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DevelopmentandIn-VitroEvaluation ofCiticolineSodium andRisperidoneControlled Release TabletsforBipolarDisorder

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ABSTRACT

Bipolardisorderposesmajortreatmentchallenges,whichdemandnoveldrugdeliverystrategiestoprovidethemosteffective treatmentwithminimalsideeffects.Theobjectivewastoprepareandevaluatecontrolledreleasetabletsofciticolinesodium and risperidoneforimprovedtreatmentinmanagementofbipolardisorder.Themultiparticulate(combinationtherapy)was prepared by wet granulation process with the matrix polymers hydroxypropyl methylcellulose (HPMC K100M) and ethyl cellulose. Nine formulations of different drug-to-polymer ratios were prepared and characterized. The technique included qualifying pre compression characteristics, post compression features, and in vitro dissolution studies employing USP Apparatus II. It was concluded from the results that formulation F7 with 30% HPMC and 60% ethyl cellulose showed best controlled releasing behavior i.e., 89.4% drug release at the end of 12 hours according to zero-order release kinetics. The drug'sreleaseprofilewasneutralpHindependentanduniformthroughouttherangeofmediatested.Releaseratewasfound to have comparable relationship with polymer concentration ($p<0.05$). The resulting formulation exhibited good bioavailability potential with less dosing frequency. This study successfully shows the potential of a controlled release combinationtherapyforbipolardisordertreatmenttoachievesustaineddrugrelease,leadingtoreducedsideeffects,and,in turn, enhance the treatment compliance and therapeutic efficacy

Keywords:Controlledrelease;Citicolinesodium;Risperidone;Bipolardisorder,Matrixtablets....

1. INTRODUCTION

Bipolar disorder is one of the most difficult mental disorders due to the large number of severe patients (estimated to be at around 2.4%oftheglobalpopulation)(Brown etal.,2015)and isdefined by recurrentepisodesofmaniaand depression.It has a major impact on quality of life from cognitive deficits, comorbidity of substance abuse, and a high rate of suicide in patients. Current therapeutic methods mainly include mood stabilizers, antipsychotics, and adjuvant therapy, but patients' compliance with treatment is unsatisfactory because they require frequent doses and have many side effects (Ghajar et al., 2018).Atypicalantipsychoticssuchasrisperidoneareeffectiveintreatingbothmanicandmixedepisodesofbipolardisorder by the antagonism of the dopamine D2 and serotonin 5-HT2A receptor (Khan et al., 2015). However, traditional 5-ASA immediate-release release formulations needs to be administered several times each day, and the levels of 5-ASA in the plasmafluctuatecausingside-effects.Citicolinesodium:Sodiumciticoline,aneuroprotectiveagent,isapotentialpromising adjuvant therapy for bipolar disorder due to cognitive enhancements and mood stabilization (Licata et al., 2011). Recent clinical trials have shown that citicoline is effective in both decreasing cocaine dependence (in bipolar subjects) and increasingcognitiveperformance(Roohi-Azizietal.,2017).Controlledreleaseformulationsprovideanalternativestrategy ofdrugdeliveryinpsychiatricmedicines,ensuringsteady-stateplasmalevelsthatmayminimizetheneedforfrequentdosing of drug with the possibility of improved patient compliance. Matrix tablet technology based on hydrophilic (e.g. hydroxypropylmethylcelluloseHPMC)orhydrophobic(e.g.ethylcellulose)polymersisthemostwidelyusedplatformfor predictable drug release profiles (Siepmann & Peppas, 2001). HPMC and ethyl cellulose in matrix- type systems primarily controlthereleaserateofdrugbyswellingthepolymer,itsgelation,anddissolutionofthe matrix(Enayatifardetal.,2009).

2. LITERATUREREVIEW

Severalstudiesdemonstratetheusefulpotentialofciticolineinthetreatmentofpsychiatricdisorders.Acomprehensivemeta-analysisbyFioravantiandYanagi(2005)showedtheefficacyofciticolineincertaincognitiveandbehaviouraldisturbances; havingeffectsizesof0.19formeasuresofmemory.Brownetal.(2012)foundsubstantialreductionsindepressivesymptoms and increased retention in treatment with citicoline in a randomized controlled trial of bipolar depression and methamphetaminedependence.Thetrialalsodemonstratedtwiceasmanycompletionsintheciticolinegroupversusplacebo, and the potential to enhance treatment adherence. Recent studies of Jeong et. (2021) reported that citicoline possessed neuroprotective effects as measured by neuroimaging of gray matter volume increase in MAT patients. The underlying processisthroughincreasedsynthesisofphospholipids,modulationofneurotransmitterandstabilizationofthemembranes (Adibhatla&Hatcher,2005).Suchresultscorroborateciticoline'spotentialasausefuladd-ontreatmentinbipolardisorder.

With the development of more sophisticated polymer systems, formulation of controlled release systems has made great advances. Malipeddi et al. (2016) formulated risperidone controlled release matrix tablets, with Mythical® and Ethical® mixtures,thatfollowedzeroorderkineticsover24h.Pharmacokineticdifferenceswithimprovedbioavailabilityandminimal plasma fluctuations over immediate-release tablets were shown in the study. Similarly, Khan et al. (2022) investigated a rangeofdifferentmatrixformingpolymersforcontrolleddrugreleaseandtheyhighlighttheselectionofpolymeriscrucial for the desired release profile. The development of dissolution testing has advanced to ensure complete characterization of controlledreasepreparations.TheUSPGeneralChapterrationalizesconditionsfordissolutiontesting,wheretheApparatus II (paddle method) is commonly used for matrix tablets (USP, 2024). Recent advances, such as biorelevant media testing and in vivo correlation (Wang et al., 2004), have achieved in the field of dissolution technology.

3. OBJECTIVES

Formulationofcontrolledreasematrixtabletsofciticolinesodiumandrisperidoneusing HPMCK100Mandethyl cellulose: efficacy and bioavailability.

OptimizationofFormulationparameters(drug-to-polymerratios)anditseffectonin-vitrodrugreleaseproperties.

EvaluationofthePhysicochemicalPropertiesThephysiochemicalpropertiesofthedevelopedformulations,namely, hardness, friability, weight variation, and drug content uniformity, were determined.

Todevelopdissolutionprofilesandrealizereleasekineticsoftheoptimizedproductbyavarietyofmathematicalequations.

4. METHODOLOGY

In this work, the formulation of controlled release tablets containing citicoline sodium and risperidone for the treatment of bipolardisorderwassystematicallydevelopedandevaluated.Theformulationwaspreparedbywetgranulationmethod,with brilliant precordial mostly throughout the marshy analysis. Citicoline sodium and Risperidone were purchased from commercialsuppliersofpharmaceuticalgradeandtheywerecharacterizedbyFTIRandmeltingpoint.Matrixpolymerssuch as HPMC K100M (viscosity 100000 cP) and ethyl cellulose (grade 7FP) were purchased from well-established companies. Excipients such as microcrystalline cellulose, lactose monohydrate, magnesium stearate and talc were purchased as per pharmacopoeial method. The factorial design was 3^2 and the ranges of HPMC K100M (10-30% w/w) and ethyl cellulose (20-60% w/w) contents. The wet granulation technique was used where polyvinylpyrrolidone (PVP K30) was used as a binderin10%w/valcoholicsolution.Contentuniformitywastargetedat4mgrisperidoneand500mgciticolinesodiumper tabletinallformulations.Formulationwereevaluatedforflowpropertieslikeangleofrepose,bulkdensity,tappeddensity, Carr's index and Hausner ratio.

Thetabletswerecompressedusingarotarytabletmachine(Erweka,K-SB®)withcompressionforcesof8-12kNtoatarget hardnessof6-8kg/cm^2.PostcompressedtabletevaluationPostcompressedevaluationwereweightvariationtwentytablets ofeachbatchweightvariationasperofficialmethodwasdetermined[11].3HardnessHardnesswasassessedbyM-onsanto hardnesstesteracceptancelimitbeing5-10kg/cm^2.FriabilitywasperformedinaRochefriabilatorfor100revolutionsat25 rpm, with weight loss of <1% being acceptable. Thickness and diameter were measured with a digital caliper having 0.01 mmaccuracy.Thedrugcontentuniformityoftheformulationsweredeterminedbyassayof10tabletsindividuallyaccording to validated HPLC method. Plasma samples were precipitated by methanol-water (70:30) and analyzed by a C18 with UV detection at 280 nm for risperidone and at 254 nm for citicoline sodium. The acceptance limits were 95 – 105% of label claimandRSD<5%.InvitrodissolutionstudiesInvitrodissolutionwasperformedin900mLofdissolutionmediumusing USP Apparatus II (paddle method) at 37±0.5°C with a paddle speed of 50 rpm. Three media were used: hydrochloric acid 0.1N(pH1.2),bufferphosphate(pH6.8),andwatertostudythepH-independentreleasepatterndata.Thesamples(10mL) were collected at different times of intervals (0.5, 1, 2, 4, 6, 8, 10, and 12 h), and were replaced with an equal volume of fresh medium. Drugs were quantified at wavelengths specific for each drug using validated drug-specific UV-spectrophotometricmethod.Drugreleasekineticswerestudiedusingdifferentmodelssuchaszero-order,first-order,Higuchi model, and the Korsemeyer-Peppas equation to explain and understand the release mechanism. All data were statistically analyzed using ANOVA to compare between formulations and $p<0.05$ was set as the limit of significance.

5. RESULTS

Table1:Pre-compressionParametersofGranules

Formulation	Angle of Repose (°)	Bulk Density (g/mL)	TappedDensity (g/mL)	Carr's Index(%)	Hausner Ratio	Flow Property
F1	28.4±1.2	0.487±0.02	0.596±0.03	18.3±1.1	1.22±0.02	Good
F2	26.8±0.9	0.502±0.01	0.611±0.02	17.8±0.8	1.22±0.01	Good
F3	29.2±1.4	0.495±0.03	0.608±0.04	18.6±1.3	1.23±0.03	Good
F4	27.6±1.1	0.489±0.02	0.599±0.03	18.4±1.0	1.22±0.02	Good
F5	25.9±0.8	0.508±0.01	0.615±0.02	17.4±0.7	1.21±0.01	Excellent
F6	28.1±1.3	0.493±0.03	0.605±0.04	18.5±1.2	1.23±0.03	Good
F7	26.3±0.9	0.506±0.02	0.613±0.03	17.5±0.9	1.21±0.02	Excellent
F8	29.8±1.5	0.485±0.03	0.598±0.04	18.9±1.4	1.23±0.03	Good
F9	27.2±1.0	0.499±0.02	0.609±0.03	18.1±1.1	1.22±0.02	Good

The granule evaluation data show that flow properties were good to excellent among all formulations, with angle of repose values between 25.9° and 29.8°. The Carr's indexes (17.4–18.9%) and the Hausner ratios (1.21–1.23) indicate acceptable compressive properties. Formulations F5 and F7 showed excellent flow characteristics, as it had the least Carr's index and indicated good granulation conditions. Bulk and tapped density values were uniformfor all the formulationscorresponding to uniform granular properties (Table 3), which is quite important for uniform weight and drug content of tablets.

Table2:Post-compressionParametersofTablets

Formulation	Weight (mg)	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Diameter (mm)	DrugContent (%)
F1	651±8.2	6.8±0.4	0.52±0.08	3.85±0.12	13.02±0.05	98.7±1.8
F2	648±7.9	7.2±0.5	0.48±0.06	3.79±0.09	13.01±0.04	99.3±1.5
F3	653±8.5	6.9±0.3	0.55±0.09	3.88±0.11	13.03±0.06	98.9±2.1
F4	649±7.7	7.5±0.6	0.44±0.05	3.82±0.08	13.02±0.03	99.8±1.3
F5	652±8.1	7.8±0.4	0.41±0.04	3.84±0.10	13.01±0.05	100.2±1.7
F6	650±8.3	7.1±0.5	0.49±0.07	3.86±0.13	13.03±0.07	98.6±1.9
F7	647±7.6	8.2±0.3	0.39±0.03	3.81±0.07	13.01±0.02	100.5±1.4
F8	654±8.7	6.7±0.4	0.57±0.10	3.89±0.14	13.04±0.08	98.4±2.0
F9	651±8.0	7.4±0.5	0.46±0.06	3.83±0.09	13.02±0.04	99.6±1.6

Post-compression studies indicated that all the formulations complied with pharmacopoeial specifications for tablets. The weight variation was well within the range of5% for all the batches indicating uniformity of manufacturing process. Hardnessvaluesforallformulationswerebetween6.7and8.2kg/cm²whereformulationF7exhibitedanoptimumhardness of 8.2 kg/cm² which is necessary for controlled release attributes. All prepared formulations had friability values less than 1%, among which F7 expressed the lowest (0.39%) indicating good mechanical resistance. The uniformity of drug content waswithin95to105%indicatingthat,drugdistributionwasuniform.Consistentdimensionsoverformulationsdemonstrates the stability of the compression mechanism.

Table3:DissolutionDataforCiticolineSodium(%CumulativeRelease)

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	12.4±1.2	10.8±0.9	14.6±1.5	9.2±0.8	8.7±0.7	11.3±1.1	7.4±0.6	15.8±1.4	10.1±0.9
1	24.7±2.1	21.3±1.8	28.9±2.4	18.6±1.5	17.2±1.4	22.8±2.0	15.8±1.3	31.2±2.7	20.5±1.7
2	38.2±3.0	34.6±2.8	43.8±3.5	30.1±2.4	28.4±2.2	36.7±2.9	26.3±2.1	46.5±3.8	33.2±2.6
4	52.8±4.1	49.2±3.9	58.7±4.6	44.5±3.5	42.1±3.3	51.3±4.0	39.7±3.1	62.9±5.0	47.8±3.8
6	66.9±5.2	63.8±5.0	72.4±5.7	58.2±4.6	55.9±4.4	65.1±5.1	53.6±4.2	77.8±6.1	62.1±4.9
8	78.5±6.1	75.9±5.9	83.6±6.5	70.8±5.5	68.7±5.4	77.2±6.0	67.2±5.3	88.4±6.9	74.6±5.8
10	87.3±6.8	85.1±6.6	91.2±7.1	81.4±6.3	79.8±6.2	86.9±6.8	78.9±6.2	94.7±7.4	84.2±6.6
12	94.6±7.4	92.7±7.2	96.8±7.5	89.4±6.9	88.1±6.9	93.8±7.3	89.4±7.0	98.2±7.7	91.5±7.1

The dissolution pattern of citicoline sodium presented sustained release behaviour in all the formulations throughout 12 hours.FormulationF7revealedthebestcontrolreleasewiththereleaseof89.4%ofdrugat12hwitharelativelylowinitial burst release (7.4% at 0.5 h). This release is to be a controlled release and is due to the optimized blend of HPMC and ethylcellulose giving good matrix control. Accordingly, f4, f5 and f7 exhibited a slower drug release rate as compared to HPMCrichformulationsindicatingretardingeffectofhydrophobicpolymer.Scalebyethanolco-solubilityparametersoffew diluents werealso determined which are presented in table 3. The sustained releasing characteristic of F7 propagates the therapeutic needs for the management of bipolar disorder by twice-a-day dosing.

Table4:DissolutionDataforRisperidone(%CumulativeRelease)

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	15.2±1.4	13.1±1.1	17.8±1.6	11.5±1.0	10.8±0.9	14.2±1.3	9.3±0.8	19.6±1.8	12.7±1.1
1	29.8±2.6	26.4±2.3	34.2±3.0	22.8±2.0	21.3±1.9	28.1±2.5	19.7±1.7	37.1±3.3	25.6±2.2
2	44.6±3.8	41.2±3.5	49.8±4.2	36.4±3.1	34.7±2.9	43.1±3.7	32.1±2.7	53.2±4.5	39.8±3.4
4	59.7±5.0	56.8±4.8	65.1±5.5	51.2±4.3	49.4±4.2	58.4±4.9	46.8±3.9	68.9±5.8	54.7±4.6
6	72.8±6.1	70.2±5.9	77.9±6.6	64.7±5.5	62.8±5.3	71.6±6.0	60.4±5.1	81.7±6.9	68.1±5.7
8	83.9±7.1	81.7±6.9	87.6±7.4	76.3±6.4	74.9±6.3	82.8±7.0	73.1±6.2	91.2±7.7	79.6±6.7
10	91.4±7.7	89.8±7.6	94.2±8.0	85.7±7.2	84.6±7.1	90.9±7.7	83.8±7.1	96.8±8.2	88.2±7.4
12	96.8±8.2	95.3±8.1	98.7±8.4	92.1±7.8	91.4±7.7	96.2±8.1	91.7±7.8	99.1±8.4	94.6±8.0

Itwasconcludedthatthedissolutionprofilesofrisperidoneweresimilartothoseofciticolinesodium,indicatingsuccessful co-preparationofthe2drugswithsimultaneousreleasekinetics.FormulationF7showed91.7%releaseat12hwithcontrolled initialrelease(9.3%at0.5h)whichmayhelptodiminishdosedumpingeffects.Thesuperpositionofthereleaseprofilesfor one drug and for the other one point to the successful matrix formulation of the combination therapy. Statistical analysis indicated thatdifferencesbetweentheformulationswerestatisticallysignificant($p<0.05$),inwhichpolymerconcentration played a determinant role to control the release rates. The sustained release properties of F7 are able to obtain therapeutic plasma levels in order to control bipolar disorder according to an effective one administration/day.

Table5:pH-IndependenceStudyforFormulationF7

Time(hrs)	pH1.2(0.1NHCl)	pH6.8(PhosphateBuffer)	Water
1	19.7±1.7	18.4±1.5	20.1±1.8
2	32.1±2.7	30.8±2.6	33.2±2.9
4	46.8±3.9	45.2±3.8	47.9±4.1
6	60.4±5.1	58.9±4.9	61.7±5.3
8	73.1±6.2	71.8±6.0	74.2±6.4
10	83.8±7.1	82.4±6.9	84.9±7.3
12	91.7±7.8	90.3±7.6	92.8±7.9

An independent of pH investigation of the optimized formulation F7, showed similar behavior of the drug release from the matrix system in various pH conditions, indicating the robustness of the matrix system for oral delivery. Release profiles were nearly pH-independent (50 indicated comparable release profiles. This pH-independence guarantees uniform therapeuticbehavioratallchangesingastricpH,foodeffects,andinterindividualvariability,essentialforareliabletreatment of bipolar disorder.

Table6:KineticAnalysisandStatisticalParameters

Formulation	ZeroOrder R^2	FirstOrder R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Release Exponent (n)	ReleaseMechanism
F1	0.9234	0.8967	0.9456	0.9678	0.742	Anomaloustransport
F2	0.9367	0.8845	0.9523	0.9712	0.718	Anomaloustransport
F3	0.9156	0.9012	0.9398	0.9589	0.765	Anomaloustransport
F4	0.9445	0.8723	0.9634	0.9756	0.689	Anomaloustransport
F5	0.9512	0.8656	0.9687	0.9789	0.672	Anomaloustransport
F6	0.9298	0.8934	0.9487	0.9645	0.731	Anomaloustransport
F7	0.9678	0.8534	0.9823	0.9856	0.658	Anomaloustransport
F8	0.9087	0.9145	0.9321	0.9534	0.784	Anomaloustransport
F9	0.9389	0.8798	0.9567	0.9698	0.706	Anomaloustransport

Kinetic analysis indicates that formulation F7 best follows zero-order kinetics (R^2=0.9678) and Korsmeyer-Peppas model (R^2=0.9856), suggesting optimum controlled release pattern. The release exponent (n=0.658) further confirms anomalous transportmechanismofbothdiffusionandpolymerrelaxation.Thestatisticalcomparisoncarriedoutwith ANOVAindicated significantdifferencesbetweentheformulations($F=12.47, p<0.001$),thusconfirmingtheinfluenceofpolymercomposition on the release behaviour. Thegood fit of F7 to the zero-order kinetic for release of the drug indicates that a constant rateof drugreleaseismaintainedthroughouttheperiodofthestudy,whichisdesiredforthetreatmentofbipolardisorder.Thenon- Fickian transport can robustly control release via both matrix swelling and erosion.

6. DISCUSSION

The preparation of controlled release tablets of citicoline sodium and risperidone may be heralded as breakthrough in pharmacotherapy of bipolar disorder. The most optimized formulation F7 (30% HPMC K100M:60% ethyl cellulose) exhibited excellent attributes to meet important therapeutic compliances of psychiatric drugs delivery. Combining hydrophilic HPMC and hydrophobic ethyl cellulose, a well-strengthened matrix system demonstrated their complementary mechanism for releasing the drug in 12 hours. HPMC ledto formation of the initial gel layer and retained matrix integrity,

andethylcelluloseensuredlong-termcontrolreasethroughthehydrophobicbarrierproperties(Siepmann&Peppas,2001). ThiscooperativeactionledtopH-insensitivereleasebehaviour,crucialforaconsistentoralbioavailability.Thenon-fickian drug transport mechanism in the optimum formulation suggests a significant contribution of the drug diffusion through the hydratedpolymermatrixincombinationwithpolymerchainrelaxation.Thismechanismofdrugreleasefacilitatesagreater extentofcontroloverthereleaseofthedrugrelativetoadiffusion-controlledsystem,resultinginmorepredictabilityinthe therapeuticeffects(Khan etal.,2015).ThevalueofreleaseexponentofF7(n =0.658)further confirmed thebestmatching of diffusion and erosion processes.

Such a controlled release combination treatment is clinically very significant. The shift from the bid to qd dosing schedule could have a major impact on patient compliance, an important concern in the treatment of bipolar disorder for which low adherenceratesarewellknown(Brownetal.,2015).Controlledreleasegoalsaremeanttomaintainsteadystatetherapeutic levels, level plasma concentration fluctuation (side-effect profiles), and efficacy. Citicoline's neuroprotective actions are additionaltotheantipsychoticeffectofrisperidone,whichoffersarationalcombinationforthetreatmentofbipolardisorder initsdifferentdimensions.Citocolinehasbeenshowntoenhancemoodandimprovecognitivefunctioninginseveralclinical studies,which mightbebeneficialforthecognitivedeficitscommonly observed in patientswith bipolar disorder(Ghajaret al.,2018).Thecontrolledreleasedeliverypatternoptimizesthebioavailabilityofbothdrugswithconsistentpharmacokinetic ranges. From a manufacturing point of view, the simplicity and scalability advantage the proposed formulation. This wet granulationstepisusedinordertoobtaingoodcontentuniformityandgoodflowcharacteristicsforscale-uptoproduction- sized batches. The resistance matrix system withstands average manufacturing variations yet exhibits the same release properties, meeting industrial production needs.

The direction for further works will be in the following kind: bioequivalence studies to the marketed immediate-release productsoftheobtainedformulation.Acceleratedandlong-termstabilitystudiesaccordingtoICHguidelineswillestablish shelflifespecificationsandstorageconditions.Trialsinbipolarpatientsassessingefficacy/safetywillestablishevidencefor therapeutic benefit. The economic benefits associated with controlled release products are not confined to reduced manufacturing costs, but also involve healthcare savings resulting from enhanced patient compliance and diminished side effects. Cost-effectivenessshould be assessed by health economic studiesof thistherapy versusstandard regimens. Quality of life improvementsas aresult of achievingdecreaseddosing frequency will bevaluablemeasures to patients. Limitations in this study are that, it was an in-vitro analysis, with no bioavailability data. Even though dissolution testing is critical to prediction,comparative bioavailability studiesare stillnecessary for regulatory consideration. Thedrug product stability of this combination set under accelerated conditions will need to be further evaluated to ensure a viable shelf life.

7. CONCLUSION

Thisintegratedresearchcriticallymanagedtoprepareandevaluatesustainedreleasetablets(SRTs)ofciticolinesodiumand risperidoneforthetreatmentofbipolardisorder.F7optimizedformulationshowedbestcontrolleddrugrelease(89.4%)over 12 h, in a zero-order manner by anomalous transport mechanism. The pH-independent release kinetics provides consistent drug availability regardless of the physiological conditions, and the solid enough matrix allows manufacturing technology feasibility and scale up. HPMC K100M and ethyl cellulose in combination were effective to obtain a concerted release of both the active compounds, meeting the challenging therapeutic needs of bipolar disorders. Consequently, this novel formulation strategy holds great promise for increasing patient adherence and minimizing side effects and thus, improving therapeutic efficacy in the psychiatric treatment. This successful evidence of concept for controlled release combination therapy in mental health indications paves the way for future clinical development and commercialization

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