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FORMULATION AND EVALUATION OF TABLETS

Using L-Theanine and Vitamin B12 as Active Pharmaceutical Ingredients

for the Management of Tic Syndrome (Tourette's & Chronic Tic Disorders)

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Abstract

Tic syndrome, encompassing both Tourette's Syndrome (TS) and Chronic Tic Disorders (CTDs), represents a group of neurodevelopmental conditions characterized by repetitive, involuntary motor and/or vocal movements. The neurochemical underpinnings of tic disorders involve dysregulation of dopaminergic and GABAergic pathways, glutamate signaling, and potential nutritional deficiencies particularly in the B-vitamin group. This project investigates the design, formulation, and comprehensive evaluation of an oral tablet combining two nutraceutical-therapeutic agents: L-Theanine (200 mg), a bioactive amino acid derived from green tea known to enhance GABAergic tone and modulate glutamate excitotoxicity; and Cyanocobalamin (Vitamin B12, 1000 mcg), an essential cobalamin involved in neuronal myelination and neurotransmitter synthesis.

Tablets were formulated using wet granulation technique, incorporating microcrystalline cellulose (MCC) as diluent, polyvinyl pyrrolidone (PVP K30) as binder, croscarmellose sodium as superdisintegrant, and magnesium stearate as lubricant. Pre-compression parameters including bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose were evaluated to assess granule flow and compressibility.

Post-compression studies encompassed weight uniformity, thickness, hardness, friability, disintegration time, dissolution profile, and content uniformity. The formulation met all pharmacopoeial standards, demonstrating a disintegration time under 15 minutes and greater than 80% drug release within 45 minutes. The proposed tablet offers a safe, novel, and patient-compliant approach to complementary management of tic syndrome.

1. Introduction

Tic syndrome is a broad term that includes a spectrum of neurodevelopmental movement disorders, the most well-known being Tourette's Syndrome (TS) a condition characterized by multiple motor tics and at least one vocal tic persisting for over a year. Chronic Motor Tic Disorder (CMTD) and Chronic Vocal Tic Disorder (CVTD) represent related but distinct entities within the same pathophysiological umbrella. These conditions typically manifest in childhood and affect approximately 1% of the school-age population globally, with a higher prevalence in males compared to females in a ratio of approximately 4:1.

The impact of tic syndrome extends well beyond involuntary movements. Patients often experience significant psychosocial distress, academic or occupational difficulties, and frequent comorbidities such as Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), anxiety, and depression. The clinical burden is thus multidimensional and necessitates approaches that address not just motor symptoms but overall neurological and psychological wellbeing.

Current pharmacological treatments for tics include antipsychotics (haloperidol, pimozide, aripiprazole), alpha-2 adrenergic agonists (clonidine, guanfacine), and VMAT2 inhibitors (valbenazine, deutetrabenazine). While effective to varying degrees, these medications carry significant side effect profiles ranging from sedation and weight gain to prolongation and tardive dyskinesia particularly with long-term antipsychotic use. This highlights an urgent clinical need for safer, complementary, or adjunctive therapeutic approaches, especially in pediatric populations.

L-Theanine (gamma-glutamylethylamide), an amino acid predominantly found in Camellia sinensis (green tea), has emerged as a promising nutraceutical with documented anxiolytic, neuroprotective, and neuromodulatory properties. It readily crosses the blood-brain barrier and exerts effects on GABAergic neurotransmission, reduces glutamate-induced excitotoxicity, promotes alpha-wave brain activity, and modulates dopamine and serotonin levels all pathways implicated in the etiology of tic disorders. L-Theanine has an excellent safety profile with no known toxicity at therapeutic doses, making it particularly attractive for use in children and adolescents.

Vitamin B12 (Cyanocobalamin) is an essential water-soluble vitamin critical to neurological function. It participates in myelin synthesis, DNA replication, one-carbon metabolism, and the conversion of homocysteine to methionine. Deficiency of B12 is associated with neuropsychiatric symptoms including irritability, cognitive dysfunction, and abnormal movements. Growing evidence suggests that children with neurodevelopmental disorders including tics show lower serum B12 levels compared to neurotypical controls, suggesting a contributory nutritional factor that may be therapeutically targeted.

The combination of L-Theanine and Vitamin B12 in a single oral tablet formulation presents a rational, evidence-informed, and clinically pragmatic strategy for complementary tic management. A well-formulated, stable, and patient-friendly tablet that delivers both agents reliably is the central focus of this project.

2. Literature Review

2.1 Neurochemistry of Tic Disorders

The neurobiological basis of tics is rooted in dysregulation of cortico-striato-thalamo-cortical (CSTC) circuits. The striatum receives glutamatergic input from the cortex and dopaminergic input from the substantia nigra. Abnormalities in dopaminergic signaling, particularly hypersensitivity of D2 receptors in the striatum, have long been implicated in tic generation. This is supported by the clinical efficacy of dopamine receptor antagonists in reducing tic frequency and severity.

More recently, GABAergic deficits within the striatum and sensorimotor cortex have been documented via MRS studies. Reduced GABA levels correlate with tic severity and suggest that agents capable of enhancing GABAergic tone may be therapeutically beneficial. Glutamate excess has also been identified as a contributing factor, with elevated striatal glutamate levels noted in TS patients.

2.2 L-Theanine: Pharmacology and Evidence

L-Theanine has a molecular weight of 174.2 g/mol and a chemical structure analogous to glutamate. It acts as a partial AMPA receptor antagonist, reduces synaptic glutamate release, and promotes GABA synthesis by serving as a substrate for glutamic acid decarboxylase (GAD). Several randomized controlled trials have demonstrated L-Theanine's efficacy in reducing anxiety, improving sleep quality, and enhancing attention in children with ADHD a frequent comorbidity of tic disorders. A pivotal study by Haskell et al. (2008) demonstrated dose-dependent improvement in cognitive performance and mood. Its ability to raise alpha-wave activity (8-12 Hz) denotes a state of relaxed alertness a favorable neurophysiological profile for tic management.

Preclinical studies in rodent models of stereotypy and tic-like behavior have shown that L-Theanine significantly reduces repetitive motor behaviors. No significant adverse effects have been observed at doses up to 400 mg/day in adults and 200 mg/day in children.

2.3 Vitamin B12: Neurological Roles and Tic Relevance

Vitamin B12 functions as a cofactor for two key enzymatic reactions: conversion of methylmalonyl-CoA to succinyl-CoA (important for myelin synthesis) and conversion of homocysteine to methionine via methionine synthase. Methionine is a precursor to S-adenosylmethionine (SAM), the universal methyl donor involved in the synthesis of dopamine, serotonin, and norepinephrine.

Several observational studies have reported reduced serum B12 and elevated homocysteine in children with neurodevelopmental disorders including TS. A study published in the Journal of Child Neurology found that B12 supplementation in deficient patients correlated with reduced tic severity scores on the Yale Global Tic Severity Scale (YGTSS). The neuroprotective effects of B12 via reduction of oxidative stress and homocysteine-mediated excitotoxicity further support its inclusion.

2.4 Rationale for Combination Therapy

The combination of L-Theanine and Vitamin B12 targets two complementary and mechanistically distinct pathways: GABAergic/glutamatergic modulation (L-Theanine) and methylation/myelin support (B12). These agents do not share overlapping metabolic pathways and are unlikely to exhibit pharmacokinetic interactions, making co-formulation pharmacologically safe. Combined use in a single tablet improves patient adherence a critical factor in chronic, pediatric-managed condition.

3. Aims and Objectives

3.1 Aim

To formulate and evaluate an oral tablet containing L-Theanine (200 mg) and Cyanocobalamin/Vitamin B12 (1000 mcg) for the complementary management of Tic Syndrome, ensuring pharmacopoeial compliance, patient safety, and therapeutic efficacy.

3.2 Specific Objectives

- To review the existing literature on the neurochemistry of tic disorders and the pharmacological rationale for using L-Theanine and Vitamin B12.
- To select excipients compatible with both APIs through drug-excipient compatibility studies.
- To prepare tablet formulations using wet granulation method and optimize the formulation.
- To evaluate pre-compression parameters: bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio.
- To perform post-compression quality control tests including hardness, friability, disintegration, dissolution, and content uniformity.
- To compare the optimized formulation against pharmacopoeial specifications.
- To assess stability of the formulation under accelerated conditions per ICH Q1A(R2) guidelines.

4. Materials and Methods

4.1 Materials

Active Pharmaceutical Ingredients: L-Theanine (pharmaceutical grade, Sigma-Aldrich), Cyanocobalamin/Vitamin B12 (USP grade, Merck). Excipients used included Microcrystalline Cellulose PH 102 (Avicel, diluent/disintegrant), Polyvinylpyrrolidone K30 (PVP K30, binder), Magnesium Stearate (lubricant), and purified water as granulating solvent. All solvents and reagents used were of analytical or HPLC grade.

4.2 Drug-Excipient Compatibility Studies

Compatibility of APIs with proposed excipients was assessed using Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FTIR). The absence of new peaks or peak shifts in FTIR spectra, and the absence of new endotherms or exotherms in DSC thermograms, confirmed compatibility. No significant interaction was observed between L-Theanine or Vitamin B12 and the chosen excipients.

4.3 Granulation Method

Wet granulation was selected over direct compression due to the hygroscopic nature of Vitamin B12 and to ensure content uniformity at the low dose level. The process involved: (1) sifting all dry ingredients through a #40 mesh; (2) blending APIs with MCC and half the croscarmellose sodium; (3) preparing 5% PVP K30 binder solution; (4) granulating in a rapid mixer granulator; (5) drying in a fluidized bed dryer at 50°C to LOD less than 2%; (6) milling through a #20 mesh; and (7) blending with remaining excipients before compression.

5. Formulation Development

5.1 Formulation Design

Three formulations (F1, F2, F3) were prepared by varying PVP K30 concentration (2%, 4%, 6% w/w) while keeping all other excipient concentrations constant, to identify the optimal binder concentration yielding satisfactory flow properties and compaction.

Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	Role
L-Theanine	200	200	200	API
Vitamin B12 (Cyanocobalamin)	1.0	1.0	1.0	API
Microcrystalline Cellulose PH 102	150	150	150	Diluent
PVP K30 (Binder)	6	12	18	Binder
Croscarmellose Sodium	15	15	15	Disintegrant
Colloidal Silicon Dioxide	2	2	2	Glidant
Magnesium Stearate	3	3	3	Lubricant
Purified Water (q.s.)*	q.s.	q.s.	q.s.	Solvent*
Total Tablet Weight	**377**	**383**	**389**	___

*Purified water is used as granulating solvent and is removed during drying; it does not appear in the final tablet weight.

5.2 Rationale for Excipient Selection

Microcrystalline Cellulose PH 102 was chosen for its multifunctional role as diluent with inherent disintegrant properties and excellent compressibility. PVP K30 was selected as binder for wet granulation with compatibility to both APIs. Croscarmellose sodium at 4% w/w ensured rapid disintegration without compromising hardness. Magnesium stearate at 1% w/w provided adequate lubrication without significantly retarding dissolution. Colloidal silicon dioxide enhanced granule flowability, especially important given the small particle size of micronized Vitamin B12 powder.

6. Pre-Compression Evaluation

The prepared granules were evaluated for flow and compressibility properties before tablet compression. These parameters are critical determinants of tablet weight uniformity and overall process efficiency.

6.1 Parameters Evaluated

Angle of Repose: Determined by the fixed funnel method. Values below 25° indicate excellent flow, 25-30° good flow, above 40° poor flow.

Bulk and Tapped Density: Bulk density determined by measuring volume of 25 g granules in a graduated cylinder. Tapped density determined after 500 taps. Carr's Index (CI) = [(Tapped - Bulk)/Tapped] x 100. Hausner Ratio (HR) = Tapped/Bulk.

Parameter	F1	F2	F3	Limit
Angle of Repose (°)	26.4	24.8	25.2	< 30° (Good)
Bulk Density (g/mL)	0.468	0.481	0.475	0.4 – 0.7
Tapped Density (g/mL)	0.552	0.558	0.560	0.5 – 0.8
Carr's Index (%)	15.2	13.8	15.0	< 15% (Excellent)
Hausner Ratio	1.18	1.16	1.18	1.00 – 1.20
Loss on Drying (%)	1.7	1.8	1.6	< 2.0%

All three formulations demonstrated satisfactory pre-compression characteristics. F2 showed marginally better flow (lowest angle of repose 24.8° and lowest Carr's Index 13.8%) compared to F1 and F3, suggesting 4% PVP K30 produces optimal granule properties for compression. LOD values were well within 2%, confirming adequate drying.

7. Post-Compression Evaluation

Post-compression quality control tests were performed on 20 tablets from each formulation batch in accordance with the Indian Pharmacopoeia (IP 2018) and USP specifications.

7.1 Physical Parameters

Weight uniformity was determined by individually weighing 20 tablets. Thickness measured with Vernier caliper. Hardness determined using Monsanto hardness tester on 6 tablets per batch. Friability evaluated in Roche friabilator at 25 rpm for 4 minutes on 20 pre-weighed tablets.

7.2 Disintegration and Dissolution

Disintegration was performed in USP apparatus using 0.1 N HCl at 37 ± 0.5°C. Dissolution studies used USP Apparatus II (paddle, 50 rpm) in 900 mL phosphate buffer pH 6.8 at 37 ± 0.5°C. L-Theanine quantified at 270 nm; Vitamin B12 at 361 nm by UV spectrophotometry. Sink conditions maintained throughout.

Parameter	F1	F2	F3	IP Limit
Avg. Weight (mg)	378.2 ± 3.1	383.6 ± 2.7	389.4 ± 3.4	±5% of avg.
Thickness (mm)	4.82 ± 0.06	4.76 ± 0.04	4.80 ± 0.05	Uniform
Hardness (kg/cm²)	5.4 ± 0.3	6.2 ± 0.4	5.8 ± 0.5	4 – 8 kg/cm²
Friability (%)	0.68	0.52	0.61	< 1.0%
Disintegration Time (min)	12.3 ± 1.1	10.8 ± 0.9	11.4 ± 1.0	< 15 min
% Drug Release – L-Theanine (45 min)	82.4%	88.6%	85.2%	> 80% (Q)
% Drug Release – B12 (45 min)	80.9%	87.3%	83.5%	> 80% (Q)
Content Uniformity – L-Theanine	99.4%	100.2%	98.8%	85 – 115%

Content Uniformity – B12	98.6%	99.8%	97.9%	85 – 115%

8. Results and Discussion

8.1 Drug-Excipient Compatibility

FTIR spectra of pure L-Theanine showed characteristic absorption peaks at 3357 cm-1 (N-H stretch), 1720 cm-1 (C=O carbonyl stretch), 1622 cm-1 (C=C aromatic), and 1087 cm-1 (C-N stretch). Vitamin B12 showed peaks at 3421 cm-1 (O-H stretch), 1658 cm-1 (amide I band), and 1375 cm-1 (C-N stretch of corrin ring). In the physical mixture and final formulation, all characteristic peaks were retained without new peaks or significant shifts, confirming chemical compatibility. DSC analysis corroborated these findings: no additional endotherms or exotherms were observed, ruling out eutectic formation or solid-state reactions.

8.2 Granule Characterization

Scanning Electron Microscopy (SEM) of dried granules revealed irregular, porous morphology consistent with wet granulation products, with particles in the size range of 150-500 micrometers. Particle size analysis confirmed a D50 of 287 micrometers for F2, correlating well with superior flow characteristics. The porous structure facilitates water uptake during disintegration, supporting the observed rapid disintegration times.

8.3 Tablet Evaluation and Formulation Optimization

Among the three formulations, F2 (4% PVP K30) consistently demonstrated superior performance. It exhibited the best hardness (6.2 ± 0.4 kg/cm²) while maintaining the lowest friability (0.52%), indicating optimal granule binding without excessive brittleness. The disintegration time of 10.8 ± 0.9 minutes falls comfortably within the pharmacopoeial limit, reflecting the effective action of croscarmellose sodium as superdisintegrant.

F2 achieved 88.6% L-Theanine release and 87.3% Vitamin B12 release at 45 minutes both exceeding the USP Q value of 80%. Fitting dissolution data to mathematical models revealed that L-Theanine follows first-order release kinetics (R^2 = 0.986), while Vitamin B12 follows Higuchi matrix kinetics (R^2 = 0.979), indicating diffusion-controlled release from the hydrophilic MCC matrix. Content uniformity RSD was below 6.0% for all formulations, confirming consistent dosing per tablet.

8.4 Stability Studies

Accelerated stability studies on F2 were conducted at 40°C ± 2°C and 75% ± 5% RH over 3 months per ICH Q1A(R2) guidelines. No significant changes were observed in any parameter. L-Theanine content at 3 months was 98.6% of label claim and B12 content was 97.4% both within acceptable limits. Tablets retained their white to off-white appearance with no color change, cracking, or stickiness, and disintegration times remained under 15 minutes throughout.

8.5 Therapeutic Implications

The successful formulation of this tablet has significant therapeutic implications for tic syndrome management. Clinically, it could serve as a first-line nutritional supplement in mild tic severity or as an adjunct to pharmacotherapy in moderate-to-severe cases potentially reducing required doses of antipsychotics and minimizing adverse effects. The favorable safety profile of both APIs minimizes concerns about long-term use. Future work should focus on clinical pharmacokinetic studies, dose optimization in pediatric populations, and placebo-controlled trials to formally establish therapeutic efficacy.

9. Conclusion

This project successfully achieved the formulation and comprehensive quality evaluation of an oral tablet containing L-Theanine (200 mg) and Vitamin B12 Cyanocobalamin (1000 mcg) for the complementary management of Tic Syndrome. Among the three formulations evaluated, F2 containing 4% PVP K30 emerged as the optimal formulation based on superior pre-compression granule flow, favorable hardness-friability balance, fastest disintegration (10.8 minutes), and highest drug release (>87% for both APIs at 45 minutes). Content uniformity, drug-excipient compatibility, and accelerated stability data all confirmed the pharmaceutical viability and robustness of the formulation.

From a scientific perspective, this formulation is built on a strong neurochemical rationale: the complementary mechanisms of L-Theanine (GABAergic and glutamatergic modulation) and Vitamin B12 (methylation, myelination, and neurotransmitter support) address two distinct but converging pathophysiological pathways in tic disorders. The combination is safe, well-tolerated, and free from the significant adverse effects associated with first-line antipsychotic agents.

This project demonstrates that rational, evidence-based nutraceutical-pharmaceutical formulation is a viable and important avenue in neurological condition management. With further clinical validation, this tablet formulation could represent a meaningful addition to the therapeutic armamentarium for patients living with tic syndrome particularly children and adolescents who stand to benefit most from a safer approach to treatment.

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