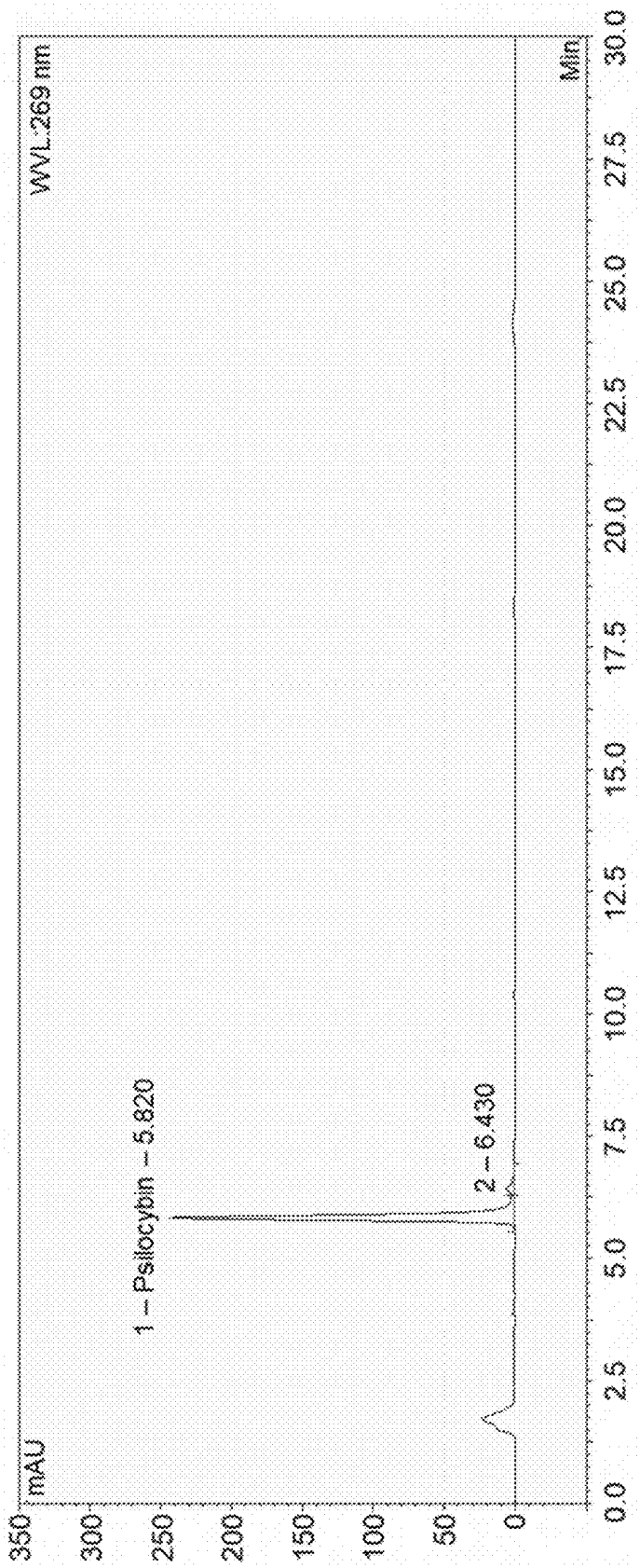

WVL:269 nm
mAU
Min
1 – Psilocybin – 5.820
2 – 6.430
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 19A

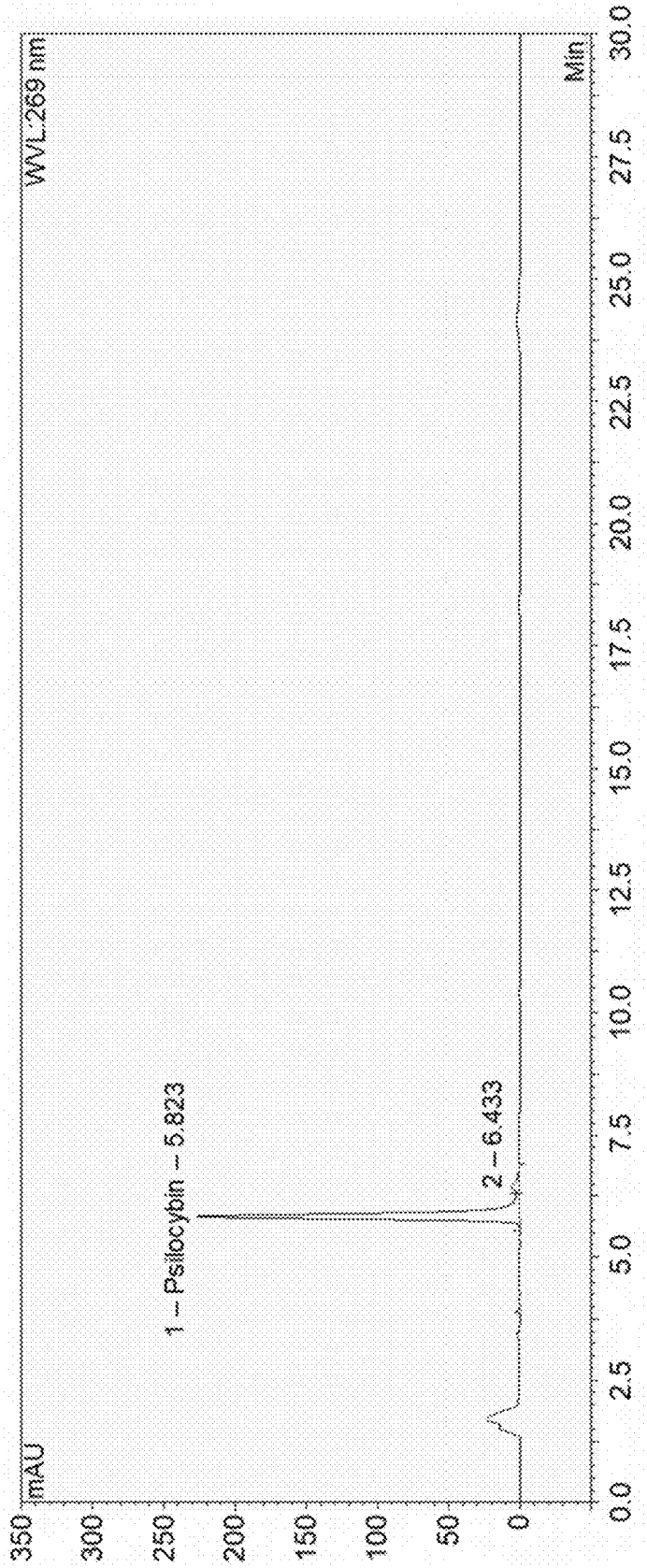

WVL:269 nm
mAU
Min
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0
1 – Psilocybin – 5.823
2 – 6.433

Figure 19B

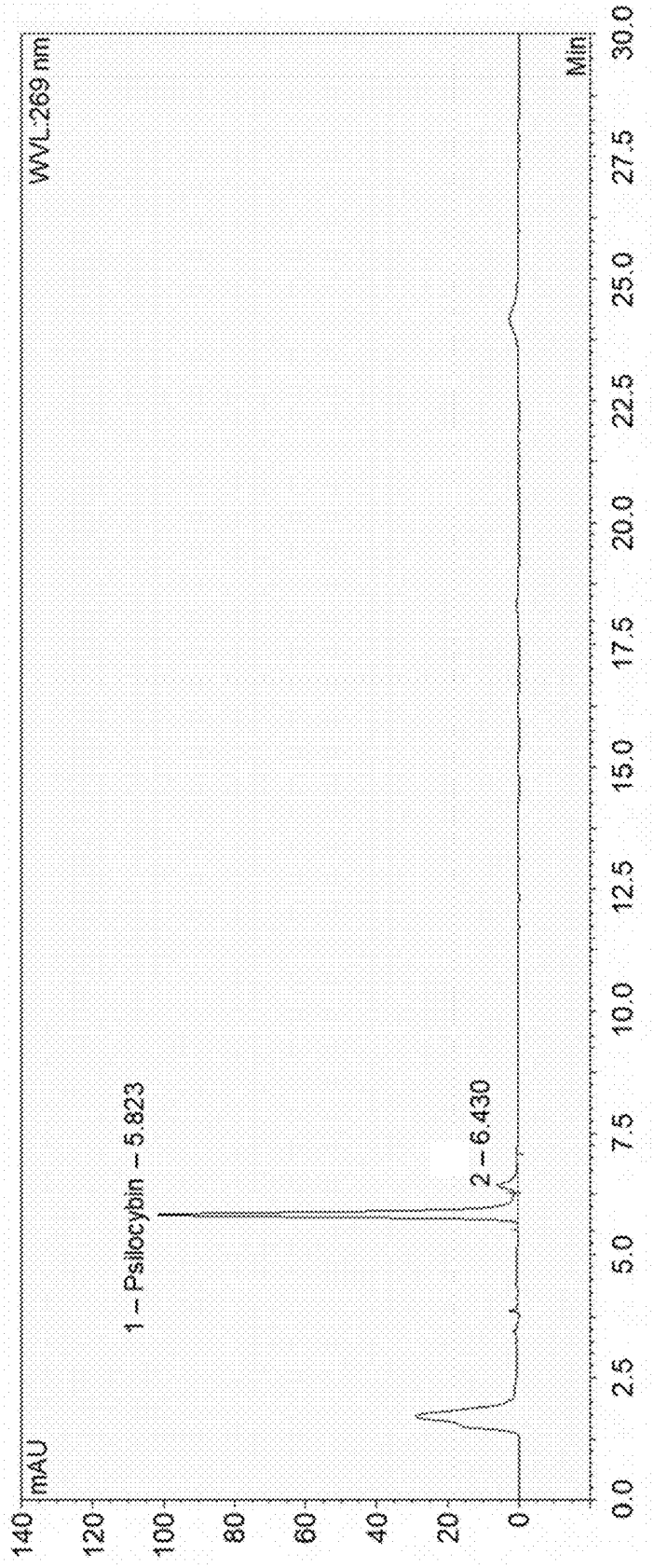

WVL:269 nm
mAU
Min
1 – Psilocybin – 5.823
2 – 6.430
140
120
100
80
60
40
20
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 20A

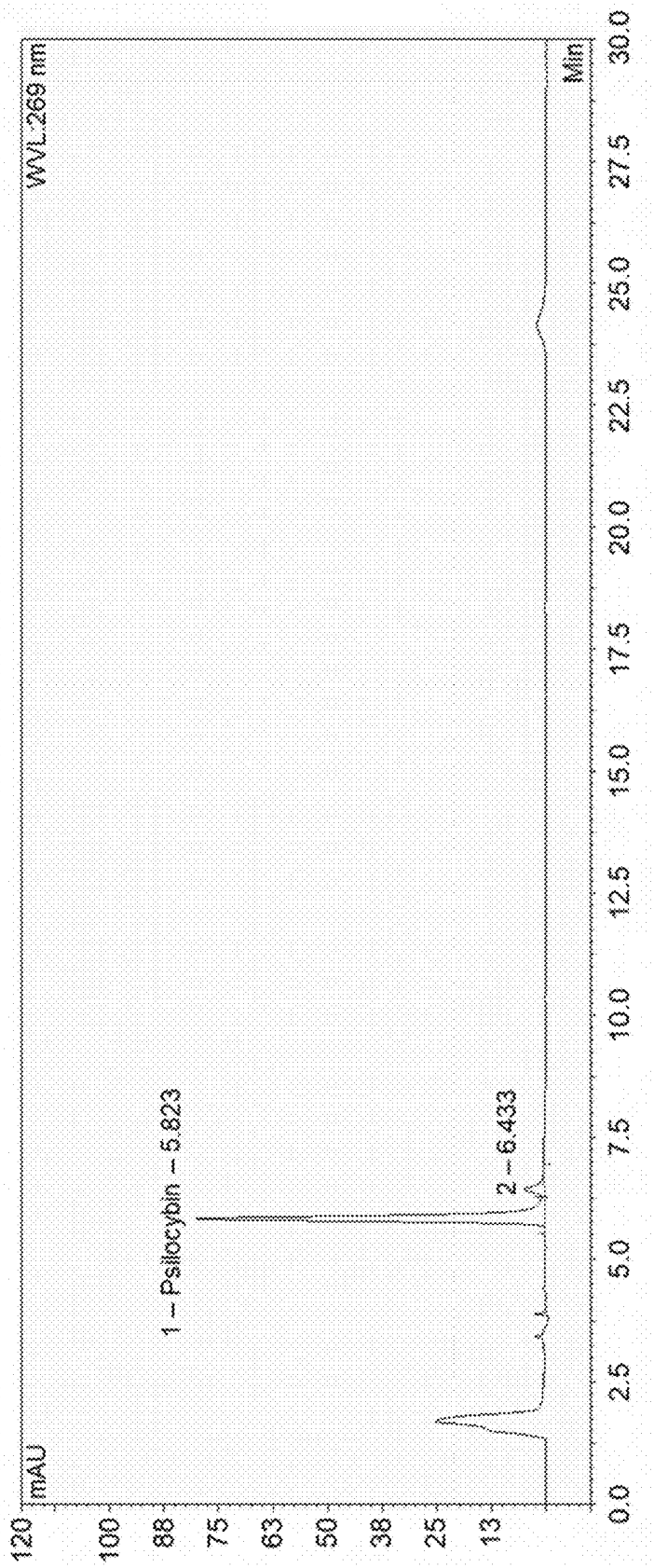

WVL:269 nm
mAU
Min
120
100
88
75
63
50
38
25
13
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0
1 – Psilocybin – 5.823
2 – 6.433

Figure 20B

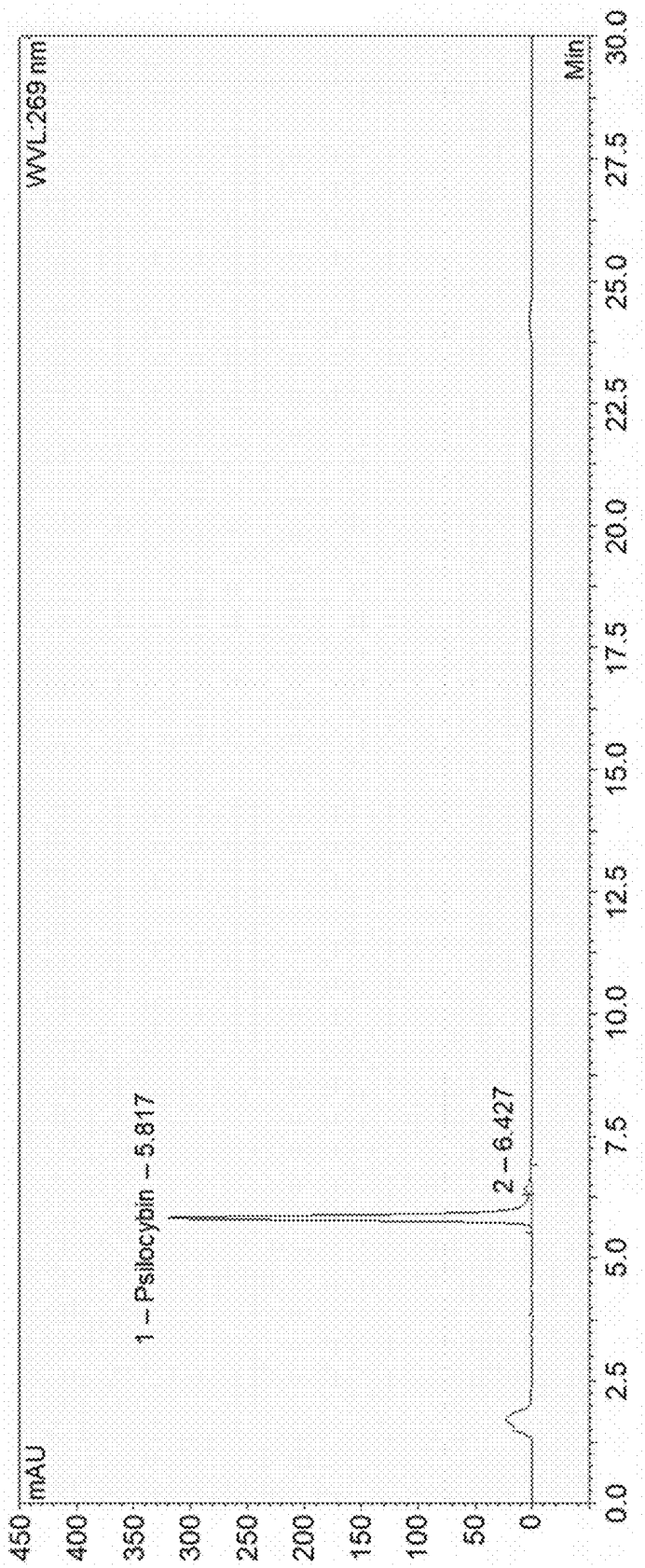

WVL:269 nm
mAU
Min
1 – Psilocybin – 5.817
2 – 6.427
450
400
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 21A

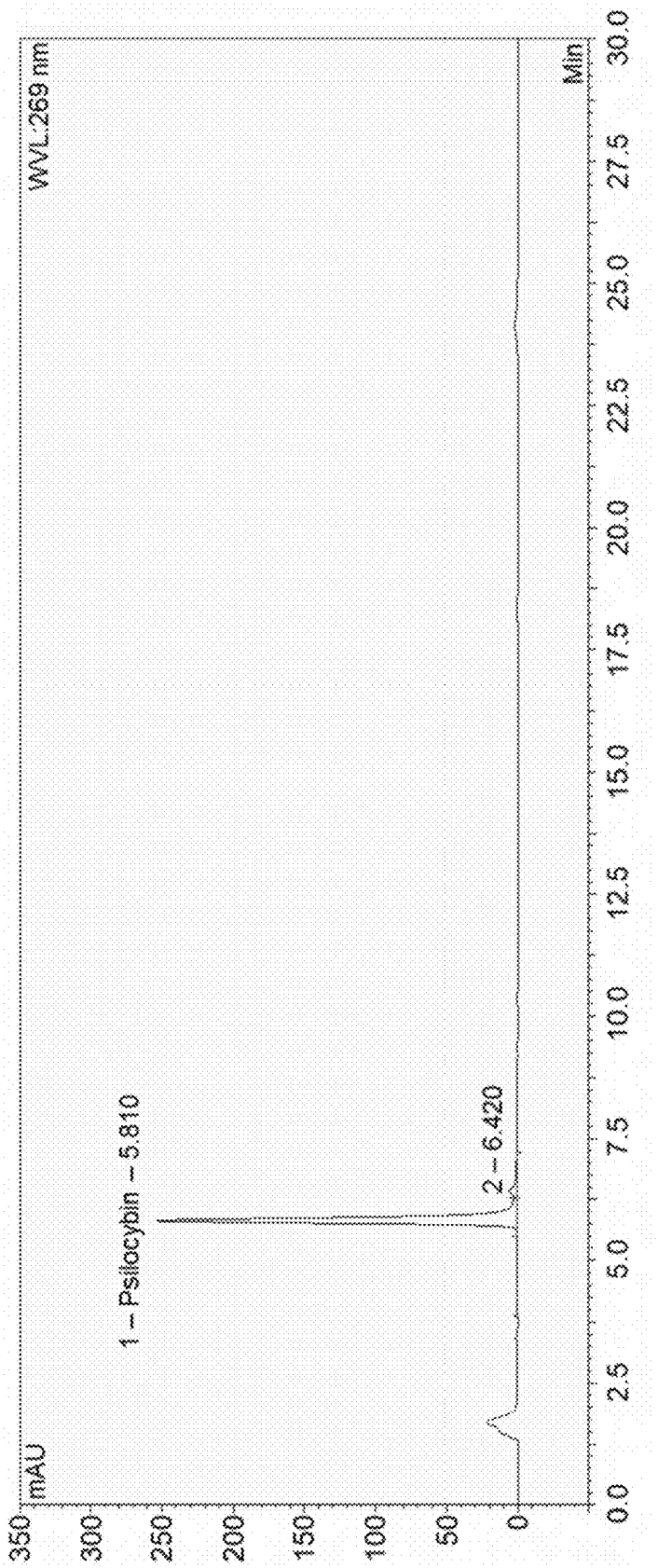

WVL:269 nm
mAU
Min
1 – Psilocybin – 5.810
2 – 6.420
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 21B

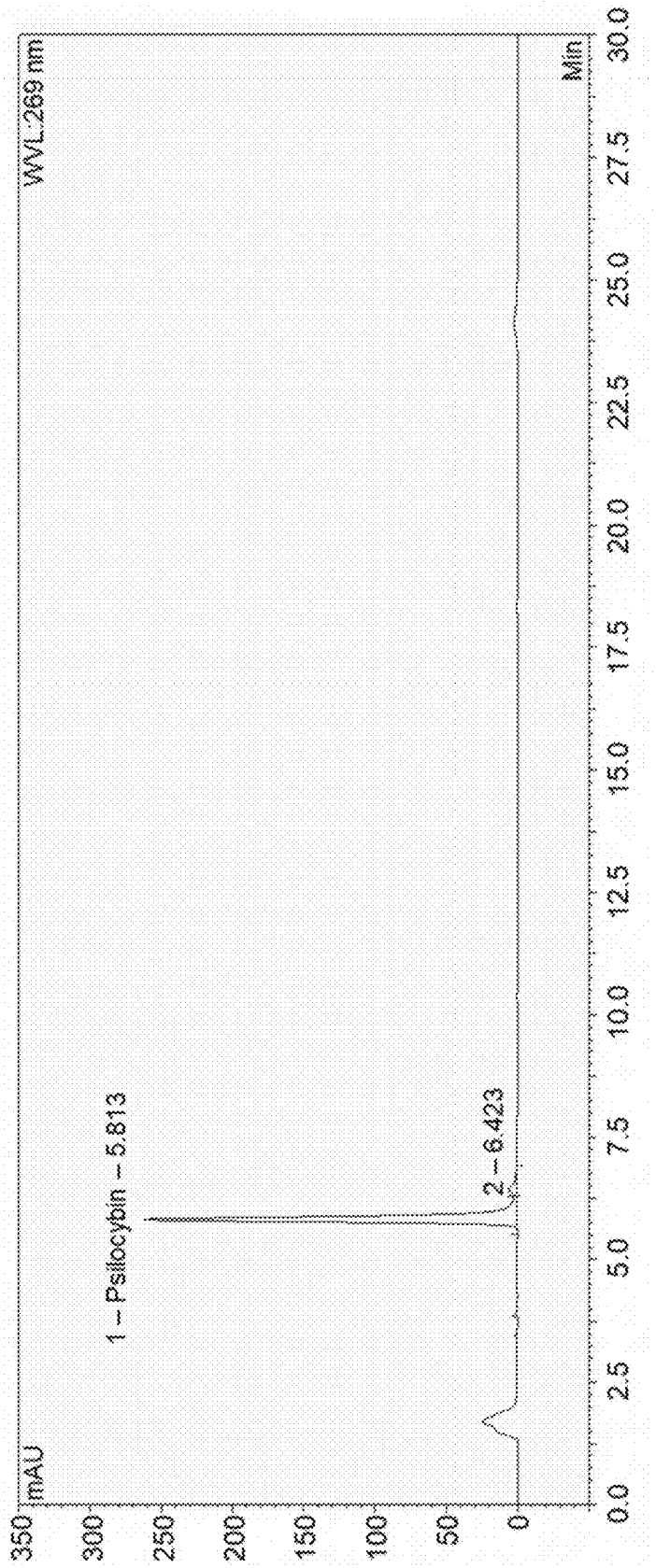

WVL:269 nm
mAU
Min
1 – Psilocybin – 5.813
2 – 6.423
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 22A

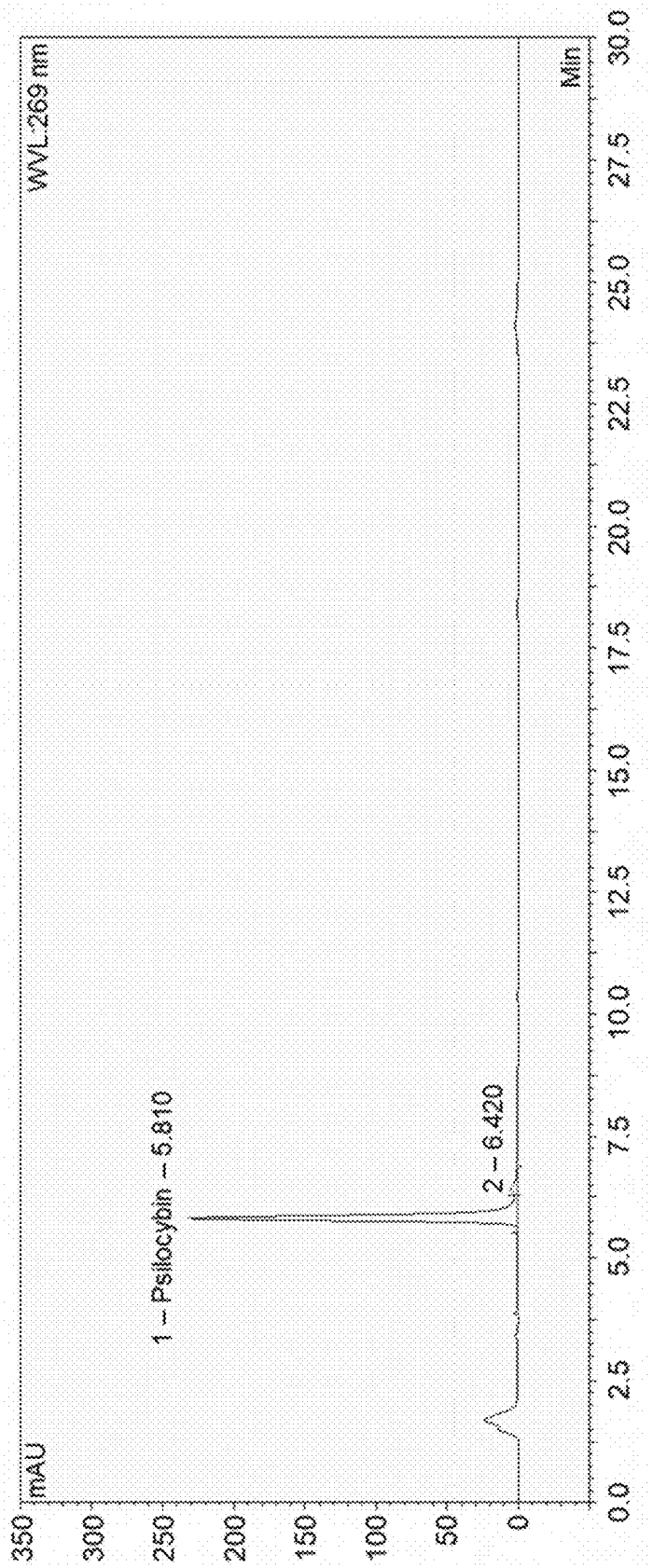

WVL:269 nm
mAU
Min
1 – Psilocybin – 6.810
2 – 6.420
350
300
250
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 22B

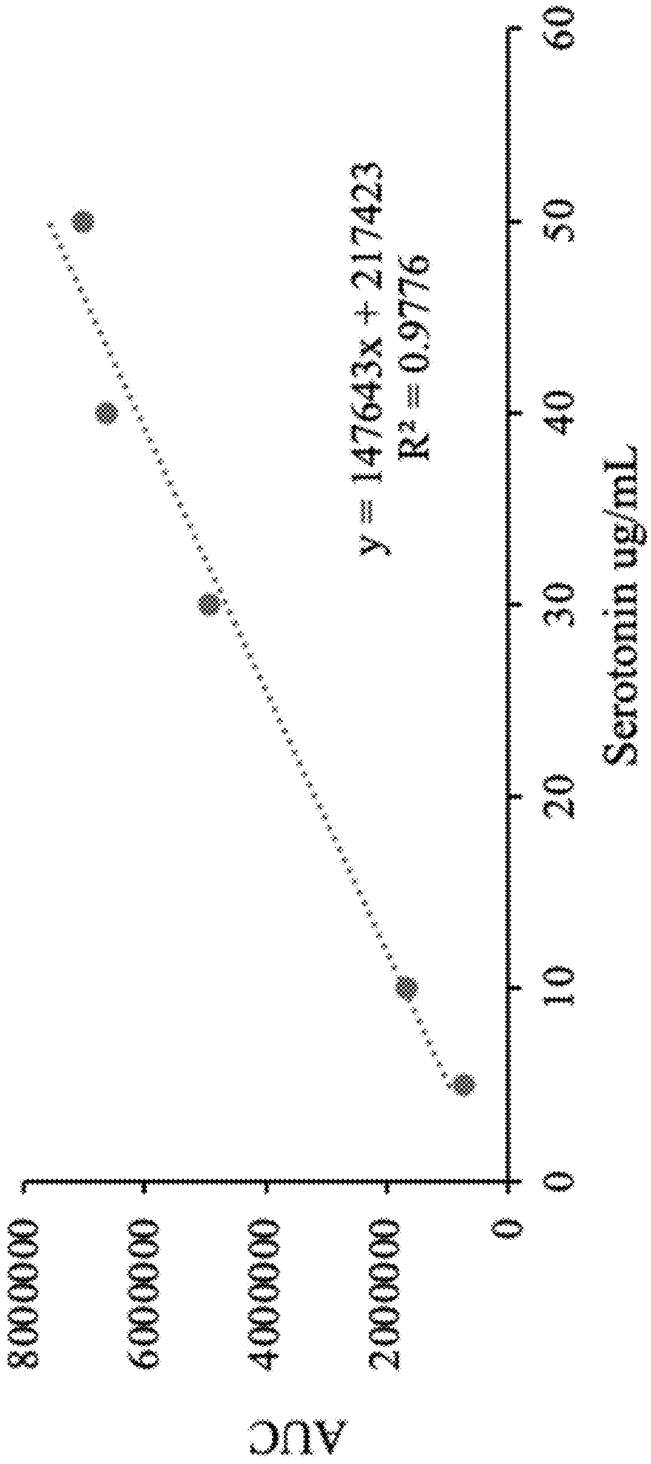

AUC
8000000
6000000
4000000
2000000
0
0
10
20
30
40
50
60
Serotonin ug/mL
y = 147643x + 217423
R² = 0.9776

Figure 23

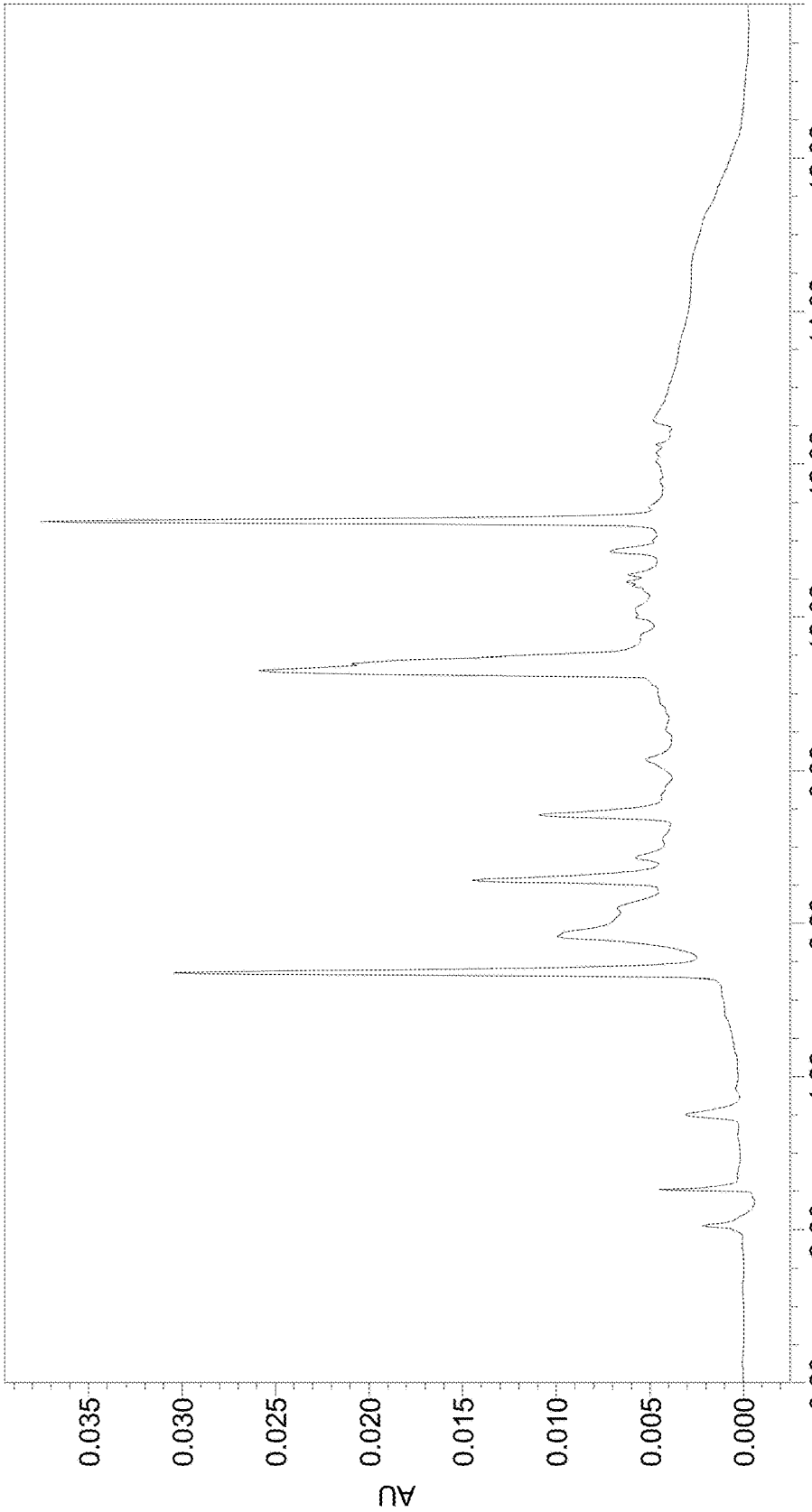

AU
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
Minutes

Figure 24A

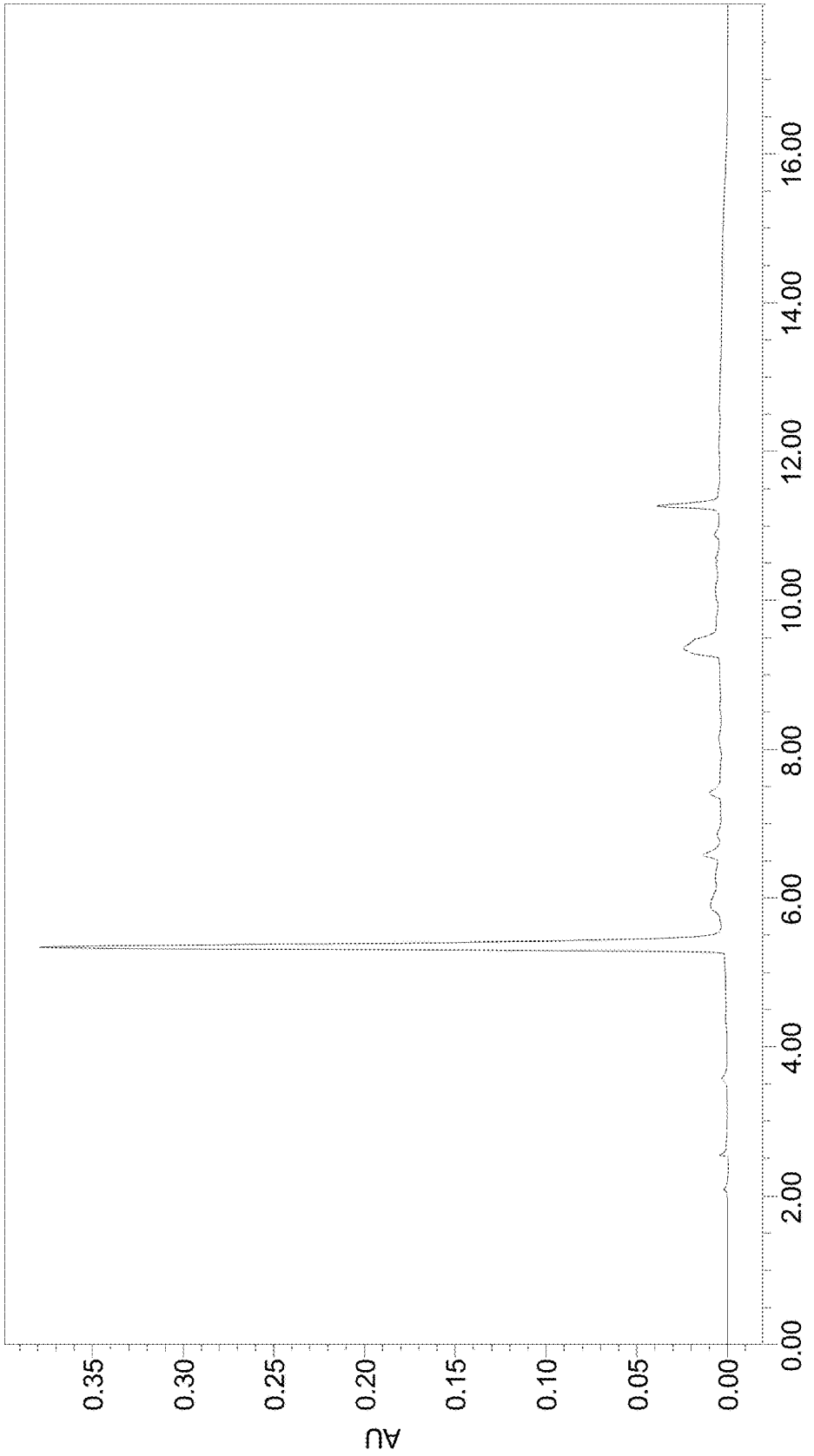

AU
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
Minutes

Figure 24B

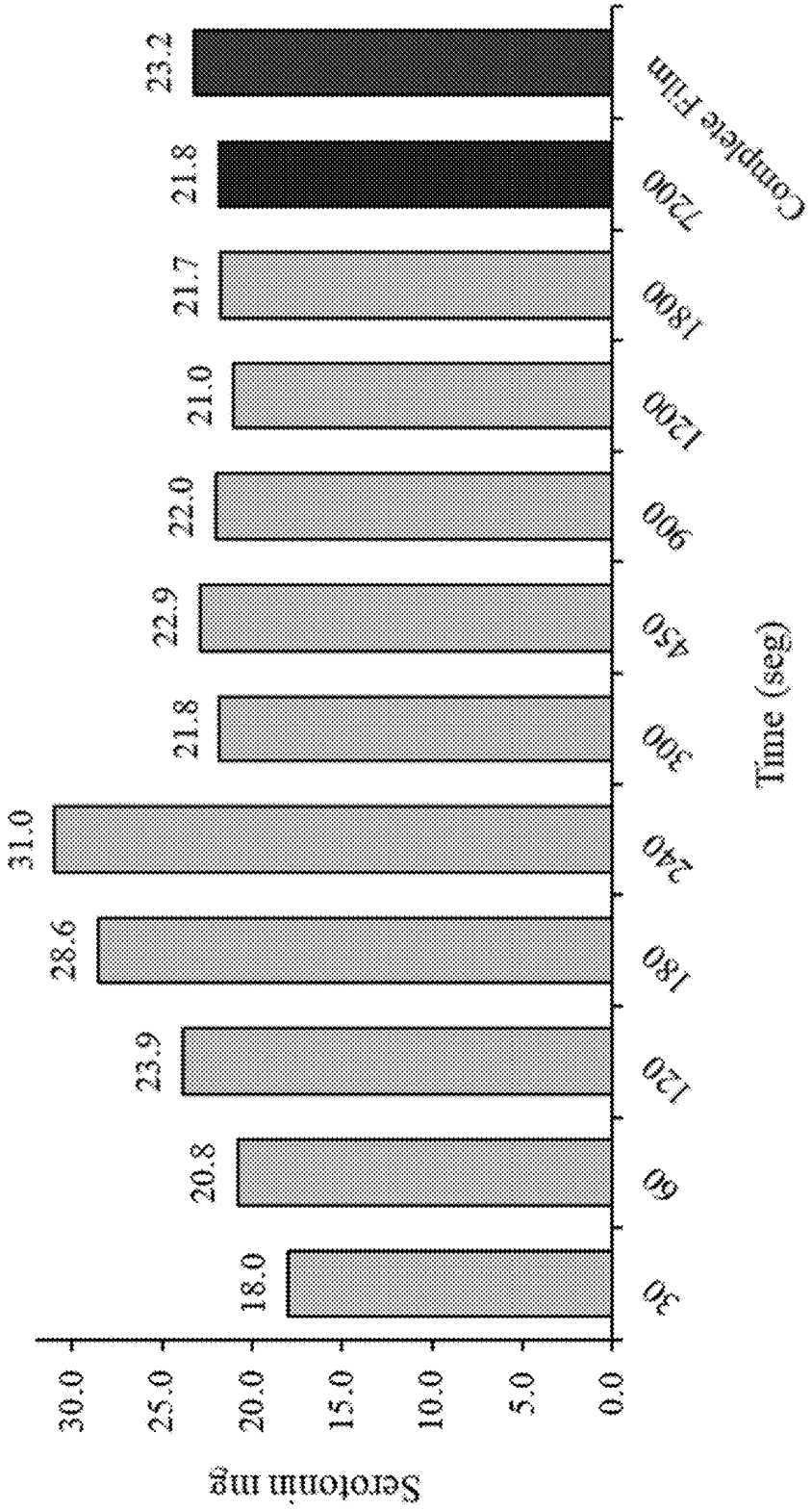

Serotonin mg
30.0
25.0
20.0
15.0
10.0
5.0
0.0
18.0
20.8
23.9
28.6
31.0
21.8
22.9
22.0
21.0
21.7
21.8
23.2
30
60
120
180
240
300
450
900
1200
1800
7200
Complete Film
Time (sec)

Figure 25

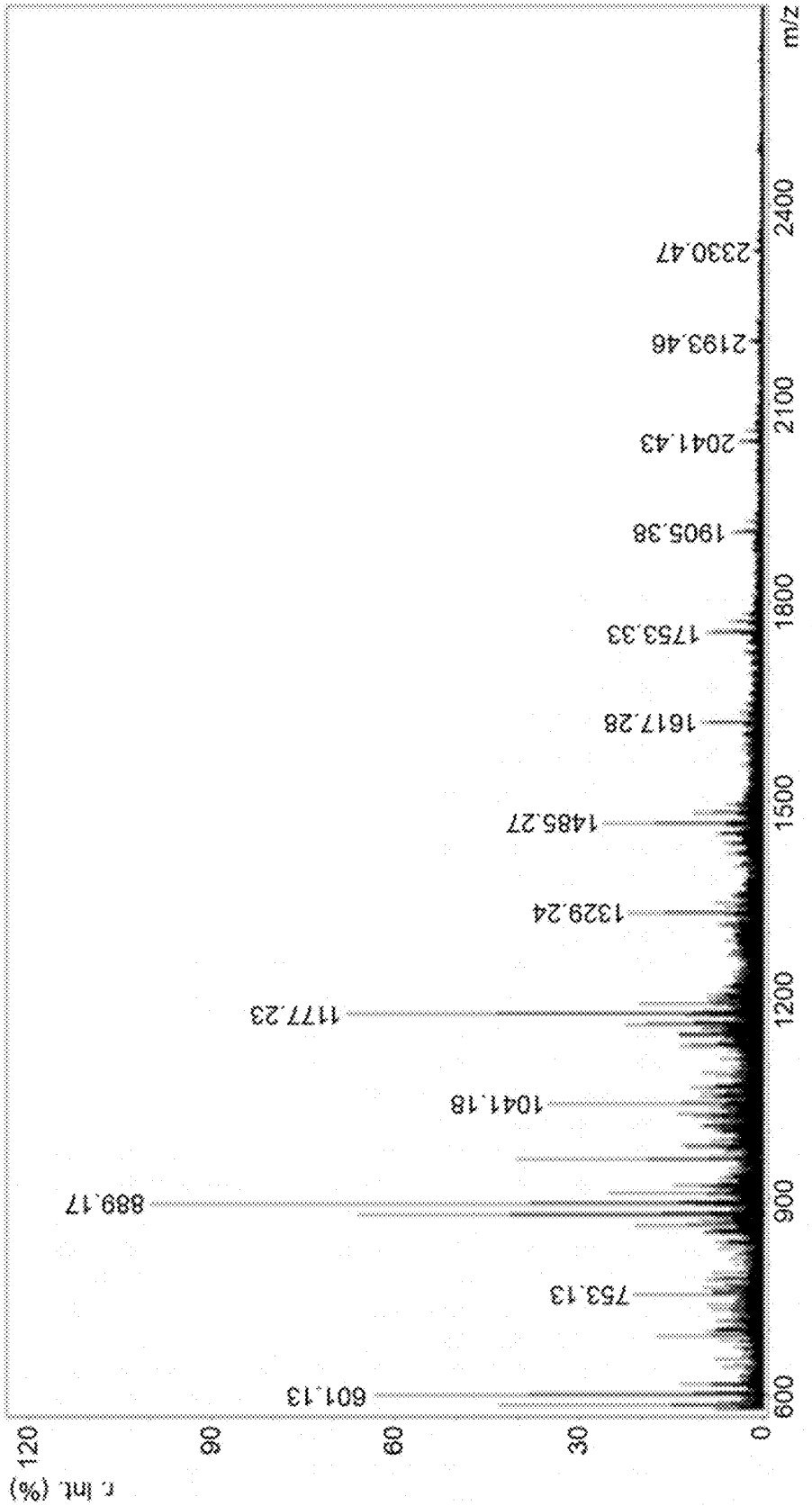

r. Int. (%)
120
90
60
30
0
m/z
600
900
1200
1500
1800
2100
2400
601.13
753.13
889.17
1041.18
1177.23
1329.24
1485.27
1617.28
1753.33
1905.38
2041.43
2193.46
2330.47

Figure 26

COMPOSITE CHITOSAN-TANNIN-ACTIVE AGENT COMPOSITIONS AND METHODS OF MAKING AND USING SAME

BACKGROUND

Natural polymers have been used in many pharmaceutical applications. Chitosan, in particular, has been used for the preparation of nanoparticles, hydrogels, films, fibers, and tablets. In addition, chitosan has been used in formulations for oral, nasal, parenteral, transdermal, and ophthalmic drug delivery. However, chitosan-based materials have suffered from limited stability, biodegradability, and tensile strength. Chitosan-based materials suitable for pharmaceutical applications that overcome at least some of these deficiencies are needed.

SUMMARY OF THE INVENTION

The invention provides tannin-chitosan composite thin-films and other composite forms incorporating active pharmaceutical ingredients, including psilocybin (a psychedelic), biosimilars (melatonin and serotonin), and other active agents.

Exemplary films are fabricated with a tannin (grape seed extract):chitosan (fungal source) at a ratio of (10:90; w/w). Similar methods can be used for formulating thin-films with tannins and chitosan from alternative sources and at different w/w ratios. The tannin and chitosan powders can be mixed in water to first form a hydrogel. The active agent(s) can be solubilized in either water, ethanol, or other solvents at various doses (<1 mg-20 mg). The liquid solutions can be cast in silicone molds and dried, for example, at <40° C. over 72 hours in an oven. When removed from the molds, films of the invention demonstrate flexibility. The films of the invention can be dissolved in a small volume of water, simulating the dissolution that would occur in the oral cavity. The active agents can be released in dissolution tests in less than 5 minutes with up to 100% recovery as determined by quantitative high performance liquid chromatography with photodiode array detection.

The invention provides a better delivery platform than encapsulation or tableting because tannin-chitosan thin-films can dissolve quickly in the oral cavity, providing rapid release and early onset of the incorporated psilocybin (psychedelics) and biosimilars (melatonin, serotonin). Rapid release and onset of the active agent is a desirable attribute for certain indications such as, e.g., anxiety, panic attack. Tablets and capsules must first undergo dissolution in the GI tract, delaying onset of activity.

In addition, the invention provides tamper-resistant or abuse-deterrent formulations, which is particularly important for the envisioned payloads (e.g., psychedelic drugs). This is a high priority for the FDA when formulating Schedule I substances, including psilocybin, opioids, and other controlled substances. The active agents in the compositions of the invention, for example, are not easily purified and concentrated from the compositions without laboratory equipment.

The objects and advantages of the invention will appear more fully from the following detailed description of the preferred embodiment of the invention made in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Chitosan lactate-tannin (CHTL-TAN) films with or without melatonin. Quebracho TAN: quebracho tannin. GSE TAN: grape seed extract tannin. cPAC TAN: cranberry proanthocyanidin tannin.

FIG. **2**. Chitosan lactate-quebracho tannin (CHTL-TAN) film with melatonin.

FIG. **3**. Chitosan lactate-grape seed extract (GSE) tannin (CHTL-TAN) film with melatonin.

FIG. **4**. HPLC chromatogram of melatonin at 100 μg/mL, recorded at 280 nm.

FIG. **5**. Calibration curve of melatonin.

FIG. **6**. HPLC chromatogram of CHTL-TAN composite film loaded with melatonin after dissolution in phosphate buffer, recorded at 280 nm.

FIG. **7**. HPLC chromatogram of CHTL-TAN composite film after dissolution in phosphate buffer, recorded at 280 nm.

FIG. **8**. HPLC chromatogram of CHTL-TAN composite film loaded with melatonin after dissolution in phosphate buffer, recorded at 280 nm.

FIG. **9**. HPLC chromatogram of CHTL-TAN composite film loaded with melatonin after dissolution, recorded at 280 nm.

FIG. **10**A. HPLC chromatogram of melatonin at 150 μm/mL, recorded at 280 nm.

FIG. **10**B. UV spectra of melatonin at 150 μm/mL from FIG. **10**A.

FIG. **11**A. HPLC chromatogram of TAN (quebracho) at 200 μg/mL, recorded at 280.

FIG. **11**B. UV spectra of the TAN (quebracho) at 200 μm/mL of FIG. **11**A.

FIG. **12**. HPLC chromatogram of TAN (quebracho) at 200 μg/mL and melatonin at 150 μm/mL, recorded at 280 nm. Inserts are the UV spectra.

FIG. **13**. HPLC chromatogram of CHTL-TAN (Quebracho) at 200 μg/mL and melatonin at 150 μm/mL, recorded at 280 nm. Inserts are the UV spectra.

FIG. **14**A. HPLC chromatogram of CHTL-TAN (quebracho) composite films after dissolution in water, recorded at 280 nm.

FIG. **14**B. UV spectra of peak from FIG. **14**A.

FIG. **15**A. HPLC chromatogram of CHTL-TAN (quebracho) composite films loaded with melatonin after dissolution in water, recorded at 280 nm.

FIG. **15**B. UV spectra of Peak 1 from FIG. **15**A.

FIG. **15**C. UV spectra of Peak 2 from FIG. **15**A.

FIG. **16**. HPLC chromatogram of CHTL-TAN (GSE) composite film after dissolution in water, recorded at 280 nm.

FIG. **17**. HPLC chromatogram of CHTL-TAN (GSE) composite film after dissolution loaded with melatonin after dissolution in water, recorded at 280 nm.

FIG. **18**: Chitosan-tannin (CHT-TAN) films with or without psilocybin.

FIG. **19**A: Chitosan-tannin (CHT-TAN) film with 7.6 mg psilocybin (Film 2) diluted in water.

FIG. **19**B: Chitosan-tannin (CHT-TAN) film with 7.6 mg psilocybin (Film 2) diluted in mobile phase.

FIG. **20**A: Chitosan-tannin (CHT-TAN) film with 9 mg psilocybin (Film 3) diluted in water.

FIG. **20**B: Chitosan-tannin (CHT-TAN) film with 9 mg psilocybin (Film 3) diluted in mobile phase.

FIG. **21**A: Chitosan-tannin (CHT-TAN) film with 20 mg psilocybin (Film 4) diluted in water.

FIG. **21**B: Chitosan-tannin (CHT-TAN) film with 20 mg psilocybin (Film 4) diluted in mobile phase.

FIG. **22**A: Chitosan-tannin (CHT-TAN) film with 20 mg psilocybin (Film 5) diluted in water.

FIG. **22**B: Chitosan-tannin (CHT-TAN) film with 20 mg psilocybin (Film 5) diluted in mobile phase.

FIG. **23**. Standard curve of serotonin.

FIG. **24**A. HPLC chromatogram of CHTL-TAN (GSE) composite film after dissolution, recorded at 280 nm.

FIG. **24**B. HPLC chromatogram of CHT-TAN (GSE) composite film loaded with serotonin after dissolution, recorded at 280 nm.

FIG. **25**. Serotonin release in mg versus time.

FIG. **26**. MALDI-TOF spectra of Tan'Activ GUT gran (Grape seed extract) from SILVA TEAM.

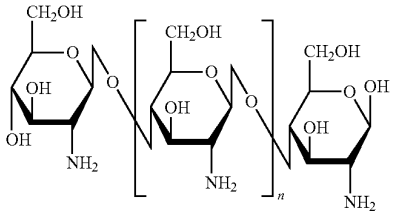
DETAILED DESCRIPTION OF THE INVENTION

The invention provides composite compositions. "Composite" is used herein to refer to a material comprising two or more constituent materials with significantly different physical or chemical properties.

The compositions of the invention comprise chitosan, tannin, and an active agent. In preferred versions, each of the chitosan, the tannin, and the active agent is evenly distributed throughout the composition with respect to each other.

Chitin is a biopolymer composed of substituted or unsubstituted glucosamine (such as N-acetyl glucosamine) polymer subunits. Chitin is the second most abundant biopolymer on earth, after only cellulose. It is commonly found in the exoskeleton or cuticles of many invertebrates, such as the shells of marine arthropods, and in the cell wall of most fungi and some algae. Chitin is generally insoluble in water but can be deacetylated by treatment with a caustic, such as sodium hydroxide, to form the soluble cationic polysaccharide, chitosan. The chemical name of an exemplary form of chitosan is poly(β-(1→4)-2-amino-2-deoxy-D-glucopyranose). In some versions, chitosan has two types of reactive groups that can be grafted: the amine groups on deacetylated units, and the hydroxyl groups on the C3 and C6 carbons on either acetylated or deacetylated units (Scheme 1).

Scheme 1. Exemplary Chitosan Structure.



In some versions, the amine groups are substituted with various moieties, such as lactate. Versions of chitosan in which the amine groups are substituted with lactate are referred to as "chitosan lactate."

Chitosan is commonly used in water processing and in agriculture. Chitosan can also form a polycationic, biodegradable, and biocompatible matrix with blood clotting and antimicrobial properties. Kumar et al. (*Chemical Reviews* (2004) 104:6017-6084) and Rinaudo (*Progress in Polymer Science* (2006) 31:603-632) have reviewed the properties and applications of chitosan. Due to its unique polycationic nature, chitosan and its derivatives have been used for various applications in many different fields, including biomedicine, food, agriculture, biotechnology and pharmaceutics. Chitosan has been developed for a variety of biomedical applications including wound dressings and drug delivery systems.

Chitosan is commercially available from many chemical suppliers, such as Sigma Aldrich Co., St. Louis, MO. Chitosan is offered in various grades, average molecular weights, and degrees of deacetylation.

In some versions, the chitosan has a number average molecular weight of at least about 50 kDa, at least about 75 kDa, at least about 100 kDa, at least about 125 kDa, at least about 150 kDa, at least about 175 kDa, at least about 200 kDa, or at least about 250 kDa. In some versions, the chitosan has a number average molecular weight up to about 250 kDa, up to about 275 kDa, up to about 300 kDa, up to about 325 kDa, up to about 350 kDa, up to about 375 kDa, up to about 400 kDa, up to about 425 kDa, up to about 450 kDa, up to about 475 kDa, or up to about 500 kDa. In some versions, the chitosan has number average molecular weight from about 100 kDa to about 500 kDa, such as from about 200 kDa to about 350 kDa, or about 250 kDa to about 300 kDa. In some versions, the chitosan has number average molecular weight from about 100 kDa to about 400 kDa, from about 120 kDa to about 400 kDa, from about 150 kDa to about 400 kDa, from about 170 kDa to about 400 kDa, from 100 kDa to about 300 kDa, from about 120 kDa to about 300 kDa, from about 150 kDa to about 300 kDa, or from about 170 kDa to about 300 kDa. The value of n in Scheme 1 can be any number or range that results in approximately the values for the molecular weights of chitosan described herein. As would be readily recognized by one of skill in the art, chitosan as illustrated in Scheme 1 may also be partially acetylated, partially substituted with lactate, and/or partially substituted with other moieties.

Other embodiments may include low molecular weight chitosan. Low molecular weight chitosan refers to chitosan molecules with less than 100 polymer subunits (less than about 18 kDa or less than about 20 kDa). Molecular weights of chitosan can be determined, for example, by gel permeation chromatography.

The chitosan can have a degree of deacetylation that is typically at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 99%, or the chitosan can be substantially fully deacetylated.

In some versions, the chitosan completely lacks lactate moieties or contains less than about 1 lactate moieties per polymer subunit, less than about 5×10^{-1} lactate moieties per polymer subunit, less than about 1×10^{-1} lactate moieties per polymer subunit, less than about 5×10^{-2} lactate moieties per polymer subunit, less than about 1×10^{-2} lactate moieties per polymer subunit, less than about 5×10^{-3} lactate moieties per polymer subunit, less than about 1×10^{-3} lactate moieties per polymer subunit, less than about 5×10^{-4} lactate moieties per polymer subunit, less than about 1×10^{-4} lactate moieties per polymer subunit, less than about 5×10^{-5} lactate moieties per polymer subunit, less than about 1×10^{-5} lactate moieties per polymer subunit, less than about 5×10^{-6} lactate moieties per polymer subunit, less than about 1×10^{-6} lactate moieties per polymer subunit, less than about 5×10^{-7} lactate moieties per polymer subunit, less than about 1×10^{-7} lactate moieties per polymer subunit, less than about 5×10^{-8} lactate moieties per polymer subunit, less than about 1×10^{-8} lactate moieties per polymer subunit, less than about 5×10^{-9} lactate moieties per polymer subunit, less than about 1×10^{-9} lactate moieties per polymer subunit, less than about 5×10^{-10} lactate moieties per polymer subunit, less than about 1×10^{-10} lactate moieties per polymer subunit, less than about 5×10^{-15} lactate moieties per polymer subunit, less than about 1×10^{-15} lactate moieties per polymer subunit, less than about 5×10^{-20} lactate moieties per polymer subunit, or less than about

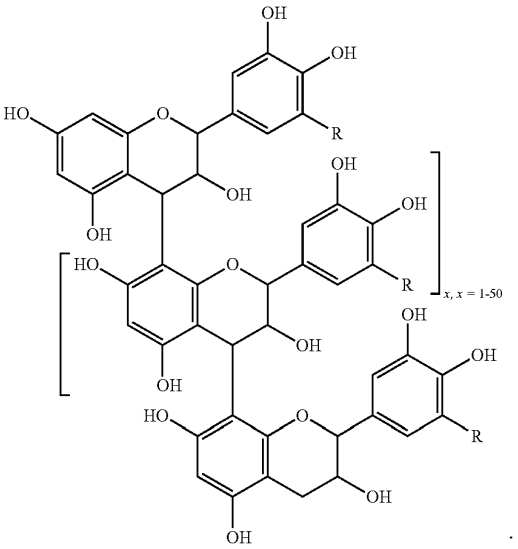
1×10^{-20} lactate moieties per polymer subunit, wherein "polymer subunit" unit refers to a unsubstituted or substituted glucosamine (2-amino-2-deoxy-D-glucopyranose) moiety. As shown in the following examples, compositions of the invention made with lactate-containing chitosan ("chitosan lactate") leads to compositions that are sticky. Therefore, preferred compositions of the invention either lack chitosan with lactate moieties or contain chitosan with low amounts of lactate moieties per polymer subunit as described above.

Tannins include oligomeric polyphenols that occur naturally in a variety of plants, and modified forms thereof. Isolated tannins typically form a heterogeneous mixture of tannin compounds. Tannin compounds can be subdivided into two groups: condensed tannins, also known as proanthocyanidins ("PA" or "PAC"), and hydrolyzable tannins (HT). Tannin oligomers typically occur as dimers, trimers, tetramers, pentamers, hexamers, heptamers, octamers, nonamers, or decamers. Oligomers with greater than ten monomeric units can also be isolated, such as oligomers that include up to 50 units. For a review of tannin nomenclature, see Beecher (*J. Nutrition* 2003, 3248S-3254S), which is incorporated herein by reference. In some embodiments, certain monomerics or tannins with a low degree of polymerization (DP) can be excluded from a particular composition. For example, a composition may exclude catechin, tannic acid, or other monomers, dimeric tannins, trimers, or tetramers, PA tannins, or alternatively, HT tannins, a certain molecular weight range of tannins, or a type, class, or specific tannin cited in Beecher.

Proanthocyanidins are polymers of flavan-3-ols and flavans linked through an interflavan bond between carbon 4 of the C ring and carbon 8 of the A ring, as shown in Scheme 2. Scheme 2 illustrates a cranberry polyflavan-3-ol showing structural variation in the nature of interflavan linkage and substitution to an anthocyanin terminal unit through a CH_3—CH bridge.

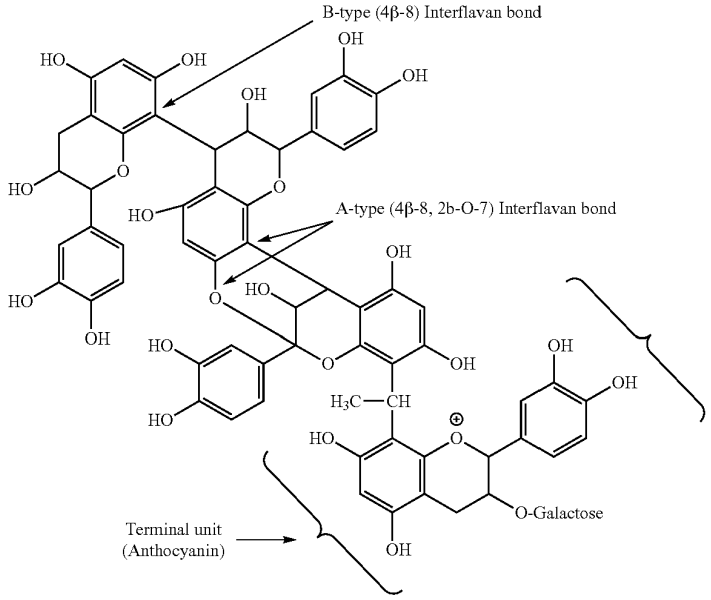
Scheme 3 illustrates two other types of condensed tannins (PAs): procyanidins and prodelphinidins (for the trimer x=1; for the tetramer, x=2; for the pentamer, x=3; for the hexamer, x=4; for the heptamer, x=5; for the octamer, x=6; for the nonamer, x=7; and for the decamer, x=8). Procyanidins (R=H) contain catechin and/or epicatechin (CE) subunits; prodelphinidins (R=OH) contain gallocatechin and/or epigallocatchin (GE) subunits.

Scheme 3. Representative structures of proanthocyanidin (PA).



R = H and/or OH

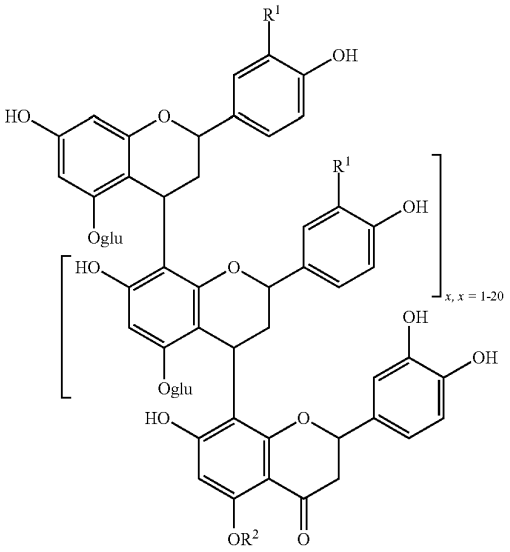
Scheme 2. Representative structures of a proanthocyanidin (PA).



In various proanthocyanidins, the R groups of Scheme 3 can each independently be H or OH. In some embodiments, one or more hydroxyl groups may be glycosylated. In some embodiments, x is 1 to about 50, 1 to about 25, 1 to about 20, 1 to about 12, 1 to about 10, or a range of between any to integers from 1 to 50. The condensed tannins (PAs) can have various interflavanoid linkages (such as A-type 4→8 or 4→6 interflavan bonds, or B-type 4→8, 2→O-7 interflavan bonds, each α or β), cis- or trans-stereochemistry, and one or more hydroxyl groups can optionally be absent on the A-ring, B-ring, C-ring, or a combination thereof.

Other PA tannins include glycosylated heteropolyflavans, such as those illustrated in Scheme 4. Representative compounds shown in Scheme 4 include proluteolinidin (R^1=OH); proapigininidin (R^1=H); eriodictyol (R^2=H); and eriodictyol 5-O-β glucoside (R^2=glucose). Krueger et al. has described a variety of known heteropolyflavans-3-ols and glycosylated heteropolyflavans (see *J. Agric. Food Chem.* 2003, 51, 538-543, which is incorporated herein by reference).

Scheme 4. Representative structures of proanthocyanidins (PAs).



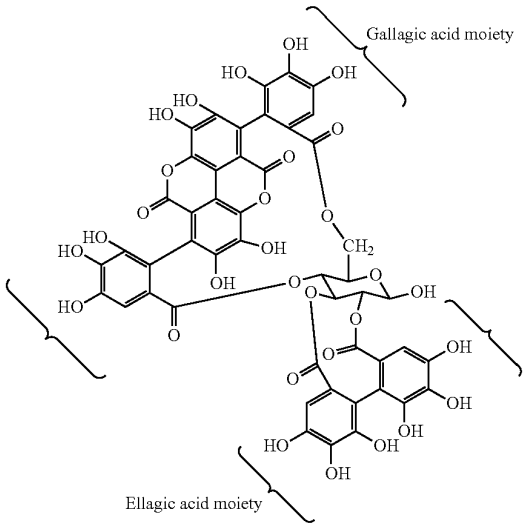
where R^1 is H or OH; R^2 is H or glucose; and glu is glucose (e.g., a β-glucoside).

In some embodiments, x of Scheme 4 is 1 to about 50, 1 to about 25, 1 to about 20, 1 to about 12, 1 to about 10, or a range of between any to integers from 1 to 50. Several examples of condensed tannins are described in U.S. Pat. No. 7,122,574 (Romanczyk et al.), which is incorporated herein by reference.

A review by Reed et al. (*Phytochem.* 66(18): 2248-2263 (2005)) describes the structural heterogeneity of tannin polyphenols from cranberries, grape seed extracts, sorghum, and pomegranates as characterized by MALDI-TOF MS. Examples of plants that produce proanthocyanidins include cranberries, blueberries, grapes, sorghum, and pine.

Hydrolyzable tannins include gallic acid and ellagic acid esters of polyol core moieties, such as sugars. Scheme 5 illustrates a pomegranate ellagitannin showing structural variation in nature of esterification of the glucose core molecule.

Scheme 5. Representative structure of a hydrolyzable tannin.



Hydrolyzable tannins, such as the compound shown in Scheme 5, can be isolated in oligomeric forms that include 2 to about 12 hydrolyzable tannin moieties, for example, linked by oxidative C—O coupling between galloyl and hexahydroxydiphenoyl moieties of the monomeric precursors. Common coupling also occurs between two ellagic acid moieties, or by addition of gallic acid moieties to the saccharide core of an oligomer. See Quideau and Feldman, *Chem. Rev.* 1996, 96, 475-503, which is incorporated herein in its entirety.

Accordingly, in some embodiments of compositions described herein, the hydrolyzable tannins employed will be oligomeric hydrolyzable tannins. Thus, in some embodiments, oligomeric hydrolyzable tannins include at least two saccharide core moieties. In some embodiments, a hydrolyzable tannin will include one or more (e.g., 1, 2, 3, 4, 5, or more) ellagic acid moieties, and in some embodiments, a hydrolyzable tannin will include one or more (e.g., 1, 2, 3, 4, 5, or more) gallagic acid moieties.

Examples of plants that produce hydrolyzable tannins include pomegranates, strawberries, raspberries, blackberries, and sumac. Significant quantities of hydrolyzable tannins can be isolated from, for example, pomegranate husks. Specific hydrolyzable tannins include punicalin and punicalagin (the alpha or beta isomer of 2,3-(S)-hexahydroxydiphenoyl-4,6-(S,S)-gallagyl-D-glucose, with a molecular weight of 1084) and stereochemical isomers thereof, as well as the hydrolyzable tannins described by Quideau and Feldman (*Chem. Rev.* 1996, 96, 475-503).

In some versions of the invention, the tannin in the composition comprises a condensed tannin, and the condensed tannin comprises a weight average molecular weight (M_w) of from about 100 Da to about 100,000 Da, such as from about 500 Da to about 100,000 Da or from about 1,000 Da to about 10,000 Da.

In some versions of the invention, the tannin in the composition comprises a hydrolyzable tannin, and the hydrolyzable tannin comprises a weight average molecular weight (M_w) of from about 100 Da to about 100,000 Da, such as from about 300 Da to about 30,000 Da or from about 1,000 Da to about 10,000 Da.

In some versions, the compositions of the invention comprise the chitosan and the tannin in a ratio by mass (mass chitosan:mass tannin) of about 99:1, about 95:5, about 90:10, about 85:15, about 80:20, about 75:25, about 70:30, about 65:35, about 60:40, about 55:45, about 50:50, about 45:55, about 40:60, about 35:65, about 30:70, or 25:75 or within a range between any two of the foregoing ratios. Exemplary ranges include from about 99:1 (mass chitosan: mass tannin) to about 60:40 (mass chitosan:mass tannin), from about 99:1 to about 80:20, or from about 95:5 (mass chitosan:mass tannin) to about 85:15 (mass chitosan:mass tannin).

Some tannins can contain sulfonate groups. In some versions of the invention, the tannin in the composition completely lacks sulfonate moieties or contains less than about 1 sulfonate moieties per polymer subunit, less than about 5×10^{-1} sulfonate moieties per polymer subunit, less than about 1×10^{-1} sulfonate moieties per polymer subunit, less than about 5×10^{-2} sulfonate moieties per polymer subunit, less than about 1×10^{-2} sulfonate moieties per polymer subunit, less than about 5×10^{-3} sulfonate moieties per polymer subunit, less than about 1×10^{-3} sulfonate moieties per polymer subunit, less than about 5×10^{-4} sulfonate moieties per polymer subunit, less than about 1×10^{-4} sulfonate moieties per polymer subunit, less than about 5×10^{-5} sulfonate moieties per polymer subunit, less than about 1×10^{-5} sulfonate moieties per polymer subunit, less than about 5×10^{-6} sulfonate moieties per polymer subunit, less than about 1×10^{-6} sulfonate moieties per polymer subunit, less than about 5×10^{-7} sulfonate moieties per polymer subunit, less than about 1×10^{-7} sulfonate moieties per polymer subunit, less than about 5×10^{-8} sulfonate moieties per polymer subunit, less than about 1×10^{-8} sulfonate moieties per polymer subunit, less than about 5×10^{-9} sulfonate moieties per polymer subunit, less than about 1×10^{-9} sulfonate moieties per polymer subunit, less than about 5×10^{-10} sulfonate moieties per polymer subunit, less than about 1×10^{-10} sulfonate moieties per polymer subunit, less than about 5×10^{-15} sulfonate moieties per polymer subunit, less than about 1×10^{-15} sulfonate moieties per polymer subunit, less than about 5×10^{-20} sulfonate moieties per polymer subunit, or less than about 1×10^{-20} sulfonate moieties per polymer subunit. As shown in the following examples, compositions of the invention made with sulfonate-containing tannin leads to compositions that are brittle and unevenly distribute the active agent therein. Therefore, preferred compositions of the invention either lack sulfonated tannin or contain tannin with low amounts of sulfonate moieties per polymer subunit as described above.

In some versions, the active agent comprises a hallucinogen. Hallucinogens include various indole alkaloids, indoline alkaloids, indazole alkaloids, benzofuran alkaloids, and phenethylamines.

In some versions, the active agent comprises an indole alkaloid, an indoline alkaloid, an indazole alkaloid, a benzofuran alkaloid, or a phenethylamine. Indole alkaloids are alkaloids (both natural and synthetic) containing a structural moiety of indole. Indoline alkaloids are alkaloids (both natural and synthetic) containing a structural moiety of indoline. Indazole alkaloids are alkaloids (both natural and synthetic) containing a structural moiety of indazole. Benzofuran alkaloids are alkaloids (both natural and synthetic) containing a structural moiety of benzofuran. Phenethylamines are a chemical class of organic compounds that have a phenethylamine base structure and include unsubstituted phenethylamine and substituted phenethylamines.

Exemplary indole alkaloids include tryptamine alkaloids, and lysergamides. Indoline, indazole, or benzofuran analogs have an indoline, indazole, or benzofuran in place of the indole group. In some versions, the indole alkaloid is hallucinogenic.

Exemplary tryptamine alkaloids include tryptamine (3-(2-aminoethyl)indole or 2-(1H-indol-3-yl)ethanamine) and substituted tryptamines, which include substituted alpha-alkyltryptamines.

Exemplary substituted tryptamines include bufotenine (5-hydroxy-N,N-dimethyltryptamine), N_{ω}-methylserotonin (norbufotenin) (5-hydroxy-N-methyltryptamine), serotonin (5-hydroxytryptamine), DMT (N,N-dimethyltryptamine), melatonin (5-methoxy-N-acetyltryptamine), N-acetylserotonin (5-hydroxy-N-acetyltryptamine), 5-bromo-DMT (5-bromo-N,N-dimethyltryptamine), 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine), 5-MeO-NMT (5-methoxy-N-methyltryptamine), NMT (N-methyltryptamine), norbaeocystin (4-phosphoryloxy-tryptamine), baeocystin (4-phosphoryloxy-N-methyl-tryptamine), psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), psilocin (4-hydroxy-N,N-dimethyltryptamine), tryptophan (α-carboxyltryptamine), DET (N,N-diethyltryptamine), DPT (N,N-dipropyltryptamine), DiPT (N,N-diisopropyltryptamine), DALT (N,N-diallyltryptamine), 5-MeO-DALT (5-methoxy-N,N-diallyltryptamine), 5-MeO-MALT (5-methoxy-N-Methyl-N-allyltryptamine), 5-MeO-DIPT (5-methoxy-N,N-diisopropyltryptamine), 5-MeO-MiPT (5-methoxy-N,N-methylisopropyltryptamine), 5-MT-NBOMe (5-methoxy-N-(ortho-methoxybenzyl)tryptamine), 5-BT (5-benzyloxytryptamine), 5-CT (5-carboxamidotryptamine), 5-ethoxy-DMT (5-ethoxy-N,N-dimethyltryptamine), 5-ethyl-DMT (5-ethyl-N,N-dimethyltryptamine), 5-fluoro-DMT (5-fluoro-N,N-dimethyltryptamine), 5-methyl-DMT (5,N,N-trimethyltryptamine), 5-(nonyloxy) tryptamine (5-nonyloxytryptamine), 4-HO-DET (4-hydroxy-N,N-diethyltryptamine), 4-AcO-DMT (4-acetoxy-N,N-dimethyltryptamine), 4-HO-MET (4-hydroxy-N-methyl-N-ethyltryptamine), 4-HO-EPT (4-hydroxy-N-ethyl-N-propyltryptamine), 4-HO-MPT (4-hydroxy-N-methyl-N-propyltryptamine), 4-HO-MiPT (4-hydroxy-N-isopropyl-N-methyltryptamine), 4-HO-McPT (4-hydroxy-N-cyclopropyl-N-methyltryptamine), 4-HO-McPeT (4-hydroxy-N-cyclopentyl-N-methyltryptamine), 4-HO-DPT (4-hydroxy-N,N-dipropyltryptamine), 4-HO-DIPT (4-hydroxy-N,N-diisopropyltryptamine), 4-HO-DSBT (4-hydroxy-N,N-disecbutyltryptamine), and zolmitriptan (5-(4-(S)-1,3-oxazolidin-2-one)-N,N-dimethyltryptamine).

Exemplary substituted α-alkyltryptamines include αMT (1-(1H-Indol-3-yl)propan-2-amine), 4-HO-αMT (3-(2-aminopropyl)-1H-indol-4-ol), 4-methyl-αMT (1-methyl-2-(4-methyl-1H-indol-3-yl)-ethylamine), 5-fluoro-αMT (1-(5-fluoro-1H-indol-3-yl)propan-2-amine), 5-chloro-αMT (1-(5-Chloro-1H-indol-3-yl)propan-2-amine), 5-HO-αMT ((3-(2-aminopropyl)-1H-indol-5-ol), 5-MeO-αMT (1-(5-methoxy-1H-indol-3-yl)propan-2-amine), 5-Ethoxy-αMT (1-(5-ethoxy-1H-indol-3-yl)propan-2-amine), 6-fluoro-αMT (1-(6-fluoro-1H-indol-3-yl)propan-2-amine), N-Methyl-5-MeO-αMT ([1-(5-methoxy-1H-indol-3-yl)propan-2-yl](methyl)amine), N,N-dimethyl-αMT (α,N,N-TMT), ((2-(1H-Indol-3-yl)-1-methyl-ethyl)dimethylamine), N,N-dimethyl-5-MeO-αMT ((2-(5-methoxy-1H-Indol-3-yl)-1-methyl-ethyl)dimethylamine), αMDiPT ((2-(1H-Indol-3-yl)-1-methyl-ethyl)diisopropylamine), BW-723C86 (1-[5-(2-Thienylmethoxy)-1H-indol-3-yl]-2-propanamine), AL-37350A (4,5-dihydropyrano-αMT) ((S)-(+)-1-(2-Aminopropyl)-8,9-dihydropyrano[3,2-e]indole), αET (1-(1H-indol-3-yl)butan-2-amine), 4-methyl-αET (1-(4-Methyl-1H-indol-3-yl)butan-2-amine), 4-HO-αET (1-(4-hydroxy-1H-indol-3-yl)butan-2-amine), 5-fluoro-αET (1-(5-fluoro-1H-indol-3-yl)butan-2-amine), 5-methyl-αET (1-(5-methyl-1H-indol-3-yl)butan-2-amine), 5-MeO-αET (1-(5-methoxy-1H-

indol-3-yl)butan-2-amine), 7-methyl-αET (1-(7-methyl-1H-indol-3-yl)butan-2-amine), MPMI (3-[(1-methylpyrrolidin-2-yl)methyl]-1H-indole), lucigenol ((R)-3-(N-methylpyrrolidin-2-ylmethyl)-4-hydoxyindole), 5-MeO-MPMI (5-methoxy-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-1H-indole), 5-F-MPMI (5-fluoro-3-[(1-methylpyrrolidin-2-yl)methyl]-1H-indole), 5-Br-MPMI (5-bromo-3-[(1-methylpyrrolidin-2-yl)methyl]-1H-indole), and eletriptan (3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-5-[2-(benzenesulfonyl)ethyl]-1H-indole).

Exemplary lysergamides include LSA/LAA (ergine, d-lysergic acid amide), DAM-57 (N,N-dimethyllysergamide), ergometrine (ergonovine), ergotamine, methergine, methysergide, amesergide, LY-215840, cabergoline, LAE-32 (D-lysergic acid ethylamide), LSB (lysergic acid 2-butyl amide), LSP (lysergic acid 3-pentyl amide), DAL (N,N-diallyllysergamide), MIPLA (methylisopropyllysergamide), ECPLA (N-ethyl-N-cyclopropyllysergamide), ETFELA (N-ethyl-N-(2,2,2-trifluoroethyl)lysergamide), LSD (lysergic acid diethylamide), ETH-LAD (6-ethyl-6-nor-lysergic acid diethylamide), AL-LAD (6-allyl-6-nor-LSD), IP-LAD (6-isopropyl-6-nor-lysergic acid diethylamide), BU-LAD (6-butyl-6-nor-lysergic acid diethylamide), ALD-52 (1-acetyl-LSD), 1P-LSD (1-propionyl-lysergic acid diethylamide), 1B-LSD (N1-butyryl-lysergic acid diethylamide), 1cP-LSD (N1-(cyclopropylmethanoyl)-lysergic acid diethylamide), 1P-ETH-LAD (1-propionyl-6-ethyl-6-nor-lysergic acid diethyamide), MLD-41 (N1-Methyl-lysergic acid diethylamide), LSM-775 (N-Morpholinyllysergamide), LPD-824 (N-Pyrrolidyllysergamide), LSD-Pip, LSD-Azapane, and LA-SS-Az (lysergic acid 2,4-dimethylazetidide)).

Other indole alkaloids include ibogaine, mitragynine, and yohimbine.

Exemplary substituted phenethylamines include metatyramine (3-hydroxyphenethylamine), para-tyramine (4-hydroxyphenethylamine), dopamine (3,4-dihydroxyphenethylamine), epinephrine (adrenaline) (β,3,4-trihydroxy-N-methylphenethylamine), norepinephrine (noradrenaline) (β,3,4-trihydroxyphenethylamine), meta-octopamine (β3-dihydroxyphenethylamine), para-octopamine (β,4-dihydroxyphenethylamine), phenylephrine (β3-dihydroxy-N-methylphenethylamine), 6-hydroxydopamine (2,4,5-trihydroxyphenethylamine), salbutamol (β,4-dihydroxy-3-hydroxymethyl-N-tert-butylphenethylamine), β-methylphenethylamine, amphetamine (α-methylphenethylamine), N-methylphenethylamine, N,N-dimethylphenethylamine, methamphetamine (N-methylamphetamine; N,α-dimethylphenethylamine), phentermine (α-methylamphetamine; α,α-dimethylphenethylamine), ortetamine (2-methylamphetamine; 2, α-dimethylphenethylamine), methylphenidate (N,α-butylene-β-methoxycarbonylphenethylamine), ephedrine/pseudoephedrine (N-methyl-β-hydroxyamphetamine), cathine (d-β-hydroxyamphetamine), cathinone (β-ketoamphetamine), methcathinone (N-methylcathinone), mephedrone (4-methylmethcathinone), ethcathinone (N-ethylcathinone), bupropion (3-chloro-N-tert-butyl-β-ketoamphetamine), norfenfluramine (3-trifluoromethyl-amphetamine), fenfluramine (3-trifluoromethyl-N-ethylamphetamine), 5-APB (5-(2-aminopropyl)benzofuran), 6-APB (6-(2-aminopropyl)benzofuran), MDA (3,4-methylenedioxy-amphetamine), MDEA (3,4-methylenedioxy-N-ethylamphetamine), MDMA (3,4-methylenedioxy-N-methylamphetamine), MDMC (3,4-methylenedioxymethcathinone), MMDA (5-methoxy-3,4-methylenedioxy-amphetamine), MMDMA (5-methoxy-3,4-methylenedioxy-N-methylamphetamine), mescaline (3,4,5-trimethoxyphenethylamine), proscaline (2-(3,5-dimethoxy-4-propoxyphenyl)ethanamine), metaescaline (2-(3-ethoxy-4,5-dimethoxyphenyl)ethanamine), allylescaline (4-Allyloxy-3,5-dimethyloxyphenylethylamine), methallylescaline (4-methallyloxy-3,5-dimethoxyphenethylamine), asymbescaline (3,4-diethoxy-5-methoxyphenethylamine), DOM (2,5-dimethoxy-4-methylamphetamine), DOB (2,5-dimethoxy-4-bromoamphetamine), DOI (2,5-dimethoxy-4-iodoamphetamine), DON (2,5-dimethoxy-4-nitroamphetamine), DOC (2,5-dimethoxy-4-chloroamphetamine), 2C-B (2,5-dimethoxy-4-bromophenethylamine), βk-2C-B (2,5-dimethoxy-4-bromo-β-ketophenethylamine), 2C-C (2,5-dimethoxy-4-chlorophenethylamine), 2C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-D (2,5-dimethoxy-4-methylphenethylamine), 2C-E (2,5-dimethoxy-4-ethylphenethylamine), 2C-P (2,5-dimethoxy-4-propylphenethylamine), 2C-F (2,5-dimethoxy-4-fluorophenethylamine), 2C-N (2,5-dimethoxy-4-nitrophenethylamine), 2C-T-2 (2,5-dimethoxy-4-ethylthio-phenethylamine), 2C-T-4 (2,5-dimethoxy-4-isopropylthio-phenethylamine), 2C-T-7 (2,5-dimethoxy-4-propylthio-phenethylamine), 2C-T-8 (2,5-dimethoxy-4-cyclopropylmethylthio-phenethylamine), 2C-T-19 (2,5-dimethoxy-4-tert-butylthio-phenethylamine), 2C-T-21 (2,5-dimethoxy-4-(2-fluoroethylthio)-phenethylamine), 25B-NBOMe (2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine), 25C-NBOMe (2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl) methyl]ethanamine), 25I-NBOMe (2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine), 25D-NBOMe (2-(4-methyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine), 25E-NBOMe (2-(4-ethyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine), 25P-NBOMe (2-(4-propyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine), 25F-NBOMe (2-(4-fluoro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine), mescaline-NBOMe (N-(2-methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)ethanamine), 25I-NBOH (N-(2-hydroxybenzyl)-2,5-dimethoxy-4-iodo-phenethylamine), 25C-NBOH (N-(2-hydroxybenzyl)-2,5-dimethoxy-4-chloro-phenethylamine), 25B-NBOH (N-(2-hydroxybenzyl)-2,5-dimethoxy-4-bromo-phenethylamine), 25I-NBF (N-(2-fluorobenzyl)-2,5-dimethoxy-4-iodo-phenethylamine), amfepramone (diethylpropion) (N-diethyl-(3-ketoamphetamine), and 1,3-benzodioxole alkaloids.

In some versions, the active agent is present in the composition in an amount of 0.001-500 mg, or any subrange therebetween. Amounts above and below this range are acceptable in other versions. Exemplary amounts include 0.001 mg, 0.005 mg, 0.01 mg, 0.05 mg, 0.1 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg, or any range between any two of the foregoing values.

In some versions, the composition has a volume in a range of 1-300 mL, or any subrange therein. Volumes above and below this range are acceptable in other versions. Exemplary volumes include 1 mL, 5 mL, 10 mL, 50 mL, 100 mL, 150 mL, 200 mL, 250 mL, or 300 mL, or any range between any two of the foregoing values.

The active agent can be synthesized or obtained from natural sources. The active agents obtained from natural sources can be in the form of a crude or refined extract from a botanical source (e.g., magic mushrooms), typically in combination with a mixture of other isolated compounds.

In addition to the chitosan, tannin, and active agent, the compositions of the invention can include any of a number of other components. Such components can include sweeteners (e.g., sucralose, sucrose), flavoring agents (e.g., essential oil), carboxymethylcellulose, sodium lauryl sulfate, citric acid, ascorbic acid, glycerol, and excipients.

The compositions of the invention can take any of a number of forms. Exemplary forms include films (e.g., thin

films or oral thin films), foams, wafers (e.g., oral wafers; dissolvable products that are not thin films), gels (e.g., hydrogels), and nanoparticles. See, e.g., Bala et al. 2013 (Rajni Bala, Pravin Pawar, Sushil Khanna, and Sandeep Arora. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm Investig. 2013 April-June; 3(2): 67-76), which is incorporated by reference in its entirety, for information on oral thin films and oral wafers.

The compositions of the invention preferably have a characteristic of dissolving in an aqueous solution in a short amount of time. In various versions of the invention, the composition dissolves in an aqueous solution within 1 minute, with 1.5 minutes, within 2 minutes, within 2.5 minutes, within 3 minutes, within 3.5 minutes, within 4 minutes, within 4.5 minutes, within 5 minutes, within 5.5 minutes, within 6 minutes, within 6.5 minutes, or within 7 minutes. "Dissolves" as used in this context refers to when the composition begins to break down in the aqueous solution, regardless of the amount of time it takes to completely bread down and disappear. "Aqueous solution" refers to a solution containing at least 75% w/w water, such as at least 80% w/w water, at least 85% w/w water, at least 90% w/w water, at least 95% w/w water, at least 96% w/w water, at least 97% w/w water, at least 98% w/w water, or at least 99% w/w water. An exemplary aqueous solution is saliva. Other exemplary aqueous solutions are those in the following examples designed to mimic saliva.

Preferred versions of the invention are directed to compositions that comprise a characteristic selected from the group consisting of being non-sticky, being non-brittle, having the chitosan, the tannin, and the active agent being evenly distributed throughout the composition, dissolving in an aqueous solution within a short amount of time, and any combination thereof. "Non-sticky" refers to the characteristic of being able to be removed from a surface, such as a silicon surface without tearing, breaking or separating. "Non-brittle" refers to the characteristic of having at least some degree of flexibility without cracking. The characteristic of having the chitosan, the tannin, and the active agent being evenly distributed throughout the composition refers to a homogeneous dispersal or distribution of each throughout the composition. The characteristic of dissolving in an aqueous solution within a short amount of time refers to having any of the parameters described in the immediately foregoing paragraph. In some versions, such compositions consists essentially of chitosan lacking lactate moieties, condensed tannin lacking sulfonate moieties, an active agent consisting essentially of any one or more of an indole alkaloid and a phenethylamine, and, optionally, one or more additional ingredients that do not materially affect one or more of the characteristics outlined above. In some versions, such compositions are in the form of a film or a foam.

Methods of making the compositions of the invention can comprise mixing the chitosan, the tannin, and the active agent in a solvent to form a mixture and drying the mixture to form the composite composition. The solvent preferably comprises at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w of a polar protic solvent. Exemplary polar protic solvents include water, alcohols such as methanol, ethanol, and isopropyl alcohol, acetic acid, formic acid, nitromethane, and combinations thereof. To generate films of the invention, the drying can be performed at room temperature or in an oven. The drying may be performed with or without a vacuum to aid in drying efficiency. To generate foams of the invention, the drying can be performed by freeze-drying.

In some versions, the films can be produced by continuous extrusion onto a moving surface and/or in large pans that are subjected to forced-air drying or vacuum-assisted drying. The drying can be done on a moving bed following continuous extrusion.

The mixture preferably has a pH from about 4 to about 7.5, such as about 5.0 to about 6.5.

The chitosan, tannin, and active agent employed in the methods can include any type of chitosan, tannin, or active agent described herein in any amount and/or relative weight ratio.

The mixture can include other elements or components, such as any other type of element or component described herein.

The invention also provides methods of administering an active agent to a subject. The methods can comprise a composition as described herein to the subject. In some versions, the administering comprises orally administering the composition to the subject. In some versions, the oral administration comprises oral mucosal administration. Oral mucosal administration is administration in which an active agent is applied to the oral mucosa, diffuses through the oral mucosa, and enters directly into the bloodstream. Oral mucosal administration comprises buccal administration. In some versions, the composition is in the form of a film, wherein the film is placed in the subject's mouth and permitted to dissolve in the subject's mouth without the need to swallow the composition intact. In some versions, the administering comprises parenterally administering the composition. In some versions, the composition is in the form of a hydrogel and the composition is administered by injection.

As used herein, "polymer subunit" refers to a repeating subunit or type of subunit that makes up a given polymer.

U.S. Pat. No. 10,104,888 is incorporated herein by reference in its entirety.

The compositions of the invention can consist essentially or consist of any one or more elements described herein as being comprised by the compositions of the invention.

The elements and method steps described herein can be used in any combination whether explicitly described or not.

All combinations of method steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

As used herein, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise.

Numerical ranges as used herein are intended to include every number and subset of numbers contained within that range, whether specifically disclosed or not. Further, these numerical ranges should be construed as providing support for a claim directed to any number or subset of numbers in that range. For example, a disclosure of from 1 to 10 should be construed as supporting a range of from 2 to 8, from 3 to 7, from 5 to 6, from 1 to 9, from 3.6 to 4.6, from 3.5 to 9.9, and so forth.

All patents, patent publications, and peer-reviewed publications (i.e., "references") cited herein are expressly incorporated by reference to the same extent as if each individual reference were specifically and individually indicated as being incorporated by reference. In case of conflict between the present disclosure and the incorporated references, the present disclosure controls.

It is understood that the invention is not confined to the particular construction and arrangement of parts herein illustrated and described, but embraces such modified forms thereof as come within the scope of the claims.

EXAMPLES

Example 1

Chitosan-Tannin Composite Films

Background

Fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in the gastrointestinal tract and first-pass effects can be avoided. The present examples provide chitosan-tannin composite films containing active agents. The films are suitable for use for buccal administration of the active agents.

CHT-TAN Composite Films—Thickness

The purpose of study was to determine the effect of total volume and effect of chitosan-tannin concentration on film thickness. Results indicate that smaller volumes cast into molds result in thinner films and that lower concentrations of chitosan and tannins in similar volumes result in thinner films.

Chitosan (CHT) stock solutions of 5 and 10 mg/mL low molecular weight were prepared by dissolving CHT (>98.0% deacetylated, Product No. C-M-95-401132, Lot No. 351821, ChitoLytic, Ontario, Canada) in acetic acid (0.5% v/v). Stock solutions of tannins (TAN) (quebracho extract, TAN'ACTIVE QS-SOL, Silvateam, Wilton, CT) of 5 and 10 mg/mL were prepared in ethanol. CHT-TAN composite solutions were prepared as follows: the TAN stock solution was added to the CHT stock solution under continuous stirring for 10 min at a weight ratio of 90:10 (CHT:TAN). The mixture was left under constant mechanical stirring for 20 min at room temperature.

Volumes of 10, 20, and 30 mL of the CHT-TAN composite solutions were added to a silicon mold (7.9×5.6×2.5 cm). The samples were placed in an oven at 36° C. for 48 hours. After drying, samples were kept in a desiccator for long term storage. See Table 1.

TABLE 1

	Chitosan (CHT)			Tannin (TAN)		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
Chitosan 5 mg/mL CHT:TAN 90:10 Volume 10 mL 0.03 mm	5.0	9.0	45.0	5.0	1.0	5.0
Chitosan 5 mg/mL CHT:TAN 90:10 Volume 20 mL 0.03 mm	5.0	18.0	90.0	5.0	2.0	10.0
Chitosan 5 mg/mL CHT:TAN 90:10 Volume 30 mL 0.05 mm	5.0	27.0	135.0	5.0	3.0	15.0
Chitosan 10 mg/mL CHT:TAN 90:10 Volume 10 mL 0.03 mm	10.0	9.0	90.0	10.0	1.0	10.0
Chitosan 10 mg/mL CHT:TAN 90:10 Volume 20 mL 0.05 mm	10.0	18.0	180.0	10.0	2.0	20.0
Chitosan 10 mg/mL CHT:TAN 90:10 Volume 30 mL 0.08 mm	10.0	27.0	270.0	10.0	3.0	30.0

CHT-TAN Composite Films—Acid Effect

CHT stock solutions of 10 mg/mL low molecular weight CHT (>98.0% deacetylated, Product No. C-M-95-401132, Lot No. 351821, ChitoLytic, Ontario, Canada) were prepared by dissolving CHT in acetic acid (0.5% v/v). A stock solution of TAN (10.0 mg/mL) (quebracho extract, TAN'ACTIVE QS-SOL, Silvateam, Wilton, CT) was prepared in ethanol. CHT-TAN composite solutions were prepared as follows: First, the pH of the CHT solutions were adjusted to 4.0, 4.5, 5.0, 5.5, or 6.0 using 1M NaOH or 1M HCl. Then, the TAN stock solution was added to the CHT stock solutions at the different pH levels under continuous stirring for 10 min at a weight ratio of 90:10 (CHT:TAN). The mixture was left under constant mechanical stirring for 20 min at room temperature.

The CHT-TAN composite solutions were added to a silicon mold (7.9×5.6×2.5 cm) and placed in an oven at 36° C. for 48 hours. After dried, samples were kept in a desiccator for long term storage. See Table 2.

TABLE 2

	Chitosan (CHT)			Tannin (TAN)		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
CHT:TAN (90:10) pH 4.0	10.0	27.0	270.0	10.0	3.0	30.0
CHT:TAN (90:10) pH 4.5	10.0	27.0	270.0	10.0	3.0	30.0
CHT:TAN (90:10) pH 5.0	10.0	27.0	270.0	10.0	3.0	30.0
CHT:TAN (90:10) pH 5.5	10.0	27.0	270.0	10.0	3.0	30.0
CHT:TAN (90:10) pH 6.0	10.0	27.0	270.0	10.0	3.0	30.0

The films were evaluated subjectively for flexibility and fragility. Films in the lower pH range (4, 4.5) were fragile and less desirable than at the higher pH ranges.

Sucralose Loading of CHT-TAN Composite Films

CHT stock solutions of 10 mg/mL low molecular weight was prepared by dissolving CHT (>98.0% deacetylated, Product No. C-M-95-401132, Lot No. 351821, ChitoLytic, Ontario, Canada) in acetic acid (0.5% v/v). A stock solution of TAN (40.0 mg/mL) (quebracho extract, TAN'ACTIVE QS-SOL, Silvateam, Wilton, CT) was prepared in ethanol, and stock solution of sucralose (1.0 and 20.0 mg/mL) were prepared in water. CHT-TAN composite solutions were prepared as follows: the TAN stock solution was added to the CHT stock solution under continuous stirring for 10 min at a weight ratio of 90:10 (CHT:TAN), then the sucralose solution was added to the mixture while stirring continuously to constitute 0.03% w/w, 0.10% w/w, 0.20% w/w, 0.83% w/w, 1.66% w/w, 2.50% w/w, 3.33% w/w, and 5.00% w/w of the combined total of the chitosan, tannin, and sucralose. Then, the CHT-TAN composite solutions were added to a silicon mold (7.9×5.6×2.5 cm). The mold was placed in an oven at 36° C. for 48 hours. After dried, samples were kept in a desiccator for long term storage. See Table 3.

TABLE 3

	Chitosan (CHT)			Tannin (TAN)			Sucralose		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
CHT:TAN (90:10) 0.0% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	1.0	0	0
CHT:TAN (90:10) 0.03% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	1.0	0.1	0.1
CHT:TAN (90:10) 0.1% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	1.0	0.3	0.3
CHT:TAN (90:10) 0.2% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	1.0	0.6	0.6
CHT:TAN (90:10) 0.83% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	20.0	0.125	2.5
CHT:TAN (90:10) 1.66% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	20.0	0.250	5.0
CHT:TAN (90:10) 2.50% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	20.0	0.375	7.5
CHT:TAN (90:10) 3.33% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	20.0	0.500	10.0
CHT:TAN (90:10) 5.00% Sucralose	10.0	27.0	270.0	10.0	3.0	30.0	20.0	0.750	15.0

Example 2

Melatonin-Loaded Chitosan-Tannin Composite Films

Melatonin Loading of CHTL-TAN Composite Films

A stock solution of chitosan lactate (CHTL) (>95.0% deacetylated, Product No. AL-10131, Lot No. 22022) at 10 mg/mL was prepared in water. Stock solutions of different preparations of tannin (TAN) at 10 mg/mL were prepared in ethanol. The TAN preparations were quebracho extract (TAN'ACTIVE QS-SOL, Silvateam, Wilton, CT), grape seed extract (GSE) (TAN'ACTIVE GUT, Batch: 010417, Silvateam, Wilton, CT), and cranberry proanthocyanidin extract (cPAC) prepared using common methods known in the art. A stock solution of melatonin at 50.0 mg/mL was prepared in ethanol. CHTL-TAN composite solutions were prepared as follows: TAN stock solution was added to the CHTL stock solution under continuous stirring for 10 min at a weight ratio of 90:10 (CHTL:TAN). Then, the melatonin solution was added to the mixture while stirring continuously (yielding 7.00% w/v of the solution). Volumes of 30 mL of the CHTL-TAN composite solutions were added to a silicon mold (7.9×5.6×2.5 cm). The samples were placed in an oven at 36° C. for 3 days. See Table 4.

TABLE 4

	Chitosan Lactate (CHTL)			Tannin (TAN)			Melatonin		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
CHTL:TAN (90:10) 0 mg of Melatonin Quebracho	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatonin Quebracho	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6
CHTL:TAN (90:10) 0 mg of Melatonin Grape Seed Extract	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatcnin Grape Seed Extract	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6
CHTL:TAN (90:10) 0 mg of Melatonin Cranberry PAC	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatonin Cranberry PAC	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6

The chitosan lactate and quebracho tannin+/−melatonin resulted in undesirable film characteristics (FIG. **1**, left column, and FIG. **2**). The films stuck to the mold, the melatonin was not homogeneously dispersed through film, and the films fractured. These observations were unexpected, as the source of tannins and chitosan was not expected to have an impact the ability to form stable films. Quebracho tannins are sulfonated during the extraction and production process. We predict the sulfur substitution with the chitosan lactate results in brittle film characteristics. Chitosan lactate is a water soluble chitosan ingredient, the pH of the chitosan lactate in solution and the interaction with the sulfonated tannins could also be responsible for the brittle films.

The chitosan lactate and grapeseed extract+/−melatonin and the chitosan lactate and cranberry proanthocyanidins+/−melatonin resulted in more desirable film characteristics in that the films were not brittle. (FIG. **1**, center and right columns, and FIG. **3**). However even these formulations stuck to the silicone molds. It is predicted that the chitosan lactate (pH) drove the interactions with the mold. For this reason, we moved away from both chitosan lactate and sulfonated tannins as present in the quebracho tannin as less desirable ingredients.

Strip Dissolution in Water and Quantification of Melatonin Release

Melatonin-loaded CHTL-TAN films as prepared above were removed from the silicon mold to yield strips of film. Each strip was placed individually in a beaker containing 10 mL of dd water and submitted to a slight stirring (100 rpm). Dissolution time was defined as the time at which the strip started to disappear. Results are shown in Table 5.

TABLE 5

CHTL-TAN Film	Dissolution Time (min)
CHTL-TAN (quebracho)	4
CHTL-TAN (quebracho) with melatonin	5
CHTL-TAN (GSE)	3
CHTL-TAN (GSE) with melatonin	3

The released melatonin after dissolution was quantified. After dissolution of the film, an aliquot of the sample (200 ul) was taken, and the concentration of the released melatonin was determined by HPLC-DAD. The HPLC solvents employed were 0.1% (v/v) trifluoroacetic acid/water (solvent A) and 0.1% (v/v) acetonitrile (solvent B). Results are shown in FIGS. **10-17**. Comparisons are shown in FIGS. **4-9**.

Melatonin Loading of the CHTL-TAN Composite Films—Effect of pH

A stock solution of chitosan lactate (CHTL) (>95.0% deacetylated, Product No. AL-10131, Lot No. 22022) at 10 mg/mL was prepared in water. Stock solutions of tannin (TAN) (grape seed extract (GSE), TAN'ACTIVE GUT, Batch: 010417, Silvateam, Wilton, CT) at 10 mg/mL was prepared in ethanol. A stock solution of melatonin at 50.0 mg/mL was prepared in ethanol. CHTL-TAN composite solutions were prepared as follows: First, the pH of the CHT solution was adjusted to 4.0, 5.0, or 5.5 100 mg/mL sodium acetate. Then, TAN stock solution was added to the CHTL stock solution under continuous stirring for 10 min at a weight ratio of 90:10 (CHTL:TAN). Then, the melatonin solution was added to the mixture while stirring continuously. Volumes of 30 mL of the CHTL-TAN composite solutions were added to a silicon mold (7.9×5.6×2.5 cm). The samples were placed in an oven at 36° C. for 3 days. See Table 6.

TABLE 6

	Chitosan Lactate (CHTL)			Tannin (TAN)			Melatonin		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
CHTL:TAN (90:10) 0 mg of Melatonin pH 4.0	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatonin pH 4.0	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6
CHTL:TAN (90:10) 0 mg of Melatonin pH 5.0	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatonin pH 5.0	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6
CHTL:TAN (90:10) 0 mg of Melatonin pH 5.5	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Melatonin pH 5.5	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6

All films were fragile, and they are stuck to the silicone mold. It was impossible to extract the films without breaking them. This was likely the result of the chitosan lactate. This experiment was focused on GSE. We eliminated quebracho tannins because they were not a good tannin source. The use of GSA with chitosan lactate was better but still resulted in fragile films, again, likely due to the chitosan lactate.

Example 3

Psilocybin-Loaded Chitosan-Tannin Composite Films

The objective of this example was to show that psilocybin can be incorporated into chitosan-tannin composite hydrogel solutions, cast into molds, form stable flexible thin films after drying, and release psilocybin upon dissolution in water.

Chitosan-Tannin (CHT-TAN) Psilocybin Films

A stock solution of chitosan (CHT) (>98.0% deacetylated, Product No. C-M-95-401132, Lot No. 351821, ChitoLytic, Ontario, Canada) at 10 mg/mL was prepared in acetic acid (0.5% v/v). A stock solution of tannin (TAN) (grape seed extract (GSE), TAN'ACTIVE GUT, Batch: 010417, Silvateam, Wilton, CT) at 10 mg/mL was prepared in ethanol. CHT-TAN composite solutions were prepared as follows: TAN stock solution was added to the CHT stock solution under continuous stirring for 10 min at a weight ratio of 10-90 TAN to CHT. Then, psilocybin solutions (see below) were added to the mixture while stirring continuously. Volumes of 30 mL of the CHT-TAN solutions with or without psilocybin was added to a silicon mold (7.9×5.6×2.5 cm). The samples were placed in an oven at 36° C. for 72 hours. See Table 7.

TABLE 7

	Chitosan Lactate (CHTL)			Tannin (TAN)			Psilocybin
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Total (mg)
Film 1 CHTL-TAN-Psilocybin 0 mg Psilocybin	10.0	27.0	270.0	10.0	3.0	30.0	0
Film 2 CHTL-TAN-Psilocybin 7.6 mg Psilocybin	10.0	27.0	270.0	10.0	3.0	30.0	7.6
Film 3 CHTL-TAN-Psilocybin 9 mg Psilocybin	10.0	27.0	270.0	10.0	3.0	30.0	9
Film 4 CHTL-TAN-Psilocybin 20 mg Psilocybin	10.0	27.0	270.0	10.0	3.0	30.0	20
Film 5 CHTL-TAN-Psilocybin 20 mg Psilocybin	10.0	27.0	270.0	10.0	3.0	30.0	20

Psilocybin for Film 2 was dissolved in 200 μL of ethanol. Psilocybin for Film 3 was dissolved in 400 μL of CHT-TAN solution. Psilocybin for Film 4 was dissolved in 200 of high purity water. Psilocybin for Film 5 was dissolved in 200 μL of ethanol. Films 1-5 are shown in FIG. **18**.

Chitosan-Tannin (CHT-TAN) Psilocybin Film Dissolution

The films were each placed in a beaker containing 50 mL of dd-water or 50 mL of 5% ethanol and 1% acetic acid in water and submitted to a slight stirring (100 rpm). After dissolution, the concentration of psilocybin in solution was determined by HPLC-DAD.

HPLC method: Samples are analyzed on an analytical HPLC with the following conditions.

Column: Acclaim120 C8, 5 μm, 250×4.6 mm+appropriate pre-column

Column Temperature: Controlled at 25° C.

Injection Volume: 10 μL

Flow Rate: 1.0 mL/min

Run Time: 16 min

Mobile Phase: 95% Solvent A (1% (v/v) acetic acid)+5% Solvent B (Ethanol)

Technique: Isocratic Elution

Detector Wavelength: 269 nm

Calculations: The HPLC raw data was reported in mg/mL psilocybin in the diluted assay solution. This value was converted to % (w/w) psilocybin in the original formulation using the following calculation where Vol. is the volume of the volumetric flask in which the assay sample was diluted, Mass is the sample mass that is added to the volumetric flask, and Raw Conc. is the HPLC result.

Equation: Final Conc. % (w/w)=Raw Conc. (mg/mL)*Vol. (mL)/Mass (mg)*100%.

Example calculation: Psilocybin 100% (w/w)=0.05 mg/mL*100 mL/5 mg*100%.

Acceptance criteria: The correlation coefficient of the standard curve must be ≥0.995.

A psilocybin reference standard was analyzed by HPLC-DAD method. Results showed that psilocybin elutes at 6.0 minutes.

A CHT-TAN placebo solution (without psilocybin) was analyzed by HPLC-DAD method. Results showed placebo peaks at 1.8, 6.5 and 24.7 minutes.

A CHT-TAN placebo solution spiked with psilocybin (0.01 mg/mL) was analyzed by HPLC-DAD method. Results showed the psilocybin peak (5.9 minutes) separates and is identifiable from placebo peaks at 1.8, 6.5 and 24.7 minutes.

HPLC results for Film 2 (7.6 mg psilocybin) are shown in FIGS. **19**A and **19**B. HPLC results for Film 3 (9 mg psilocybin) are shown in FIGS. **20**A and **20**B. HPLC results for Film 4 (20 mg psilocybin) are shown in FIGS. **21**A and **21**B. The results show the psilocybin peak (5.8 minutes) separates and is identifiable and quantifiable from closest placebo peak at 6.4 minutes The theoretical amount of psilocybin loaded into Film 4 was 20 mg, and the recovery of psilocybin in the dissolved solution from Film 4 as

determined by HLPC was 20.3 mg. HPLC results for Film 5 (20 mg psilocybin) are shown in FIGS. **22**A and **22**B. The results show the psilocybin peak (5.8 minutes) separates and is identifiable and quantifiable from closest placebo peak at 6.4 minutes The theoretical amount of psilocybin loaded into Film 5 was 20 mg, and the recovery of psilocybin in the dissolved solution from Film 5 as determined by HLPC was 18.2 mg.

Conclusions

Psilocybin (dissolved in water or ethanol) can be incorporated into chitosan-tannin hydrogel solutions, cast into molds, and dried to create a flexible thin film. The film can be dissolved in water (<5 minutes). Psilocybin is released and recovery is 101% with the film in which psilocybin was initially dissolved in water and 91% with the film in which psilocybin was initially dissolved in ethanol. We predict it is possible to solubilize the tannin ingredient in an aqueous ethanol (e.g. 50%, 40%, 30% v/v) solution as opposed to 100% ethanol. We predict it is possible to dry the films as a higher temperature for shorter time duration.

Example 4

Serotonin-Loaded Chitosan-Tannin Composite Films

Serotonin Loading of CHT-TAN Composite Films

A stock solution of chitosan (CHT) (>98.0% deacetylated, Product No. C-M-95-401132, Lot No. 351821, ChitoLytic, Ontario, Canada) at 10 mg/mL was prepared in acetic acid (0.5% v/v). A stock solution of tannin (TAN) (grape seed extract (GSE), TAN'ACTIVE GUT, Batch: 010417, Silvateam, Wilton, CT) at 10 mg/mL was prepared in ethanol. A stock solution of serotonin at 50.0 mg/mL was prepared in water. CHT-TAN composite solutions were prepared as follows: TAN stock solution was added to the CHT stock solution under continuous stirring for 10 min at a weight ratio of 90:10 (CHT:TAN). Then, the serotonin solution was added to the mixture while stirring continuously (yielding 7.00% w/v of the solution). Volume of 30 mL of the CHTL-TAN composite solutions was added to a silicon mold (7.9×5.6×2.5 cm). The samples were placed in an oven at 36° C. for 3 days. See Table

TABLE 8

	Chitosan Lactate (CHT)			Tannin (TAN)			Serotonin		
	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)	Conc. (mg/mL)	Vol. (mL)	Total (mg)
CHTL:TAN (90:10) 0 mg of Serotonin	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0	0
CHTL:TAN (90:10) 22.6 mg of Serotonin	10.0	27.0	270.0	10.0	3.0	30.0	50.0	0.452	22.6

Chitosan-Tannin (CHT-TAN) Serotonin Film Dissolution

A complete film of approximately 400 mg weight was placed in a beaker containing 100 mL of dd-water and submitted to a slight stirring (100 rpm). At 30, 60, 120, 180, 240, 300, 450, 600, 900, 1200, and 1800 seconds, 500 uL of the dissolution medium was taken and replaced with an equal volume of fresh dd-water. The concentration of Serotonin was determined by HPLC-DAD.

A standard curve of serotonin in solution is shown in FIG. **23** and Table 9.

TABLE 9

Serotonin (ug/mL)	AUC
5	721300
10	1677639
30	4946028
40	6643911
50	7030060

HPLC chromatograms are shown in FIGS. **24**A and **24**B. The theoretical amount of serotonin loaded into the films were 22.6 mg, and the recovery of serotonin in two samples of dissolved film solutions as determined by HLPC were 21.8 mg (−3.4 percent error) and 23.3 (2.8 percent error). Quantitation of serotonin in solution at each timepoint is shown in FIG. **25**.

What is claimed is:

1. A composite composition comprising chitosan lacking lactate moieties, condensed tannin lacking sulfonate moieties, and an active agent, wherein:

the chitosan lacking lactate moieties has a number average molecular weight of from 125 kDa to 500 kDa;

the tannin lacking sulfonate moieties has a weight average molecular weight of from 100 Da to 10,000 Da;

the chitosan lacking lactate moieties and the tannin lacking sulfonate moieties are present in a weight ratio of the chitosan lacking lactate moieties-to-the tannin lacking sulfonate moieties of from 85:15 to 99:1;

the active agent is selected from the group consisting of serotonin, melatonin, psilocybin, and any combination thereof;

the active agent is present in the composition in an amount of from 0.001 mg to 500 mg;

the composition is in a form of a film; and

the film dissolves in saliva within 4.5 minutes.

2. The composition of claim **1**, wherein the composition dissolves in saliva within 2 minutes.

3. A method of administering an active agent to a subject, the method comprising orally administering the composition of claim **1** to the subject.

4. The method of claim **3**, wherein the administering comprises oral mucosal administration of the composition to the subject.

5. The method of claim **3**, wherein the composition dissolves in a mouth of the subject within 2 minutes.

6. The composition of claim **1**, wherein the chitosan lacking lactate moieties has a number average molecular weight of from 200 Da to 350 kDa.

7. The composition of claim **1**, wherein the chitosan is a fungal chitosan.

8. The composition of claim **1**, wherein the active agent is serotonin.

9. The composition of claim **1**, wherein the active agent is melatonin.

10. The composition of claim **1**, wherein the active agent is psilocybin.

11. The composition of claim **1**, wherein the active agent is present in the composition in an amount of from 0.1 mg to 250 mg.

12. The composition of claim **1**, wherein the active agent is present in the composition in an amount of from 0.1 mg to 30 mg.

13. The composition of claim **1**, wherein the chitosan lacking lactate moieties and the tannin lacking sulfonate moieties are present in a weight ratio of the chitosan lacking lactate moieties-to-the tannin lacking sulfonate moieties of from 85:15 to 95:5.

14. The composition of claim **13**, wherein the chitosan lacking lactate moieties has a number average molecular weight of from 200 Da to 350 kDa.

15. The composition of claim **14**, wherein the chitosan is a fungal chitosan.

16. The composition of claim **15**, wherein the active agent is serotonin.

17. The composition of claim **15**, wherein the active agent is melatonin.

18. The composition of claim **15**, wherein the active agent is psilocybin.

19. The composition of claim **15**, wherein the active agent is present in the composition in an amount of from 0.1 mg to 250 mg.

20. The composition of claim **15**, wherein the active agent is present in the composition in an amount of from 0.1 mg to 250 mg.

* * * * *