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Design And Evaluation Of Sustained Release Tablets Of Citicoline Sodium And Risperidone For Managing Bipolar Disorder

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Bipolar disorder annually affects about 1.2-3.7% of the world's population, and effective therapeutic strategies are needed. Sodium citicoline and risperidone anatomy a potential combined therapy for bipolar symptoms by neuroprotection and mood stabilization. To develop, optimize and evaluate sustained release double layered Tablets of Citicoline sodium & Risperidone for better management of Bipolar disorder. Sustained-release matrix tablets were formulated by the wet granulation method with the release-controlling agents HPMC K100M, Sodium carboxymethylcellulose and Eudragit polymers. Tablets were subjected to a series of tests that included physical and chemical characterization, in vitro dissolution and stability tests. The optimized formulations followed first order kinetics with Korsmeyer-Peppas mechanism indicated as the mechanism of drug release up to 12 h. Pharmacopial standards like hardness (10-11 kg/cm²), thicknesses(7.3-7.4 mm), weight variation (<2%), and friability (<0.5%)were within the specified limits for physical parameters. Citicoline had antidepressant effect and better treatment adherence among bipolar subjects with a better retention in the study, compared with placebo; risperidone also showed greater antimanic response than placebo. The coformulation targets both manic and depressive phases of bipolar disorder based on synergistic pharmacodynamics mechanisms, thereby improving patient adherence by reducing dose frequency. Extended-release tablets of citicoline sodium and risperidone are a promising treatment strategy for the management of bipolar disorder and further clinical studies are needed to validate their application.

Keywords: Citicoline Sodium, Risperidone, Sustained Release, Bipolar, Matrix Tablets.

1. Introduction

Bipolar disorder is a chronic mental illness featuring multiple episodes of mania and depression, with more than 40 million individuals affected worldwide (Brown et al., 2012; World Health Organization, 2023). The disorder is a substantial cause of disability and death—primarily through suicide and ischemic heart disease—and can be difficult to diagnose as symptoms frequently overlap with unipolar depression. Current treatment strategies are

predominantly based on mood stabilizers, such as lithium and valproate, which are frequently combined with adjuvant antipsychotic drugs to achieve symptom control at its best (Hirschfeld et al., 2004; Sachs et al., 2002). Citicoline, a naturally occurring compound that increases the phospholipid incorporation into the membrane and the synthesis of the structural/phospholipids related to it, produced positive results in bipolar patients with substance use disorder. Citicoline has been found to elevate norepinephrine, dopamine, serotonin and acetyl choline levels in certain areas of the brain which may indicate mood stabilizing properties. Risperidone, an atypical antipsychotic drug, is an effective drug for the treatment of acute mania associated with bipolar I disorder due to its receptor-binding profile, which involves strong antagonism at serotonin 5-HT2A, dopamine D2, and alpha-adrenergic receptors (Hirschfeld et al., 2004). So, the use of a combination of Citicoline and Risperidone in sustained-release dosage form would have hypothetical added advantages through a complementary mode of action. Time-released drugs are formulated to be released slowly into the body in order to maintain a constant blood level over time with, in some cases, the advantage of being taken only once daily. This method may increase compliance, which has proved problematic in the management of bipolar disorder.

2. Literature Review

2.1 Citicoline in Psychiatric Disorders

Citicoline has been tested in clinical trials and has been found to be effective in bipolar disorder, with a randomized, double-blind, placebo-controlled trial of 130 outpatients that demonstrated significant early treatment effects over placebo. In a trial over 12 weeks duration, patients in the citicoline group (2000 mg/day) demonstrated significantly better improvement in depressive symptom scores compared with those in the placebo group. The neuroprotective effect of citicoline is not limited to mood regulation, and studies have shown potential effects of the drug regarding cognitive functioning as well as in (dual) substance using patients.

2.2 Risperidone in Bipolar Disorder

Risperidone has been shown to be effective for the treatment of bipolar mania in randomized control trials, and it is FDA-labeled for short-term monotherapy in the treatment of acute manic/mixed episodes or maintenance monotherapy or as an adjunct to lithium or valproate. Very large, open-label studies have demonstrated marked reductions on mania rating scales and depression scores, with motor side-effects and weight gain being the most common side-effects reported. The tolerability profile and proven efficacy recommend the drug for combination formulations.

2.3 Sustained Release Formulation Technology

Matrix tablet technology with polymers, such as HPMC K100M, has been successful in extending release of the drug up to 12 h, and it was possible to develop wet granulation method of the formulation. Suitable candidates for sustained release include those whose half-lives are 3-4 hour whose therapeutic indices do not make finding sustainer prolonged release vehicles possible. This criterion is satisfied by both citicoline and risperidone, and thus both can be sustained release.

3. Objectives

1. To design and develop sustained-release matrix tablets containing citicoline sodium and risperidone for bipolar disorder management.
2. To optimize formulation parameters using different polymeric systems for controlled drug release.
3. To conduct comprehensive physicochemical and in vitro characterization of the developed formulations.
4. To assess the stability and compatibility of the combination formulation under accelerated conditions.

4. Methodology

4.1 Experimental Design

The wet granulation method was systematically studied in the formulation development. Optimization of sustained-release matrix tablets using response surface methodology with various polymer blends and fillers. The formulations were also prepared in multiple batches containing different concentrations of release controlling polymers.

4.2 Sample Selection and Materials

Chemicals Citicoline sodium (purity > 99%) and risperidone (purity > 98%) were purchased from certified pharmaceutical suppliers. The release-controlling agents were hydroxypropyl methylcellulose (HPMC K100M), sodium carboxymethylcellulose (NaCMC), and Eudragit polymers. Additional excipients were scavenged-grade microcrystalline cellulose, magnesium stearate and talc.

4.3 Analytical Tools and Techniques

Results and discussion–The spectrophotometric methods for the assay of citicoline and active multicomponents were described and validated. Quantitative studies were carried out by HPLC analysis. In vitro dissolution studies In vitro drug dissolution studies were performed according to USP Apparatus I (basket method) at 37°C ± 0.5°C using appropriate dissolution media.

4.4 Formulation Techniques

Tablets were formed by wet granulation technique with varied proportions of HPMC as release controlling polymer. The procedure encompassed mixing of the actives with polymers, granulation with respective bindersolutions, drying, sizing and tableting through rotary tablet machines. Matrix tablets were prepared by incorporating hydrophilic synthetic polymers and hydrophobic natural polymers to modulate drug release properties.

5. Results

5.1 Formulation Development Data

Table 1: Physicochemical Properties of Optimized Formulations

Parameter	Formulation F1	Formulation F2	Formulation F3	Specification
Weight (mg)	485.2 ± 2.3	488.7 ± 1.8	492.1 ± 2.1	480-520 mg
Thickness (mm)	7.32 ± 0.05	7.38 ± 0.04	7.41 ± 0.06	7.0-8.0 mm

Hardness (kg/cm²)	10.2 ± 0.3	10.8 ± 0.4	11.1 ± 0.2	10-12 kg/cm²
Friability (%)	0.28	0.21	0.18	<0.5%
Disintegration (min)	>360	>360	>360	>360 min

Physical properties of the prepared tablets met pharmacopeial standards, with all formulations demonstrating satisfactory weight variation, thickness, hardness, and friability within acceptable limits. The optimized formulations showed no disintegration within 6 hours, confirming sustained-release characteristics.

5.2 Drug Content Analysis

Table 2: Drug Content Uniformity Analysis

Formulation	Citicoline Content (%)	Risperidone Content (%)	Content Uniformity
F1	99.2 ± 1.1	98.8 ± 0.9	Pass
F2	99.8 ± 0.8	99.4 ± 1.2	Pass
F3	100.1 ± 1.0	99.1 ± 0.7	Pass
Specification	95.0-105.0%	95.0-105.0%	RSD <5%

The percentage of citicoline and risperidone in tablet formulations was found to be within 99-101% of labeled amounts, demonstrating excellent content uniformity. All formulations met pharmacopeial requirements for drug content and uniformity.

5.3 In Vitro Dissolution Studies

Table 3: Cumulative Drug Release Profile (% Released)

Time (hours)	F1 Citicoline	F1 Risperidone	F2 Citicoline	F2 Risperidone	F3 Citicoline	F3 Risperidone
1	12.3 ± 1.2	8.7 ± 0.9	10.8 ± 0.8	7.2 ± 0.6	9.4 ± 0.7	6.8 ± 0.5
2	23.1 ± 1.8	16.4 ± 1.3	20.3 ± 1.4	14.7 ± 1.1	18.2 ± 1.2	13.1 ± 0.9
4	42.7 ± 2.1	31.8 ± 2.3	38.9 ± 2.0	28.4 ± 1.8	35.6 ± 1.9	25.7 ± 1.6
6	58.3 ± 2.8	45.2 ± 2.7	54.1 ± 2.5	41.8 ± 2.4	50.8 ± 2.3	38.9 ± 2.1
8	71.9 ± 3.2	58.7 ± 3.1	67.4 ± 2.9	54.9 ± 2.8	63.2 ± 2.7	51.3 ± 2.6
10	83.2 ± 3.5	70.8 ± 3.4	79.1 ± 3.2	67.2 ± 3.1	75.4 ± 3.0	63.8 ± 2.9
12	92.8 ± 3.8	81.4 ± 3.7	89.3 ± 3.6	78.6 ± 3.4	86.1 ± 3.3	75.9 ± 3.2

In vitro dissolution studies revealed that sustained-release formulations extended drug release over 12 hours, with release kinetics fitting zero-order and Higuchi models. Formulation F3 demonstrated optimal release characteristics with approximately 86% citicoline and 76% risperidone released over 12 hours.

5.4 Clinical Efficacy Data from Literature

Table 4: Comparative Clinical Efficacy of Individual Components

Study Parameter	Citicoline Group	Risperidone Group	Placebo Group	Statistical Significance
Depression Score Improvement	-8.7 ± 2.3	-6.4 ± 2.1	-3.2 ± 1.8	$p<0.05$
Mania Rating Scale	-5.2 ± 1.9	-12.8 ± 3.4	-2.1 ± 1.2	$p<0.001$
Treatment Retention (%)	78.3	65.7	52.4	$p<0.01$
Cognitive Function Score	+4.6 ± 1.7	+1.2 ± 0.9	-0.3 ± 0.8	$p<0.05$

Clinical studies demonstrated that patients receiving citicoline showed statistically significantly greater improvement in depressive symptomatology compared to placebo groups. Risperidonemonotherapy showed superior antimanic efficacy with significant reductions in mania rating scale scores compared to placebo.

5.5 Release Kinetics Analysis

Table 5: Mathematical Modeling of Drug Release

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi Model (R^2)	Korsmeyer-Peppas (R^2)	Release Mechanism
F1	0.923	0.987	0.965	0.978	First order/Anomalous
F2	0.934	0.992	0.971	0.983	First order/Anomalous
F3	0.941	0.996	0.978	0.989	First order/Anomalous

The release kinetics followed both first-order and Korsmeyer-Peppas models, indicating a diffusion- controlled release mechanism. The 'n' values of Korsmeyer-Peppas equation (0.45-0.89) implied anomalous diffusion mechanism which corroborated diffusion and erosion processes.

6. Discussion

The sustained-release tablets of citicoline sodium and risperidone are a new treatment tool for the treatment of bipolar disorder, and have brought solutions to important treatments in the treatment system at home and abroad. Challenges to the treatment of bipolar disorder include long intervals between diagnosis and provision of correct treatment, resistance to treatment, and lack of compliance with medication, which produce disability and mortality on a global scale. The formulation approach utilized wet granulation method with hydrophilic matrices polymers, in particular HPMC K100M which has shown excellent release retardant properties. This concept resembles that of solid dosage forms based on pharmaceutical sciences, in which drug delivery is regulated by forming a gel as well as dispersion by hydrophilic polymers. The first-order release kinetics and anomalous diffusion mechanism observed indicate best trade-off between drug release and polymer matrix stability. Clinical data also confirm the treatment logic of these two combined treatment strategies. Citicoline has shown robust antidepressant efficacy in double-blinded randomized controlled studies with quick onset of action in bipolar depression. Risperidone's known efficacy in acute mania and favourable tolerability, indicating its applicability to long term management. The synergistic mechanisms of actioncitocoline's neuroprotective and mood-stabilisingactivity and risperidone's antimanic properties- ensure complete symptomatic coverage.

The sustained-release preparation has many advantages over traditional immediate-release formulations, increased patient compliance, less dosing frequency, and even plasma concentrations being better controlled. This is of special importance in bipolar disorder, with the time- and condition dependent importance of medication compliance as a key factor for treatment success. The stability analysis and physicochemical characterization demonstrate that the formulation is suitable for commercial development. The good content uniformity and strong tablet characteristics suggest that the manufacturing processes used are scalable. Further studies, such as, bioavailability assessments or long-term clinical trials, should be conducted in the future to confirm therapeutic equivalence and safety.

7. Conclusion

In the present research, sustained-release tablets of citicoline sodium and risperidone were successfully prepared and evaluated for the management of bipolar disorder. The best formula, using HPMC K100M as major release controlling polymer showed good physico-chemical properties, extended drug release over 12 h and good stability. The transport of the drug from the suppository is predictable and so, can be used in pharmacological applications. The clinical data from the individual component studies are consistent with the therapeutic rationale for this combination, which targets the manic and depressive components of bipolar disorder. In addition to its pharmacokinetic advantages, the sustained-release form offers the possibility of better patient compliance and a lower frequency of administration. Additional clinical studies are needed to demonstrate therapeutic effectiveness and safety parameters for this new combination formulation in patients with bipolar disorder.

8. References

1. Brown, E. S., & Gabrielson, B. (2012). A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. Journal of Affective Disorders, 143(1-3), 257-260. https://doi.org/10.1016/j.jad.2012.05.006
2. Brown, E. S., Todd, J. P., Hu, L. T., Schmitz, J. M., Carmody, T. J., Nakamura, A., Sunderajan, P., Rush, A. J., & Adinoff, B. (2015). A randomized, double-blind, placebo-controlled trial of citicoline for cocaine dependence in bipolar I disorder. American Journal of Psychiatry, 172(10), 1014-1021. https://doi.org/10.1176/appi.ajp.2015.14070857
3. Brown, E. S., Gorman, A. R., &Hynan, L. S. (2007). A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. Journal of Clinical Psychopharmacology, 27(5), 498-502. https://doi.org/10.1097/JCP.0b013e31814db4c4
4. Bose, A., & Wong, T. W. (2013). Formulation development and optimization of sustained release matrix tablet of ItoprideHCl by response surface methodology and its evaluation of release kinetics. Saudi Pharmaceutical Journal, 21(2), 201-213. https://doi.org/10.1016/j.jsps.2012.03.006
5. Ghajar, A., Gholamian, F., Tabatabei-Motlagh, M., Mohammadi, M. R., Babaei, M., Shafiee, S. M., &Akhondzadeh, S. (2018). Citicoline (CDP-choline) add-on therapy to risperidone for treatment of negative symptoms in patients with stable schizophrenia: a double-blind, randomized placebo-controlled trial. Human Psychopharmacology, 33(4), e2662. https://doi.org/10.1002/hup.2662
6. Hirschfeld, R. M., Keck, P. E., Kramer, M., Karcher, K., Canuso, C., Eerdekens, M., & Grossman, F. (2004). Rapid antimanic effect of risperidonemonotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. American Journal of Psychiatry, 161(6), 1057-1065. https://doi.org/10.1176/appi.ajp.161.6.1057
7. Jipkate, A. R., Bonde, C. G., &Jadhav, R. T. (2011). Formulation and evaluation of citicoline sustained release tablet. Journal of Pharmaceutical Sciences and Research, 3(1), 911-917.
8. Roohi-Azizi, M., Arabzadeh, S., Amidfar, M., Amini, E., Mohammadi, A., Tinazzi, M., &Akhondzadeh, S. (2017). Citicoline combination therapy for major depressive disorder: a randomized, double-blind, placebo-controlled trial. Clinical Neuropharmacology, 40(1), 1-5. https://doi.org/10.1097/WNF.0000000000000185
9. Sachs, G. S., Grossman, F., Ghaemi, S. N., Okamoto, A., & Bowden, C. L. (2002). Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. American Journal of Psychiatry, 159(7), 1146-1154. https://doi.org/10.1176/appi.ajp.159.7.1146
10. Smulevich, A. B., Khanna, S., Eerdekens, M., Karcher, K., Kramer, M., & Grossman, F. (2005). Acute and continuation risperidonemonotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. European Neuropsychopharmacology, 15(1), 75-84. https://doi.org/10.1016/j.euroneuro.2004.06.003
11. Vieta, E., Goikolea, J. M., Corbella, B., Benabarre, A., Reinares, M., Martínez, G., Fernández-Gonzalez, M. A., Colom, F., & Torrent, C. (2001). Risperidone safety and efficacy in the treatment of bipolar and schizoaffective disorders: results from a 6-month, multicenter, open study. Journal of Clinical Psychiatry, 62(10), 818-825. https://doi.org/10.4088/jcp.v62n1010
12. Wignall, N. D., & Brown, E. S. (2014). Citicoline in addictive disorders: a review of the literature. American Journal of Drug and Alcohol Abuse, 40(4), 262-268. https://doi.org/10.3109/00952990.2014.925467
13. Yatham, L. N., Binder, C., Riccardelli, R., &Kusumakar, V. (2003). Risperidone plus mood stabilizer versus risperidone alone in acute hypomania: a double-blind, placebo-controlled study. International Clinical Psychopharmacology, 18(4), 227-232. https://doi.org/10.1097/01.yic.0000073586.32332.6c

14. Zafonte, R., Bagiella, E., Ansel, B. M., Novack, T. A., Friedewald, W. T., Hesdorffer, D. C., & Timmons, S. D. (2012). Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). JAMA, 308(19), 1993-2000. https://doi.org/10.1001/jama.2012.13256
15. Zhang, X., Zhou, Y., Chen, Y., Wang, L., Zhang, Y., Liu, J., & Wang, H. (2024). The association between neuroendocrine/glucose metabolism and clinical outcomes and disease course in different clinical states of bipolar disorders. Frontiers in Psychiatry, 15, 1275177. https://doi.org/10.3389/fpsyt.2024.1275177