

A Comprehensive Review on API Risperidone and Pharmaceutical Formulations

Mohammed Rizwan¹ and Nasreen Sultana^{1,2}

Student, B.Pharm, Dr. V. R. K. Institute of Pharmaceutical Sciences, Hyderabad, India ¹

*Associate Professor, Department of Pharmaceutics

Dr. V.R.K. Institute of Pharmaceutical Sciences, Hyderabad, India ¹.

YNClinit Research Institute, Mehdiapatnam, Hyderabad, India ².

Abstract: *The present review emphasizes about API (active Pharmaceutical Ingredient) Risperidone, is a atypical antipsychotic medication widely known for prescribing for autism disorder and schizophrenia condition. This API available in market as pharmaceutical products solutions and tablets (oral disintegrating tablets) for immediate action and also as long acting formulations such as IM (intramuscular) & SC (subcutaneous) shots, transdermal patches, microspheres and their preparation methods and its physico-chemical properties along with its common side effects and adverse events are briefed*

Keywords: Risperidone, immediate release, long acting, side effects

I. INTRODUCTION

Risperidone is an atypical antipsychotic drug recommended for schizophrenic and autism condition. In this article we emphasize on the physical, chemical properties. Its mechanism of action and side effects in detail along with the pharmaceutical formulations and its preparation methods which are briefed as below.

Classification: -

Risperidone is classified as an **atypical (second-generation) antipsychotic** drug. It works primarily by antagonizing (blocking) dopamine D2 and serotonin 5-HT_{2A} receptors in the brain, helping to balance these neurotransmitters and regulate mood, thoughts, and behaviour.

Risperidone's Properties:

1. Absorption in the Body (BCS Class II): Risperidone is classified as "**low solubility**" and "**high permeability**."

Low Solubility: This means the drug **does not easily dissolve** in water (or in your stomach/intestine fluids).

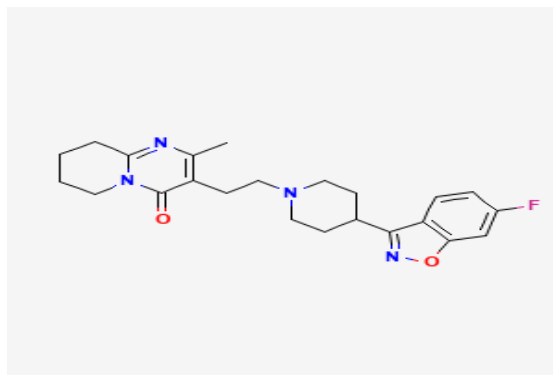
High Permeability: This means that **once it does dissolve**, it easily passes through the gut lining into your bloodstream.

Description: -

A medication used to treat many different types of mood disorders. (Schizophrenia, Bipolar disorder & Autism Spectrum disorder).



Structure: -



Weight:

Avg. 410.48

Chemical formula:

$C_{23}H_{27}FN_4O_2$

Categorized under: (Therapeutic)

Antipsychotic Agents.

Second generation (Atypical)

Mechanism:

Acts on 5-hydroxy-tryptamine receptor 2A (Blocks) → {Antagonist}.

Acts on D2 dopamine receptor (Antagonist).

About Schizophrenia & Disorders:

They are caused by an excess of release of dopaminergic D2 & serotonergic 5-HT_{2A} resulting in overactivity of central nervous system that transmits dopamine (Mesolimbic System) & mesocortical pathway (Major Dopaminergic Pathway).

Risperidone binds with a very high affinity to 5-HT_{2A} receptors & D2 receptors and reduce the overactivity through inhibition of D2 (Dopaminergic) & 5-HT_{2A} receptors (Serotonergic) in the brain.

It has High Binding affinity for 5-HT_{2A} when compared to D2 receptors {5-HT_{2A} > D2} → Binding Strength.

Both serotonergic {5-HT_{2A}} & Dopaminergic {D2} are thought to synergistically work to decrease the risk of extrapyramidal Symptoms (Side effects).

Absorption:

Well absorbed.

Bioavailability: 70 %.

The relative oral bioavailability from a tablet is 94% compared to a solution.

Volume of distribution:

1 to 2 L/Kg.

Protein binding:

Risperidone & its active metabolite 9-hydroxyrisperidone are 88 % & % Protein bound in human plasma respectively.

They each bind to both Serum albumin & alpha-1 acid glycoprotein.

Metabolism:

Extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyrisperidone.

Risperidone also undergoes N-dealkylation to a lesser extent.

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Key process in drug metabolism, breaking down N-alkyl groups containing drugs into smaller metabolites.
N-alkyl groups - Methyl or ethyl group.

Route of elimination:

Risperidone is extensively metabolized in the liver.

Half-life:

3 hours in extensive metabolizers.

20 hours in poor metabolizers.

Clearance:

Risperidone is cleared by kidneys.

Toxicity:

Overdose leads to lethargy, dystonia/spasm, tachycardia, bradycardia & seizures.

Mechanism in action: -

This is how risperidone usually works:

Risperidone's main job is to help balance two key brain chemicals: **Dopamine** and **Serotonin**. Schizophrenia is often associated with too much activity from these chemicals in certain brain areas.

1. Dopamine Control (D2 Receptors)

The Problem: Too much dopamine activity (specifically at **D2 receptors**) is linked to the **positive symptoms** of schizophrenia, like **hallucinations** and **delusions**.

Risperidone's Solution: Risperidone temporarily **inhibits** (blocks) these D2 receptors, which reduces the excess dopamine signaling and helps decrease those positive symptoms.

The Key Difference (Less Side Effects): Unlike older antipsychotics that block D2 receptors strongly and permanently, risperidone binds with **loose affinity** and **dissociates rapidly** (it quickly let's go). This prevents the blockage from being too intense or long-lasting, which significantly **reduces the risk of severe movement side effects** called **Extrapyramidal Symptoms (EPS)**.

2. Serotonin Control (5-HT_{2A} Receptors)

The Problem: Increased serotonin activity (at **5-HT_{2A} receptors**) is linked to the **negative symptoms** of schizophrenia, such as **depression** and **lack of motivation**.

Risperidone's Solution: Risperidone strongly **blocks** these 5-HT_{2A} receptors, which reduces the excess serotonin activity and helps improve the negative symptoms.

The Bonus (More Protection): Blocking 5-HT_{2A} receptors is also thought to help by slightly **increasing dopamine release** in a different area of the brain (the frontal cortex). This counteracts the strong D2 blockage and provides *further protection against those movement side effects (EPS)*.

The way risperidone balances both the **transient D2 blockage** and the **strong 5-HT_{2A} blockage** is thought to work *together (synergistically)* to effectively treat the symptoms of schizophrenia while keeping the risk of severe movement side effects low.

Evaluation (Therapeutic Use and Efficacy): -

Risperidone is widely used for treating various psychiatric conditions and has proven efficacy for:

Schizophrenia: Acute and maintenance treatment in adults and adolescents (age 13 and older). It is effective for both positive (e.g., hallucinations, delusions) and negative (e.g., flat affect, social withdrawal) symptoms.

Bipolar I Disorder: Short-term treatment of acute manic or mixed episodes (as monotherapy or adjunctively with lithium or valproate) in adults and children/adolescents (age 10 and older).

Irritability Associated with Autistic Disorder: Treatment of symptoms like aggression, deliberate self-injuriousness, and temper tantrums in children and adolescents (age 5 and older).



Formulations: -

I. Forms You Take by Mouth (Oral)

Standard Pills (Immediate-Release Tablets): Just a regular pill you swallow.

Liquid Medicine (Oral Solution): A liquid (like 1 mg/mL) that's good for people who **can't or won't swallow pills**.

Melting Tablets (Orally Disintegrating Tablets - ODT): These **dissolve very quickly** on the tongue. They are great for people who have **trouble swallowing** or might try to hide/spit out a regular pill.

II. Forms Given by Injection (Long-Acting)

These are special shots given by a doctor/nurse that last a long time, helping people **not have to take a pill every day**.

Intramuscular (IM) Shots: Given into a **muscle** (like every two weeks).

Subcutaneous (SubQ) Shots: Given **under the skin** (like once a month or less frequently).

TABLE I Risperidone forms and its recommendations

Risperidone Form	Main Benefit	Recommendations
Standard Pill	Easy, flexible dosing.	Starting treatment to find the right dose, or for reliable, compliant patients who don't mind taking a pill every day.
Liquid Solution	Easy to swallow.	For children, elderly, or patients who struggle to swallow pills.
Melting Tablet (ODT)	Dissolves instantly in the mouth.	For patients with severe difficulty swallowing or those who might resist, spit out, or hide regular pills.
Long-Acting Injection (LAI)	Lasts for weeks (improves compliance).	For maintenance treatment in patients who have trouble remembering or refuse to take daily pills, as this greatly reduces the risk of relapse (getting sick again).

Transdermal patches of Risperidone: -

They are primarily a subject of pharmaceutical research & development & are not a widely available, FDA-approved commercial product at this time. The risperidone medication itself is a commonly prescribed oral or injectable antipsychotic.

Risperidone is a second-generation antipsychotic used to treat:

Schizophrenia in adults & adolescents.

Acute manic or mixed episodes associated with bipolar-I disorder, in adults & in children at least 10 years old.

Irritability associated with autistic disorder in children & adolescents aged 5-16 yrs.

Transdermal Patches aim to provide a steady, controlled release of medication, avoiding the peaks & troughs of oral dosing & offering a potential alternative to frequent injections or daily pills, which can improve patient compliance.

Side effects: -

The side effects of Risperidone delivered via a Transdermal Patch are expected to be similar to the other forms of medication, as it is the same active substance. Side effects range from common to serious.

Common side effects: -

Drowsiness, Sleepiness (or) Fatigue.

Headache.

Movement Problems (e.g., Muscle stiffness, Restlessness).



Dizziness.

Nausea, Vomiting, Stomach Pain (or) Constipation.

Increased appetite & weight gain.

Stuffy or runny nose, Sore throat.

Increased Prolactin levels, which may lead to breast enlargements, nipple discharge, or irregular menstrual periods

Serious side effects:

Neuroleptic Malignant Syndrome (NMS): A rare but potentially fatal reaction with symptoms including high fever, severe muscle stiffness, confusion & changes in heart rate or breathing.

Tardive Dyskinesia (TD): Uncontrolled, repetitive movements of the face, tongue or other body parts that may become permanent.

Metabolic changes: Increase blood sugar levels (hyperglycemia) or cholesterol & significant gain of total weight, which increases the risk of diabetes or heart problems.

Increased risk of death in elderly patients with dementia-related Psychosis: Risperidone is not approved for this use & carries a boxed warning from the FDA due to this risk.

Priapism: A painful erection that lasts for more than four hours.

Signs of allergic reaction: Rash, itching, hives, swelling of the face, lips, tongue, or throat, or difficulty breathing.

Methods of Preparation: -

Method 1: making a quick- dissolving tablet (melt granulation)

(Based on the formulation of Risperidone Sublingual Tablet): This method creates small, drug-containing granules using a melted ingredient as a “glue”. These granules are then pressed into a tablet that dissolves quickly under the tongue (sublingual), allowing the drug to bypass the digestive system for faster absorption.

Steps:

1) Prepare the “Glue”: Gently heat a solid binder like a low- melting sugar or wax) until it melts into a liquid state. This melted material will act as a temporary “glue” to hold the drug particles together.

2) Mix and Granulate: Add the drug (e.g., Risperidone) and other ingredients (to help it dissolve quickly) into the melted binder and mix thoroughly. This process creates small, uniform clumps called granules.

3) Solidify and Sieve: Allow the mixture to cool completely, which causes the ‘glue’ to solidify. Then, break the solid material into uniform, small particles by pushing them through a sieve. This ensures every final tablet has the exact amount of drug.

4) Press the Tablet: The finished granules are fed into a machine and compressed (pressed) into the final tablet shape. This gives the tablet its strength for handling while maintaining its ability to dissolve rapidly under the tongue.

Method 2: Making a drug solubility enhancer (solid dispersion)

(Based on the solubility enhancement of risperidone). If the drug (like risperidone) does not dissolve well in body fluids, this method mixes it with a highly water-soluble material (carrier) to form a solid dispersion. This process makes the drug particles extremely small and exposed, drastically speeding up how fast it dissolves once ingested.

Steps:

1) solubilization: Dissolve both the drug and water-loving carrier material (e.g., Poloxamer, PEG, or PVP) in a common liquid (solvent). This ensures the drug is broken down to its molecular level and fully mixed with the carrier.

2) Remove the Liquids: Rapidly remove the solvent. This can be done by letting it evaporate or by using a spray-drying technique. Removing the liquid leaves behind a solid mass where the drug is finely trapped within the highly water-soluble carrier.



3) Grind the Solid: Grind the resulting solid into fine powder. This powder is the solid dispersion. When it is consumed, the carrier dissolves instantly, releasing the drug in an extremely fine state, allowing it to dissolve and be absorbed much faster than the original drug powder.

Method 3: Making a skin patch (Solvent evaporation)

Based on the Carvedilol Transdermal Patch): This method creates a thin, flexible, medicated film that sticks to the skin. The drug (Carvedilol) is delivered directly through the skin into the bloodstream at a controlled, slow rate, which is necessary to avoid the drug being metabolized too quickly by the liver.

Steps:

1) **Create the ‘Patch Liquid’:** Mix the drug, a main polymer (to create the film), and a permeation enhancer (to help the drug cross the skin) in a suitable solvent until everything is fully dissolved. The polymer creates the structure, and the permeation enhancer helps the drug move through the skin layers.

2) **Evaporate the Solvent:** Allow the liquid (solvent) to evaporate slowly and completely under controlled conditions. As the solvent leaves, the drug and polymers remain, forming a dry, thin, and flexible film- this is the medicated reservoir of the transdermal patch.

3) **Caste the Flim:** Pour the uniform “Patch Liquid” onto a flat, non-stick surface or mold. This controls the thickness and surface area of the final patch.

4) **Finish and Apply:** Peel off the dry film, cut it into the required size, and apply an appropriate adhesive layer (if needed). This final product is designed to release the drug continuously and slower for a long-term therapeutic effect.

Microspheres of Risperidone: -

Risperidone microspheres (brand names such as Risperdal Consta, Rykindo, Perseris, and Risvan) are long-acting injectable medications used to treat schizophrenia and bipolar disorder.

Risperidone microspheres are a long-acting formulation designed to provide a sustained, steady release of medication over a period of weeks (typically two weeks to two months, depending on the specific product), which helps improve patient adherence to treatment compared to daily oral pills.

Side effects: -

Common side effects: -

Drowsiness, Sleepiness (or) Fatigue.

Headache.

Movement Problems (e.g., Muscle stiffness, Restlessness).

Dizziness.

Nausea, Vomiting, Stomach Pain (or) Constipation.

Increased appetite & weight gain.

Stuffy or runny nose, Sore throat.

Increased Prolactin levels, which may lead to breast enlargements, nipple discharge, or irregular menstrual periods

Serious side effects:

Neuroleptic Malignant Syndrome (NMS): A rare but potentially fatal reaction with symptoms including high fever, severe muscle stiffness, confusion & changes in heart rate or breathing.

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Increased risk of death in elderly patients with dementia-related Psychosis: Risperidone is not approved for this use & carries a boxed warning from the FDA due to this risk.

Priapism: A painful erection that lasts for more than four hours.

Signs of allergic reaction: Rash, itching, hives, swelling of the face, lips, tongue, or throat, or difficulty breathing.



Methods of Preparation: -

The complex laboratory process of making drug microspheres can be broken down into educational steps

Method 1: The crosslinked polymer “sponge” method

This method uses a natural polymer to form a shell around the drug, then locks that shell in place using chemical hardeners (crosslinkers)

1) The Primary Mix

Action: The drug and the primary polymer (chitosan) are dissolved together in an inner solvent. The mixture is then blended vigorously into a large amount of oil.

Educational Concept: This is called Emulsification (W/O/W). It creates tiny droplets of the drug polymer mixture suspended in the oil phase. The polymer acts as the main material for the future particle.

2) The Drying and Gelling

Action: The mixture is heated to evaporate the inner solvent, which causes the polymer to condense. A “gelling” chemical (like Sodium Tripolyphosphate) and a second chemical hardener (Glutaraldehyde) are then added.

Educational Concept: This combines Solvent Evaporation and Crosslinking. The solvent removal causes the polymer chains together to form a strong, stable “sponge” or shell around the drug.

3) The Clean-up

Action: The hardening microspheres are collected, washed thoroughly with chemicals, excess solvents, and drug that didn't get encapsulated, ensuring only the pure, drug-filled micro-particles remain.

Method 2: The solvent “Drizzle” method

This method relies on the rapid evaporation of a volatile solvent instantly solidify the drug and polymer into a micro-particle.

1) The Dissolving Mix

Action: The drug (Risperidone) and the main polymer (Ethyl Cellulose, EC) are dissolved together in volatile, fast-drying solvent (like Dichloromethane, DCM).

This creates the Oil Phase in an Oil-In-Water (O/W) Emulsification. All the core materials (drug + polymer) are dissolved in the volatile organic solvent.

2) The Dispersion

Action: This “Oil Phase” solution is poured into a large amount of water that contains a stabilizer polymer and a surfactant. The entire mixture is stirred rapidly.

This step achieves Stabilization and Emulsion. The rapid stirring breaks the oil into tiny droplets in the water. The stabilizing agents in the water act as ‘traffic cops’ to stop the tiny drug/polymer droplets from sticking back together.

3) The Hardening

Action: Continuous stirring is maintained until fast-drying solvent (DCM) is completely evaporated into the air.

Educational Concept: This is Solidification by Evaporation. As the solvent leaves the tiny droplets, the drug and polymer have no choice but to precipitate and harden into solid, spherical microspheres.

4) The Cleanup

Action: The solid microspheres are filtered out of the water, washed, and dried.

This is the final Purification step to get the ready-to-use controlled-release powder.

Extended-Release Risperidone Formulation: -

Risperidone extended-release (ER) tablets are primarily used to treat schizophrenia and bipolar I disorder, and to manage irritability associated with autism.

Risperidone is an atypical antipsychotic medication that works by balancing dopamine and serotonin levels in the brain to improve mood, thoughts, and behaviour.



Side effects: -

Common side effects: -

Drowsiness, Sleepiness (or) Fatigue.

Headache.

Movement Problems observed as Muscle stiffness and Restlessness.

Dizziness.

Nausea, Vomiting, Stomach Pain, Constipation.

Increased appetite & weight gain.

Stuffy or runny nose, Sore throat.

Increased Prolactin levels, which may lead to breast enlargements, nipple discharge, or irregular menstrual periods

Serious side effects:

Neuroleptic Malignant Syndrome (NMS): A rare but potentially fatal reaction with symptoms including high fever, severe muscle stiffness, confusion & changes in heart rate or breathing.

Tardive Dyskinesia (TD): Uncontrolled, repetitive movements of the face, tongue or other body parts that may become permanent.

Metabolic changes: Increase blood sugar levels (hyperglycemia) or cholesterol & significant gain of total weight, which increases the risk of diabetes or heart problems.

Increased risk of death in elderly patients with dementia-related Psychosis: Risperidone is not approved for this use & carries a boxed warning from the FDA due to this risk.

Priapism: A painful erection that lasts for more than four hours.

Signs of allergic reaction: Rash, itching, hives, swelling of the face, lips, tongue, or throat, or difficulty breathing.

Method of preparation: -

The goal of extended- release is to make a drug last longer so you don't have to take it every day. This is achieved through two main product types: pills (mini-tablets) and injections

1) Oral Pills (Mini- Tablets) Preparations: "The Polymer Sponge"

Key idea: Mixing the drug with special, slow-dissolving materials called polymers (like a type of cellulose). These polymers act like a sponge.

Methods Summary (Wet Granulation):

Mix and wet: Mix the risperidone powder and the polymer powder with a small amount of liquid.

Force Granules: The mixture is mashed up and dries, forming small, dense grains (granules).

Compress: These uniform granules are pressed very hard into the final mini-tablet shape.

Result: Once swallowed, water slowly penetrates the polymer 'sponge', gradually dissolving and releasing the drug over 10 to 20 hours.

2) Long-Acting Injections (LIA) Preparations: "The Gelling Liquids"

This method is for creating a liquid that turns into a solid deposit under the skin, releasing the drug over a month.

Key ideas: The drug is put into a special liquid that contains a biodegradable carrier polymer.

Methods Summary (In-situ Gelling):

Form Liquid: The risperidone is dissolved in liquid containing the carrier polymer.

Inject: This ready-to-use liquid is injected under the skin (or muscle).

Solidify (The "Depot"): As soon as a liquid hits the body's tissues, the carrier polymer solidifies into tiny, solid drug deposit (a 'depot') at the injection site.

Results: The solid depot slowly breaks down inside the body over the next month, releasing the risperidone steadily. This means the patient only needs an injection once a month



II. CONCLUSION

In this review article we tried to summarize the applications, mechanisms, preparation methods and physico-chemical properties and other details of Risperidone drug of interest. This information may be useful to any researcher to find preliminary information to work on the API Risperidone and develop new formulation strategies.

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