



Review Article

Formulation and Evaluation of Gastroretentive Polyherbal Granules for Management of Stomach Inflammation: A Comprehensive Review

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Gastric inflammation, commonly known as gastritis, represents a significant health concern affecting the quality of life in millions worldwide. The conventional pharmacological approaches often result in adverse effects and limited efficacy. Recent advances in pharmaceutical technology have focused on developing gastroretentive drug delivery systems that extend residence time in the stomach, thereby improving therapeutic outcomes. Polyherbal formulations combining traditional medicinal plants offer a promising approach by harnessing synergistic phytochemical effects. This review examines the formulation development and comprehensive evaluation of gastroretentive polyherbal granules incorporating *Withania somnifera* (Ashwagandha) and *Trachyspermum ammi* (Ajwain), employing phytochemical screening, hydroalcoholic extraction via Soxhlet apparatus, and wet granulation methodology. The paper discusses the scientific rationale for plant selection, extraction techniques, formulation strategies, and critical evaluation parameters essential for characterizing granule quality and therapeutic potential.

Keywords: Gastroretentive systems, polyherbal formulation, Ashwagandha, Ajwain, wet granulation, evaluation parameters, gastritis management.

INTRODUCTION

1.1 Gastric Inflammation: Clinical Significance and Current Challenges

Gastritis, characterized by inflammation of the gastric mucosa, remains a prevalent gastrointestinal condition with multiple etiological factors including *Helicobacter pylori* infection, non-steroidal anti-inflammatory drugs (NSAIDs), stress, and dietary factors [1]. The estimated global prevalence of chronic gastritis approaches 50% in certain populations, significantly impacting patient morbidity and healthcare costs [2]. Current pharmacological interventions, including proton pump inhibitors and H₂-receptor antagonists, provide symptomatic relief; however, their prolonged use is associated with hypersensitivity reactions, electrolyte imbalances, and potential systemic side effects [3]. Traditional systems of medicine, particularly Ayurveda, have employed polyherbal formulations for centuries in

managing gastrointestinal inflammatory conditions. Recent scientific validation of these traditional approaches has demonstrated that plant-derived compounds possess significant anti-inflammatory, antimicrobial, and mucosa-protective properties [4]. The World Health Organization recognizes the importance of integrating traditional medicine with modern pharmaceutical science, emphasizing the need for rigorous scientific evaluation of herbal formulations [5].

1.2 Gastroretentive Drug Delivery Systems: Rationale and Advantages

Conventional oral dosage forms exhibit limited contact time with the gastric mucosa due to the relatively rapid gastric emptying process. The average gastric residence time ranges from 2-4 hours under fasted conditions [6]. This limited contact period

restricts the therapeutic potential of drugs targeting gastric conditions. Gastroretentive drug delivery systems (GRDDS) represent an innovative pharmaceutical approach designed to prolong drug residence time in the stomach [7].

The advantages of GRDDS include: (1) enhanced local drug concentration at the site of action, (2) reduced systemic exposure and associated toxicity, (3) improved bioavailability for drugs with narrow absorption windows, and (4) sustained therapeutic effect through prolonged contact with diseased tissue [8]. Among various GRDDS technologies, floating systems have demonstrated significant promise due to their simple formulation approach and consistent gastroretentive behavior [9].

1.3 Polyherbal Approach: Scientific Rationale

Polyherbal formulations represent a departure from single-herb systems by combining multiple botanicals with complementary pharmacological properties. This approach offers several advantages: (1) synergistic interaction of phytochemicals enhancing overall therapeutic efficacy, (2) broader spectrum of biological activity, (3) reduced individual herb dosage thereby minimizing potential adverse effects, and (4) traditional validation of combination therapy across millennia of use [10]. Recent phytopharmacological research has documented that polyherbal combinations demonstrate superior efficacy compared to individual plant extracts in managing inflammatory conditions [11].

2. Plant Materials and Phytochemical Profile

2.1 *Withania somnifera* (Ashwagandha)

2.1.1 Botanical Description and Traditional Use

Withania somnifera Dunal, commonly known as Ashwagandha, is an herbaceous shrub belonging to the Solanaceae family, indigenous to the Indian subcontinent and widely cultivated in arid and semi-arid regions [12]. In Ayurvedic medicine, Ashwagandha has been employed as a Rasayana (rejuvenating agent) for over 3000 years, with documented applications in treating gastrointestinal inflammation, stress-related disorders, and immune dysfunction [13].

2.1.2 Phytochemical Composition

Comprehensive phytochemical analysis of *Withania somnifera* has identified over 34 distinct alkaloids, primarily withanolides, as the principal bioactive constituents [14]. Withanolides, a unique class of C-28 steroidal lactones, represent approximately 0.5-1.5% of the dried root extract [15]. Major withanolides include withanolide A, withanolide B, withanferine A, and 12-deoxywithastramonolide [16]. Beyond withanolides, the plant contains flavonoids (including kaempferol and quercetin), alkaloids (somniferine, withaferin A), and polysaccharides [17]. These diverse phytochemicals collectively contribute to the plant's pharmacological effects.

2.1.3 Pharmacological Actions Relevant to Gastric Inflammation

Recent in vitro and in vivo studies have demonstrated that Ashwagandha extracts exert significant anti-inflammatory effects through multiple mechanisms: (1) inhibition of nuclear factor-kappa B (NF- κ B) signaling pathway, a critical transcription factor in inflammatory cascade, (2) suppression of pro-inflammatory cytokine production including TNF- α , IL-6, and IL-8, and (3) enhancement of antioxidant enzyme systems including superoxide dismutase and catalase [18]. Withanolides specifically have shown gastroprotective properties through strengthening of the gastric mucosal barrier via increased mucus production and enhanced tight junction protein expression [19]. Additionally, these compounds demonstrate antimicrobial activity against *H. pylori* and other gastric pathogens, providing a multi-targeted approach to gastritis management [20].

2.2 *Trachyspermum ammi* (Ajwain)

2.2.1 Botanical Description and Ethnopharmacological Application

Trachyspermum ammi (L.) Sprague, commonly known as Ajwain or Bishop's weed, belongs to the Apiaceae family and is extensively cultivated throughout South and Southeast Asia [21]. The fruits of this plant have been integral to traditional medicine systems, particularly in Indian and Middle Eastern preparations for digestive complaints, gas formation, and gastric discomfort [22].

2.2.2 Phytochemical Constituents

Ajwain fruits are characterized by high essential oil content, constituting 2-4% of the dried material [23]. The essential oil's composition varies geographically and seasonally but predominantly comprises thymol (30-55%), p-cymene (20-35%), and γ -terpinene (5-15%) [24]. Beyond essential oils, the plant contains flavonoids, coumarins, and phenolic compounds contributing to its biological activity [25]. Thymol, the major active constituent, functions as a lipophilic phenolic compound with established antimicrobial, anti-inflammatory, and antioxidant properties [26]. Recent metabolomic studies have identified additional minor constituents including carvacrol and pinene that contribute synergistically to the plant's therapeutic potential [27].

2.2.3 Mechanisms of Gastroprotection

Thymol and other Ajwain constituents exert gastroprotective effects through: (1) antimicrobial action against *H. pylori* and other gastric pathogens with minimal resistance development [28], (2) regulation of gastric acid secretion through modulation of histamine-mediated pathways [29], (3) enhancement of gastric mucosal blood flow and nutrient supply [30], and (4) stimulation of gastric mucus secretion creating a protective barrier against acid-related injury [31].

3. Extraction Methodology

3.1 Hydroalcoholic Extraction: Scientific Rationale

The selection of extraction methodology significantly impacts the quality, consistency, and bioavailability of herbal extracts [32]. Hydroalcoholic extraction represents an optimal approach for polyherbal preparations, as it effectively solubilizes both hydrophilic and lipophilic phytochemicals present in plant materials [33]. The hydroalcoholic system (typically 70-80% ethanol) demonstrates superior extraction efficiency due to: (1) ethanol's ability to penetrate plant cell walls and disrupts cellular organization, (2) enhanced solubility of alkaloids, glycosides, and essential oils, (3) antimicrobial properties preventing microbial contamination during storage, and (4) volatile nature facilitating solvent

removal without thermal degradation of heat-sensitive compounds [34].

3.2 Soxhlet Apparatus: Operational Principles and Advantages

The Soxhlet apparatus, invented in 1879, remains a gold standard for exhaustive extraction in pharmaceutical research [35]. This apparatus operates on the principle of repeated cycles of solvent percolation through plant material, achieving near-complete extraction of target compounds [36].

Operational advantages of Soxhlet extraction include: (1) repeated exposure of plant material to fresh solvent maximizes extraction efficiency, (2) relatively low operating temperatures prevent thermal degradation of thermolabile compounds, (3) high extraction reproducibility enabling consistent batch-to-batch extract composition [37], and (4) simple operation requiring minimal technical expertise [38].

The extraction process typically involves 8-12 complete cycles per hour, with each cycle lasting 15-20 minutes, continuing until the siphon chamber no longer contains solute [39]. For polyherbal preparations, individual plant materials are extracted separately to optimize solvent-to-plant ratio and prevent potential chemical interactions [40].

3.3 Phytochemical Screening Methodologies

Preliminary phytochemical screening serves as a rapid assessment tool for identifying major chemical constituents present in extracts [41]. Standard screening protocols include:

Alkaloid Detection: Conducted using Wagner's reagent, Dragendorff's reagent, and Mayer's reagent, which form characteristic color precipitates upon reaction with alkaloids [42].

Flavonoid Assessment: Performed using alkaline reagent test, lead acetate test, and ferric chloride test, providing identification of polyphenolic compounds [43].

Saponin Identification: Determined through foam test, hemolytic test, and gravimetric quantification [44].

Essential Oil Confirmation: Established through organoleptic evaluation, TLC fingerprinting with iodine detection, and GC-MS analysis for thymol and other volatile components [45]. These screening methodologies provide qualitative confirmation of extract composition prior to formulation development and subsequent quantitative analysis [46].

4. Formulation Design: Gastroretentive Polyherbal Granules

4.1 Formulation Rationale and Component Selection

The development of stable, floating gastroretentive granules requires careful selection of excipients based on their functional properties and compatibility with herbal extracts [47].

4.1.1 Active Herbal Extracts (Ashwagandha 7.5g, Ajwain 7.5g)

The incorporation of 15g total herbal extract (50% of final formulation) maximizes therapeutic phytochemical content while maintaining acceptable granule friability and flow characteristics [48]. The 1:1 ratio of Ashwagandha to Ajwain has been selected based on: (1) traditional formulation practices in Ayurvedic preparations, (2) complementary pharmacological actions (Ashwagandha providing anti-inflammatory and immunomodulatory effects while Ajwain contributes antimicrobial and acid-regulatory properties), and (3) preliminary in vitro studies demonstrating synergistic antioxidant activity in this combination [49].

4.1.2 Hydroxypropyl Methylcellulose (HPMC, 15g)

HPMC, a semi-synthetic cellulose derivative, serves as the primary binder and matrix-forming polymer in the formulation [50]. HPMC exhibits several advantageous properties: (1) non-ionic nature eliminating incompatibility concerns with herbal extracts, (2) viscosity-dependent controlled release characteristics allowing sustained drug delivery [51], (3) excellent film-forming ability facilitating granule bonding, and (4) proven biocompatibility and safety profile [52]. The 15g incorporation (30% of total formulation) provides optimal binding without

excessive viscosity that could compromise processing during wet granulation [53].

4.1.3 Effervescent System: Sodium Bicarbonate (10g) and Citric Acid (5g)

The effervescent system represents a critical component enabling gastroretention through gas generation [54]. Upon contact with gastric fluid, the reaction between sodium bicarbonate and citric acid produces carbon dioxide, creating gas-filled granules with reduced density ($< 1 \text{ g/cm}^3$), facilitating floating behavior [55]. The sodium bicarbonate to citric acid ratio of 2:1 (molar ratio of 1:1) has been optimized to ensure: (1) complete acid neutralization preventing excessive gastric pH elevation, (2) sustained gas generation throughout the residence period, and (3) safety profile compliant with pharmaceutical regulations [56].

4.1.4 Carbapol 940 (2.5g)

Carbapol 940, a synthetic polymer of acrylic acid, serves as a secondary viscosity-enhancing agent and mucoadhesive component [57]. When hydrated in the gastric environment, Carbapol swells significantly, increasing granule volume and promoting sustained contact with gastric mucosa [58]. The 2.5g incorporation (5% w/w) balances mucoadhesive benefits with processing feasibility during granulation [59].

4.1.5 Mannitol (5g)

Mannitol, a sugar alcohol, serves multiple functions in the formulation: (1) diluent providing bulk, (2) coolant improving granule texture and compressibility, (3) osmotic agent enhancing moisture uptake for controlled hydration, and (4) sweetening agent improving organoleptic properties [60]. The 5g incorporation optimizes granule flow characteristics without inducing hygroscopicity-related processing difficulties [61].

4.2 Wet Granulation Process

Wet granulation represents the most widely employed granulation methodology in pharmaceutical manufacturing, offering superior control over granule size distribution and mechanical properties [62].

4.2.1 Process Parameters and Operational Sequence

The wet granulation process involves sequential steps: (1) dry mixing of powdered excipients to achieve uniform distribution, (2) addition of herbal extracts with controlled hydration, (3) wet massing to develop granule nuclei, (4) sizing through appropriate mesh, and (5) drying to reduce moisture content to acceptable levels [63]. For polyherbal formulations, ethanol has been selected as the granulating liquid due to: (1) enhanced extract solubility facilitating uniform distribution, (2) volatile nature reducing final moisture content, (3) antimicrobial properties, and (4) compatibility with all selected excipients [64].

4.2.2 Critical Process Parameters

Process parameters critical to granule quality include: (1) mixing duration (typically 5-8 minutes) ensuring uniform distribution, (2) granulation liquid addition rate controlling granule nucleation and growth [65], (3) wet massing duration (8-15 minutes) optimizing binder distribution without excessive overwetting, and (4) drying temperature and duration (60-80°C for 30-60 minutes) balancing moisture removal with thermolabile phytochemical preservation [66].

5. Granule Evaluation Parameters and Analytical Methods

5.1 Powder Flow Characterization

5.1.1 Bulk Density and Tapped Density

Bulk density represents the ratio of mass to volume of granules under their native, loosely packed state, while tapped density reflects the volume after mechanical compaction [67]. These parameters are essential for: (1) predicting granule packing efficiency, (2) estimating fill volumes in capsules or sachets, and (3) assessing powder consolidation behavior [68]. Bulk density is determined by pouring a known mass of granules into a graduated cylinder and recording the initial volume [69]. Tapped density is measured by mechanically vibrating the graduated cylinder containing granules (typically 1250 taps at 1 Hz frequency) until the volume stabilizes [70].

5.1.2 Carr's Index and Hausner's Ratio

These dimensionless indices quantitatively assess powder flowability, which is critical for processability and dose uniformity in manufacturing [71]:

$$\text{Carr's Index (\%)} = \frac{[(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100}{**}$$

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}^{**}$$

Powders with Carr's Index <15% and Hausner's Ratio <1.25 demonstrate excellent flowability [72]. For granules with poor flow characteristics (Carr's Index >25%), glidants such as silicon dioxide may be incorporated to improve processing characteristics [73].

5.1.3 Angle of Repose

The angle of repose represents the maximum angle at which a material placed on an inclined plane remains stationary without sliding [74]. This parameter provides practical assessment of inter-particle friction and flowability. Measurement is conducted using the fixed funnel or tilting cylinder method [75].

Granules with angle of repose <30° exhibit excellent flow, while values >45° indicate poor flow requiring formulation modification [76]. For gastroretentive granules where accurate dosing is essential, angle of repose should ideally fall in the 25-35° range [77].

5.2 Gastroretention Evaluation

5.2.1 Floating Lag Time

Floating lag time (also termed floating delay time) represents the duration required for granules to initiate floating after immersion in simulated gastric fluid [78]. This parameter is critical as extended lag time may result in premature gastric emptying before buoyancy is achieved [79]. The test is conducted by placing 250 mg of granules in a 100 mL USP II dissolution vessel containing simulated gastric fluid (pH 1.2) maintained at 37°C. The time at which granules first appear on the fluid surface is recorded [80]. Acceptable floating lag time typically ranges from 5-15 minutes for practical pharmaceutical applications [81].

5.2.2 Total Floating Time

Total floating time represents the duration during which granules maintain buoyancy in simulated gastric fluid. This parameter directly correlates with potential gastric residence time and therapeutic efficacy for gastric conditions [82]. The test continues for a specified duration (typically 12 hours) with periodic visual observation [83]. Granules maintaining flotation throughout the test period demonstrate superior gastroretention capability. Advanced in vitro models utilizing biorelevant media and dynamic pH changes have demonstrated superior predictivity of in vivo gastroretention [84].

5.3 Dissolution and Release Characteristics

5.3.1 Dissolution Test Protocol

Dissolution testing evaluates the rate and extent of herbal constituent release from granules into simulated gastric fluid, providing in vitro assessment of bioavailability potential [85]. Testing is conducted using USP II (paddle) apparatus at 50 rpm in 900 mL simulated gastric fluid pH 1.2 maintained at $37 \pm 0.5^\circ\text{C}$ [86]. Samples (equivalent to 250 mg) are withdrawn at predetermined intervals (15, 30, 45, 60, 90, 120, 180, 240, 300, 360 minutes) through a $0.45 \mu\text{m}$ filter. The filtrate is analyzed via HPLC for quantification of major phytochemical markers including withanolides from Ashwagandha and thymol from Ajwain [87].

5.3.2 Kinetic Analysis

Release data are fitted to appropriate mathematical models (zero-order, first-order, Higuchi, Korsmeyer-Peppas) to characterize release mechanisms [88]. The Korsmeyer-Peppas model is particularly valuable for polyherbal granules as it accounts for complex release patterns resulting from matrix swelling and polymer degradation [89].

5.4 Quantitative Assay of Herbal Constituents

5.4.1 HPLC Analysis of Phytochemical Markers

HPLC analysis quantifies major phytochemical markers in the final granule formulation, ensuring batch consistency and validating manufacturing processes [90]. For Ashwagandha-containing formulations, withanolide A and withanolide B serve as primary marker compounds, being relatively stable

and specifically identifiable [91]. For Ajwain, thymol quantification via HPLC provides accurate assessment of essential oil retention during manufacturing processes [92]. An isocratic or gradient HPLC method employing reverse-phase C18 columns with appropriate wavelength detection (typically 220-280 nm for withanolides and 275 nm for thymol) ensures accurate, reproducible quantification [93].

5.4.2 Method Validation

HPLC methods require comprehensive validation demonstrating specificity, linearity, accuracy, precision, and robustness according to ICH Q2 (R1) guidelines [94]. Specificity is established by demonstrating that analytes are resolved from excipient peaks and degradation products. Linearity is confirmed across appropriate concentration ranges (typically 50-200% of expected concentration) with correlation coefficients >0.99 [95].

6. Quality Control Parameters and Acceptance Criteria

6.1 Granule Characterization

Quality control testing ensures consistency and safety of the final product [96]:

- **Moisture Content:** $<5\%$ w/w (determined via Karl Fischer titration or loss on drying)
- **Granule Size Distribution:** 80-120 mesh (100% passing through 80 mesh, $>80\%$ between 80-120 mesh)
- **Color and Odor:** Consistent within batch (organoleptic assessment)
- **Microbial Contamination:** Total aerobic microbial count $<10^4$ CFU/g; Escherichia coli and Salmonella absent
- **Heavy Metals:** As per WHO guidelines for herbal preparations

6.2 Stability Testing

Accelerated and long-term stability studies following ICH guidelines ensure product shelf-life determination [97]. Formulations are stored under controlled temperature ($25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH and $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH) conditions for specified periods

(typically 3, 6, 9, 12 months). Testing intervals assess: (1) phytochemical content via HPLC, (2) floating characteristics, (3) dissolution profiles, and (4) microbial quality [98].

7. Recent Advances and Future Perspectives

7.1 Emerging Technologies in Gastroretentive Formulations

Recent pharmaceutical research has investigated advanced modifications to floating granule systems. Nanotechnology-based approaches incorporating phytochemical-loaded nanoparticles within gastroretentive matrices demonstrate enhanced bioavailability and sustained release characteristics [99]. Additionally, incorporation of probiotics alongside herbal extracts represents an emerging strategy combining traditional medicine with contemporary microbiome-based therapeutics [100].

7.2 Polyherbal Combinations and Synergy

Contemporary phytopharmacological research increasingly emphasizes the importance of elucidating synergistic mechanisms in polyherbal preparations through advanced analytical and biological approaches [101]. Systems pharmacology, utilizing network analysis and in silico docking studies, provides mechanistic insights into multi-target effects of herbal combinations [102].

7.3 Regulatory Considerations

The regulatory landscape for herbal formulations has evolved significantly, with agencies including the FDA and EMA establishing comprehensive guidelines for quality, safety, and efficacy evaluation [103]. Postgraduate researchers developing herbal formulations must integrate traditional knowledge with contemporary regulatory requirements, ensuring formulations meet standards for pharmaceutical preparations [104].

CONCLUSION

The formulation and evaluation of gastroretentive polyherbal granules represents a convergence of traditional botanical knowledge and contemporary pharmaceutical science. *Withania somnifera* and

Trachyspermum ammi, selected for their documented gastroprotective properties, offer a rational, evidence-based approach to managing gastric inflammation through multiple pharmacological mechanisms. The employment of hydroalcoholic extraction via Soxhlet apparatus ensures optimal recovery and preservation of phytochemical constituents from both botanical materials. Wet granulation methodology, combined with rational excipient selection including HPMC as matrix former and sodium bicarbonate-citric acid as effervescent system, provides a stable, reproducible manufacturing process scalable to commercial production. Comprehensive evaluation parameters—encompassing powder characterization, gastroretention assessment, dissolution profiling, and phytochemical assay—provide robust quality assurance mechanisms ensuring consistency and therapeutic efficacy. The continued development of such formulations, grounded in scientific validation while respecting traditional knowledge systems, holds significant promise for offering patients safer, more efficacious alternatives to conventional pharmacotherapy for gastric inflammatory conditions. Future investigations should focus on in vivo gastroretention studies utilizing gamma scintigraphy, clinical efficacy trials demonstrating therapeutic superiority, and mechanistic studies elucidating precise molecular pathways underlying the synergistic effects of herbal combinations in the developed formulation.

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