(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 August 2017 (10.08.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/132752 A1

(51) **International Patent Classification**:
A61K 9/70 (2006.01) *A61K 47/30* (2006.01)
A61K 31/553 (2006.01) *A61P 25/18* (2006.01)
A61K 47/10 (2017.01) *C07D 267/18* (2006.01)

(21) **International Application Number**:
PCT/CA2017/050072

(22) **International Filing Date**:
25 January 2017 (25.01.2017)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
15/014,269 3 February 2016 (03.02.2016) US

(71) **Applicant**: **INTELGENX CORP.** [CA/CA]; 6420 Abrams, St-Laurent, Québec H4S 1Y2 (CA).

(72) **Inventors**: **BILAL, Mobarik**; 9052 Clark, Montreal, Québec H2N 1R8 (CA). **OBEID, Rodolphe**; 895 Rue Muir, Apt. 408, St-Laurent, Québec H4L 5P4 (CA). **PAIEMENT, Nadine**; 2244 Equateur, St-Laurent, Québec H4R 3M4 (CA).

(74) **Agent**: **BERESKIN & PARR LLP/S.E.N.C.R.L., S.R.L.**; 40th Floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/132752 A1

(54) **Title**: LOXAPINE FILM ORAL DOSAGE FORM

(57) **Abstract**: A loxapine film oral dosage form includes loxapine salt, free base, or prodrug in an amount effective to provide relief from acute agitation associated with schizophrenia or bipolar 1 disorder via oral transmucosal delivery, dispersed in a polymeric film forming system. Advantageously, the film oral dosage form further includes a sweetener, a refreshing agent, an antioxidant, a pH stabilizer, a penetration enhancer, a mucoadhesive agent and a plasticizer. The loxapine film oral dosage form provides rapid onset of relief from acute agitation associated with schizophrenia or bipolar 1 disorder without presenting pulmonary health risks, thereby reducing risks to patients and others.

LOXAPINE FILM ORAL DOSAGE FORM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority from U.S. application no. 15/014,269 filed on February 3, 2016, which is hereby incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] This disclosure relates to loxapine dosage forms that provide rapid onset of therapeutic relief from acute agitation associated with schizophrenia or bipolar 1 disorder.

BACKGROUND OF THE DISCLOSURE

[0003] Agitation associated with schizophrenia or bipolar mania is not uncommon, and if left untreated can rapidly escalate into physically aggressive behavior that can be potentially dangerous to the agitated individual and others. In a clinical setting agitation associated with schizophrenia and bipolar mania are often effectively managed with behavioral and psychological techniques, with unexpected acute agitation typically being treated with parenterally administered sedatives such as benzodiazepines and/or antipsychotic drugs such as olanzapine and ziprasidone.

[0004] On December 21, 2012, the U.S. Food and Drug Administration approved a loxapine product formulated into an inhaled powder for direct administration to the lungs and is indicated for the treatment of acute agitation associated with schizophrenia or bipolar 1 disorder in adults. A statistically significant reduction in agitation occurs at 2 hours, and an improvement is achieved at 10 minutes after administration. The onset of a statistically significant reduction in agitation occurs at 5 minutes. However, to mitigate the risk of bronchospasm, inhaled loxapine powder must be administered only in an enrolled healthcare facility, and only to patients that have been prescreened to ensure they are not susceptible to pulmonary issues.

[0005] Loxapine oral capsules have been available for the treatment of schizophrenia since about 1988, with the typical dosage being 30-50 mg twice daily. The loxapine capsules are unsuitable for treating acute agitation associated with schizophrenia or bipolar 1 disorder because

onset of therapeutic relief occurs approximately 20-30 minutes after administration. Such delayed onset of relief would significantly increase the risk of injury to a person being treated and those administering treatment.

[0006] There are patients that have been successfully treated for schizophrenia or bipolar 1 disorder so that they can be released from clinical supervision. Nevertheless, there remains a possibility that intermittent acute agitation can occur, such as when the patient fails to take prescribed antipsychotic medication or engages in risky behavior such as indulging in intoxicants. It has been found that such patients feel symptoms of impending acute agitation, and that such acute agitation can be averted if the patient is immediately medicated with loxapine upon feeling symptoms.

[0007] A fast acting loxapine dosage form that can be used to effectively treat acute agitation associated with schizophrenia or bipolar 1 disorder in non-institutionalized patients while reducing the risk of pulmonary problems is needed. Such dosage form would substantially reduce risks of violence and injury to patients and others by preventing or reducing the duration and severity of an episode of acute agitation.

SUMMARY OF THE DISCLOSURE

[0008] Disclosed is a loxapine film oral dosage form that provides rapid onset of relief from acute agitation associated with schizophrenia or bipolar 1 disorder without exposing patients to bronchospasm or other life threatening complications and without requiring prescreening of patients for pulmonary or other issues. The disclosed loxapine oral dosage form has the further advantage that it can be safely administered either in a clinical facility or outside of a clinical facility.

[0009] The disclosed loxapine dosage forms are formulated as orally administered films comprising loxapine salt, free base, or prodrug disposed within or on a polymeric film suitable for oral administration. The films can be formulated for rapid disintegration and distribution of micro- or nano-scopic particles of the active agent in the gastrointestinal tract or as mucoadhesive films that facilitate rapid absorption of loxapine via oral mucosal tissue, i.e., buccal or sublingual film dosage forms.

[0010] Also disclosed is a process for treating or ameliorating acute agitation associated with schizophrenia or bipolar 1 disorder by administering to such patients in need of treatment a loxapine film oral dosage form as described herein.

[0011] These and other features, advantages and objects of the various embodiments will be better understood with reference to the following specification and claims.

DETAILED DESCRIPTION

[0012] The films comprising loxapine salt, prodrug, or free base disposed in or on a polymeric film-forming system can beneficially include a refreshing agent, a sweetener, a permeation enhancer, an antioxidant, a pH stabilizer or pH stabilizing system, or a combination of two or more of the foregoing components.

[0013] Loxapine has the IUPAC name 2-chloro-11-(4-methylpiperazin-1-yl) dibenzo [b,f] [1,4] oxazepine. It is predominantly used as an antipsychotic medication for the treatment of schizophrenia and bipolar 1 disorder. Such medications are currently sold under the tradenames "Loxapac" and "Loxitane." An inhalable form, sold under the tradename "Adasuve" is indicated for the rapid treatment of acute agitation associated with schizophrenia or bipolar 1 disorder, but is limited to clinical use in approved facilities on prescreened patients that are not susceptible to pulmonary problems.

[0014] Pharmaceutically acceptable salts that may be used in the film dosage forms disclosed herein include generally any salt that has been or may be approved by the US FDA or other appropriate foreign or domestic agency for administration to a human. Non-limiting examples include hydrochloric, hydrobromic, nitric, carbonic, monohydrocarbonic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric acid, sulfuric acid, a hydrogen sulfuric acid, and hydroiodic acids of loxapine. Other examples include salts derived from nontoxic organic acids, including acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, and methanesulfonic acids, or combinations of these acid salts.

[0015] Pharmaceutically acceptable prodrugs that may be used in the film dosage forms disclosed herein include any pharmaceutically acceptable compounds that react *in vivo* to produce loxapine. Examples of loxapine prodrugs include the phosphonooxymethyl prodrugs of loxapine described in Krise et al., J. Pharm. Sci. (1999) 88:922.

[0016] The active loxapine agent can comprise about 2% to 25% or 5% to 20% of the weight of the film on a dry basis.

[0017] The polymeric film forming system can comprise a single pharmaceutically acceptable film-forming polymer or a combination of film-forming polymers. Examples of film-forming polymers that can be used for preparing the disclosed loxapine dosage forms include polyethylene oxide, povidone (polyvinylpyrrolidone), copovidone (copolymers of N-vinyl-2-pyrrolidone and vinyl acetate), polyvinyl alcohol, polyethylene glycol, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, polydextrose, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragancath gum, guar gum, acacia gum, arabic gum, starch and gelatin.

[0018] The selection of film-forming polymers can be made to dissolve completely over a period of time that is sufficient to ensure delivery of a therapeutically effective amount of loxapine via oral mucosa, yet not so long as to cause annoyance or discomfort to the subject being administered loxapine. For example, a film dosage form can be formulated to reside in the buccal cavity or sublingual region for a period of from 1 minute to an hour, 10 minutes to 30 minutes, or 15 minutes to 30 minutes. There is a high variation from 1 minute to an hour from subject to subject.

[0019] The film-forming polymer or combination of film-forming polymers can comprise 10% to 90%, 20% to 80% or 30% to 70% of the weight of the film oral dosage form on a dry basis. Povidone (polyvinylpyrrolidone) can be present in an amount of from 3% to 50% by weight of the film on a dry basis.

[0020] Because of the taste of loxapine, which is generally perceived as unpleasant, it is beneficial to add a sweetener, flavoring agent, refreshing agent, taste-masking agent, or a combination of these materials. Examples of sweeteners that can be used in the disclosed loxapine film dosage forms include acesulfame potassium, aspartame, aspartan-acesulfame salt, cyclamate, erythritol, glycerol, glycyrrhizin, hydrogenated starch hydrolysate, isomalt, lactitol, maltitol, mannitol, neotame, polydextrose, saccharin, sorbitol, sucralose, tagatose, xylitol, dextrose, glucose, fructose, and honey. Flavoring agents that can be added to the disclosed loxapine film dosage forms include isoamyl acetate (banana flavor), benzaldehyde (cherry flavor), cinnamaldehyde (cinnamon flavor), ethyl propionate (fruit flavor), methyl anthranilate

(grape flavor), limonene (orange flavor), ethyl decadienoate (pear flavor), allyl hexanoate (pineapple flavor), ethyl meltol, ethylanillin (vanilla flavor), and methyl salicylate (wintergreen flavor). Refreshing agents, also called cooling agents, are chemicals that trigger the cold sensitive receptors creating a cold sensation. Refreshing agents that can be added to the loxapine film oral dosage forms disclosed herein include menthol, thymol, camphor and eucalyptol.

[0021] Sweeteners, flavoring agents, and refreshing agents can be added in conventional quantities, generally up to a total amount of 5% to 10% of the weight of the film on a dry basis, e.g., 0.1% to 10%, or 0.5% to 5%.

[0022] The loxapine film oral dosage forms disclosed herein can advantageously employ an antioxidant or oxygen scavenger to prevent or reduce oxidative degradation of the loxapine salt, free base or prodrug prior to use. Examples of oxygen scavengers or antioxidants that substantially improve long-term stability of a loxapine film oral dosage form against oxidative degradation of the active agent are sulfite salts such as sodium sulfite, sodium bisulfite, sodium metabisulfite and analogous salts of potassium and calcium.

[0023] A suitable amount of salt (e.g., sodium sulfite) is from about 0.01% to 5% or 0.1% to 1% of the weight of the film on a dry basis.

[0024] It was discovered that absorption of loxapine through oral mucosa is significantly enhanced when the film formulation is maintained at a neutral pH of from 6 to 8, or 6.5 to 7.5. Because the blend of film forming polymers and other ingredients tend to create an acidic pH, it is beneficial to add an alkaline substance that increases the pH of the film product and stabilizes the film at a neutral pH. Examples of pH stabilizers that can be added to the films disclosed herein include bicarbonates (e.g., sodium bicarbonate), citrates (e.g., potassium citrate), carbonates (e.g., calcium carbonate), lactates (e.g., sodium lactate), and acetates (e.g., calcium acetate).

[0025] Sodium bicarbonate or other pH stabilizers can be added to the loxapine film oral dosage forms disclosed herein in amounts effective to stabilize the pH within a range of from 6 to 8 or 6.5 to 7.5, with a suitable amount being, for example, 0.5% to 10% or 1% to 5% based on the weight of the film on a dry basis.

[0026] To further promote absorption of loxapine salt, free-base or prodrug through oral mucosa and reduce the amount of loxapine that is introduced into the gastrointestinal tract, it is advantageous to add to the loxapine film formulation a penetration enhancer. It has been

discovered that a particularly effective penetration enhancer that promotes absorption of loxapine via oral mucosa is hyaluronic acid or salts thereof. A penetration enhancer, such as hyaluronic acid or bile salt, can be added to the loxapine film oral dosage form in an amount of from about 0.1% to about 10%, 0.5% to 5%, or 1% to 3% of the weight of the film dosage form on a dry basis to significantly enhance absorption of loxapine from the film through oral mucosa.

[0027] In order to promote adhesion of the loxapine film oral dosage form to oral mucosa, it is advantageous to add a mucoadhesive agent to the film product. Examples of mucoadhesive agents that can be added to the loxapine film oral dosage form to promote adhesion to oral mucosa include sodium alginate, sodium carboxymethyl cellulose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, karya gum, methylcellulose, polyethylene oxide, retene and tragacanth. Such mucoadhesive agent may be added to the film formulation in an amount of from about 0.5% to about 20%, or about 1% to about 5%, of the total weight of the film on a dry basis.

[0028] Plasticizers can be advantageously employed in the film formulations as needed to suitably modify the flexibility of the film to facilitate processing and allow the film to easily conform to the shape of the oral mucosa to which the film is applied. Plasticizers that can be effectively employed in the disclosed loxapine film oral dosage forms to improve flexibility of the film include ethylene glycol, propylene glycol, tributyl citrate, triethyl citrate and glycerol. Depending on the selected film-forming polymers and other components of the film formulation, a suitable amount of plasticizer is typically from about 0.1% to 10%, 0.5% to 5%, or 1% to 5%.

[0029] Bulking agents or fillers may be added as desired to increase the size of the finished film product to facilitate processing and manufacturing, or to modify properties (e.g., increase or decrease residence time or increase stiffness) of the film formulation. Suitable fillers that can be added to the disclosed film products include starch, calcium salts, such as calcium carbonate, and sugars, such as lactose. The amount of fillers that can be added to the film oral dosage forms disclosed herein are typically up to about 25%, 0.5% to 20%, 1% to 15% or about 2% to about 10% of the weight of the film on a dry basis.

[0030] The loxapine film oral dosage forms disclosed herein can be prepared by dissolving or finely dispersing the loxapine salt, free base or prodrug and film forming polymers in a solvent, along with any other desired additives, including, but not limited to a pH stabilizer, an antioxidant, a plasticizer, a penetration enhancer, a mucoadhesive agent, a flavoring agent, a

coloring agent, a freshening agent, a sweetener, a filler, or a combination of additives. The films may then be cast on a suitable substrate by removing (e.g., evaporating) the solvent or solvents from the formulation to produce a dry film. Typically, the loxapine film can be cast to produce a film having a thickness of from 100 micrometers to 1.5 millimeters or 500 micrometers to 1000 micrometers. The dry film can be cut in appropriate sizes, typically an area of from about 1 square centimeter to about 15 square centimeters, to provide an appropriate dose for transmucosal delivery of loxapine salt, free base, or prodrug, to treat acute agitation associated with schizophrenia or bipolar 1 disorder.

[0031] In accordance with a particular aspect of this disclosure it is beneficial to provide a film dosage form that concurrently maintains a neutral pH while keeping the loxapine fully or nearly completely dissolved. Unfortunately, the solubility of loxapine is especially low at or near neutral pH. However, it has been discovered that by employing methanol and/or ethanol as a solvent or cosolvent during preparation of a loxapine film, and using povidone (polyvinylpyrrolidone) as a film-forming polymer in the formulation in an amount of from 5% to 50% or 10% to 40% by weight of the film on a dry basis, it is possible to concurrently add a pH stabilizer to maintain neutral pH while maintaining the loxapine in a highly dissolved form, thereby promoting rapid transmucosal absorption and rapid onset of a desirable therapeutic effect. It is believed that the addition of polyethylene glycol (plasticizer) and sodium hyaluronate (penetration enhancer) also significantly contribute to rapid absorption and onset of a desired therapeutic effect.

[0032] The following Examples are illustrative of the present invention:

Example 1

Ingredients	% wet (w/w)	% dry (w/w)	Function
Water	22.7	-	Solvent
Methanol	53.1	-	Solvent
Sodium Bicarbonate	0.5	2.2	pH stabilizer
Sodium sulfite	0.1	0.4	antioxidant
Polyethylene Glycol	1.2	5.0	plasticizer
Sodium taurodeoxycholate	0.6	2.6	penetration enhancer
Polyethylene Oxide	1.5	6.1	mucoadhesive
Loxapine succinate	2.1	8.8	active
L-Menthol	0.1	0.6	freshening agent and taste masking agent
Sucralose	0.2	0.8	sweetener
Calcium Carbonate	1.7	7.0	filler
Povidone	4.9	20.4	film-former
Hydroxypropyl cellulose	11.2	46.1	film-former
Total	100.0	100.0	

Example 2

Ingredients	% wet (w/w)	% dry (w/w)	Function
Water	22.7	-	Solvent
Methanol	53.0	-	Solvent
Sodium Bicarbonate	0.5	2.2	pH stabilizer
Sodium sulfite	0.1	0.4	antioxidant
Polyethylene Glycol	1.2	5.0	plasticizer
Sodium Hyaluronate	0.6	2.5	penetration enhancer
Polyethylene Oxide	1.5	6.1	mucoadhesive
Loxapine succinate	3.3	13.7	active
L-Menthol	0.1	0.6	freshening agent and taste masking agent
Sucralose	0.2	0.8	sweetener
Calcium Carbonate	1.7	7.0	filler
Povidone	4.9	20.3	film-former
Hydroxypropyl cellulose	10.1	41.4	film-former
Total	100.0	100.0	

Example 3

Ingredients	% wet (w/w)	% dry (w/w)	Function
Water	23.0	-	Solvent
Methanol	53.8	-	Solvent
Sodium Bicarbonate	0.6	2.6	pH stabilizer
Butylated Hydroxytoluene	0.01	0.02	antioxidant
Polyethylene Glycol	1.3	5.5	plasticizer
Polyethylene Oxide	1.8	7.6	mucoadhesive
Sodium metabisulfite	0.01	0.2	antioxidant
Loxapine succinate	3.7	15.7	active
L-Menthol	0.4	1.6	Permeation enhancer and refreshing agent
Sucralose	0.2	0.9	sweetener
FD&C Blue No 2	0.02	0.1	Colorant
Povidone	5.0	21.7	film-former
Hydroxypropyl cellulose	10.2	44.1	film-former
Total	100.00	100.00	

Example 4

Ingredients	% wet (w/w)	% dry (w/w)	Function
Methanol	74.1	-	Solvent
Sodium Bicarbonate	0.6	2.2	pH stabilizer
Sodium bisulfite	0.1	0.2	antioxidant
Triacetin	3.3	12.7	plasticizer
Copovidone	1.7	6.7	film-former
Loxapine succinate	3.0	11.6	active
L-Menthol	0.3	1.1	Permeation enhancer and refreshing agent
Sucralose	0.3	1.1	sweetener
Povidone	5.4	21.1	film-former
Hydroxypropyl cellulose	11.2	43.3	film-former
Total	100.0	100.0	

Example 5

Ingredients	% wet (w/w)	% dry (w/w)	Function
Ethanol	71.8	-	Solvent
Water	8.0	-	Solvent
Sodium Bicarbonate	0.5	2.6	pH stabilizer
Sodium metabisulfite	0.04	0.2	antioxidant
Glycerin	0.8	3.9	plasticizer
Copovidone	1.6	7.9	film-former
Loxapine succinate	2.9	14.5	active
Sucralose	0.3	1.3	sweetener
L-Menthol	0.2	1.1	Permeation enhancer and refreshing agent
Povidone	5.9	29.1	film-former
Hydroxypropyl cellulose	8.0	39.4	film-former
Total	100.0	100.0	

Example 6

Ingredients	% wet (w/w)	% dry (w/w)	Function
Water	22.7	-	Solvent
Methanol	53.0	-	Solvent
Sodium Bicarbonate	0.6	2.2	pH stabilizer
Sodium metabisulfite	0.1	0.4	antioxidant
Polyethylene Glycol	1.2	5.0	plasticizer
Sodium glycodeoxycholate	0.6	2.5	penetration enhancer
Polyethylene Oxide	1.5	6.1	mucoadhesive
Loxapine succinate	3.3	13.7	active
L-Menthol	0.1	0.6	freshening agent and taste masking agent
Sucralose	0.2	0.8	sweetener
Calcium Carbonate	1.7	7.0	filler
Povidone	10.1	41.4	film-former
Hydroxypropyl cellulose	4.9	20.3	film-former
Total	100.0	100.0	

Example 7

Ingredients	% wet (w/w)	% dry (w/w)	Function
Water	64.5	-	Solvent
Ethanol	10.0		Solvent
Sodium taurodeoxycholate	0.7	2.6	penetration enhancer
Polyethylene Glycol	1.3	5.2	plasticizer
Sodium bicarbonate	0.7	2.6	pH stabilizer
Hypromellose	5.0	19.4	film-former
Hypromellose	1.3	5.3	film-former
Polyethylene Oxide	10.8	42.3	film-former
Loxapine succinate	5.3	21.0	active
Evospray Lime Flavor	0.4	1.6	Flavoring agent
Total	100.0	100.0	

[0033] The above description is considered that of the preferred embodiment(s) only. Modifications of these embodiments will occur to those skilled in the art and to those who make or use the illustrated embodiments. Therefore, it is understood that the embodiment(s) described above are merely exemplary and not intended to limit the scope of this disclosure, which is defined by the following claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

IN THE CLAIMS

1. A loxapine film oral dosage form, comprising:
    a. loxapine salt, free base, or prodrug in an amount that is effective to provide relief from acute agitation associated with schizophrenia or bipolar 1 disorder via transmucosal delivery route; and
    b. a polymeric film forming system including at least one film forming polymer.

2. The loxapine film oral dosage form of claim 1, further comprising a sweetener.

3. The loxapine film oral dosage form of claim 1, further comprising a refreshing agent.

4. The loxapine film oral dosage form of claim 1, further comprising an antioxidant.

5. The loxapine film oral dosage form of claim 1, further comprising a pH stabilizer.

6. The loxapine film oral dosage form of claim 1, further comprising a penetration enhancer.

7. The loxapine film oral dosage form of claim 1, further comprising a mucoadhesive agent.

8. The loxapine film oral dosage form of claim 1, further comprising a plasticizer.

9. The loxapine film oral dosage form of claim 1, in which the polymeric film-forming system comprises povidone in an amount of from 3% to 50% by weight of the film on a dry basis.

10. The loxapine film oral dosage form of claim 9, further comprising sulfite salts in an amount effective to promote the stability of the film.

11. The loxapine film oral dosage form of claim 10, further comprising polyethylene glycol

in an amount effective to increase the flexibility of the film.

12. The loxapine film oral dosage form of claim 11, further comprising sodium hyaluronate or sodium taurodeoxychlate and/or sodium glycodeoxycholate in an amount effective to promote enhanced absorption of loxapine via mucosal tissue.

13. A process of preparing a loxapine film oral dosage form, comprising:
    a. dissolving/suspending loxapine salt, free base or prodrug and a polymeric film forming system in a solvent to produce a film formulation;
    b. dispersing the film formulation on a substrate;
    c. removing the solvent from the film formulation to produce a dry film; and
    d. cutting the film into individual dosage forms.

14. The process of claim 13, in which the solvent comprises methanol and/or ethanol.

15. The process of claim 13, in which the solvent comprises a combination of methanol and/or ethanol and water.

16. The process of claim 14, in which the polymeric film-forming system comprises povidone (polyvinylpyrrolidone) in an amount of from 3% to 50% by weight of the film on a dry basis.

17. The process of claim 16, further comprising adding polyethylene glycol to the film formulation in an amount effective to increase the flexibility of the film.

18. The process of claim 17, further comprising adding sodium hyaluronate or sodium taurodeoxychlate and/or sodium glycodeoxycholate to the film formulation in an amount effective to promote enhanced absorption of loxapine via mucosal tissue.

19. The loaxapine film oral dosage form of claim 18, further comprising sulfite salts in an amount effective to promote the stability of the film.

20. The loxapine film oral dosage form of any one of claims 1 to 12 and 19 for use in treatment of schizophrenia or bipolar 1 disorder.

21. Use of loxapine in the manufacture of an oral film dosage form to treat or alleviate the effects of schizophrenia or bipolar 1 disorder.