

# Formulation and Evaluation of a Quadruple-Action Oral Liquid System for Multi- Symptomatic Relief of Cough, Cold and Fever

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## ABSTRACT:

Cough, cold, and fever are among the most common health problems affecting individuals of all age groups worldwide. These conditions are usually associated with upper respiratory tract infections and are often accompanied by symptoms such as nasal congestion, throat irritation, body ache, headache, sneezing, and mild fever. Conventional treatment generally requires multiple medications to manage individual symptoms, which may lead to poor patient compliance and an increased risk of dosing errors. Therefore, the development of a single oral liquid formulation capable of providing relief from multiple symptoms can offer significant therapeutic advantages.

The present research work focuses on the formulation and evaluation of a quadruple-action oral liquid system designed to provide multi-symptomatic relief from cough, cold, fever, and associated discomfort. The formulation was developed using a combination of antitussive, antihistaminic, decongestant, and antipyretic agents in a stable and palatable oral liquid dosage form. Different excipients such as sweetening agents, flavouring agents, preservatives, viscosity enhancers, and buffering agents were carefully selected to improve patient acceptability, stability, and therapeutic effectiveness.

The prepared formulations were evaluated for various physicochemical and pharmaceutical parameters including appearance, pH, viscosity, specific gravity, drug content uniformity, sedimentation behaviour, stability, microbial load, and in-vitro drug release. The optimized formulation demonstrated acceptable organoleptic properties, excellent stability, satisfactory drug release, and effective symptom-relieving potential.

The study concludes that the developed quadruple-action oral liquid system can serve as a convenient and patient-friendly dosage form for managing multiple symptoms associated with cough, cold, and fever. The formulation showed promising pharmaceutical characteristics and may improve

treatment adherence and patient comfort.

**Keywords:** Oral liquid system, cough, cold, fever, antitussive, antihistamine, decongestant, antipyretic, multi-symptomatic relief.

## I. INTRODUCTION

Cough, cold, and fever are among the most frequently occurring health conditions globally. These conditions are generally caused by viral infections affecting the upper respiratory tract. Although most cases are self-limiting, the symptoms can significantly affect daily life, sleep quality, appetite, work efficiency, and overall comfort.

A cough is a protective reflex mechanism that helps clear mucus, irritants, or foreign particles from the respiratory tract. However, persistent coughing can lead to throat irritation, fatigue, chest discomfort, and disturbed sleep. Similarly, the common cold is characterized by symptoms such as sneezing, nasal congestion, runny nose, sore throat, and mild headache. Fever often accompanies respiratory infections and acts as a physiological response of the body against infectious agents.

Most patients suffering from cough and cold experience multiple symptoms simultaneously. For example, an individual may suffer from cough, fever, nasal congestion, throat irritation, and body ache at the same time.

In such situations, separate medications are commonly prescribed for each symptom, increasing pill burden and reducing patient compliance.

Modern pharmaceutical research focuses not only on therapeutic efficacy but also on patient convenience and compliance. Multi-symptomatic therapy aims to reduce the number of medications required by combining multiple active pharmaceutical ingredients in a single dosage form. An oral liquid system is especially beneficial for pediatric, geriatric, and dysphagic patients who face difficulty swallowing tablets or capsules. Liquid dosage forms provide faster absorption, flexible dosing, improved patient acceptance, and better ease

of administration.

However, formulating a stable, multi-component oral liquid system is an intricate pharmaceutical challenge.

When multiple APIs with different physical properties, chemical stabilities, and pKa values are combined in a single aqueous vehicle, it often causes chemical degradation, precipitation, or incompatibilities. For instance, Paracetamol is prone to hydrolytic degradation into p-aminophenol if the pH drifts outside its narrow stability window. At the same time, maintaining the solubility of highly water-soluble salts alongside more hydrophobic compounds requires careful balance. Furthermore, the highly bitter, astringent, and chemical tastes of these active components can cause severe taste-rejection, leading to non-compliance and compromised therapeutic outcomes.

To address these challenges, this study establishes a robust formulation framework for a Quadruple-Action Oral Liquid System. It utilizes a tailored ternary cosolvent system and an advanced taste-masking matrix to deliver four targeted therapeutic actions safely and effectively in a single dose.

This paper covers the entire development lifecycle—from pre-formulation screening and cosolvent optimization to organoleptic masking, physical characterization, and accelerated stability testing.

## INGREDIENTS

### Rational Selection of Active Ingredients

The present quadruple-action oral liquid system was rationally designed to provide effective and simultaneous relief from multiple symptoms associated with cough, cold, fever, body pain, nasal congestion, and allergic reactions. The formulation combines carefully selected active pharmaceutical ingredients along with suitable excipients to ensure therapeutic efficacy, stability, palatability, and patient compliance.

The selection of ingredients was based on their pharmacological activity, compatibility, safety profile, and suitability for incorporation into an oral liquid dosage form.

### Rational Selection of Excipients

#### 1. Paracetamol

Category: Analgesic and Antipyretic Quantity: 2.5 g/100 mL

Paracetamol was selected as the primary antipyretic and analgesic agent due to its proven effectiveness in reducing fever, headache, and body pain associated with upper respiratory tract infections. It possesses a good safety profile, causes minimal gastric irritation compared to other NSAIDs, and is widely accepted for both pediatric and adult use. Its inclusion ensures rapid symptomatic relief from fever and discomfort.

#### 2. Ibuprofen

Category: Non-Steroidal Anti-Inflammatory Drug (NSAID) Quantity: 1.0 g/100 mL

Ibuprofen was incorporated to provide anti-inflammatory and additional analgesic action. During cough and cold conditions, inflammation in the throat and respiratory tract contributes to pain and irritation. Ibuprofen helps reduce inflammation, throat discomfort, muscle pain, and body ache. The combination of paracetamol and ibuprofen provides enhanced pain-relieving and fever-reducing effects through complementary mechanisms of action.

#### 3. Dextromethorphan Hydrobromide

Category: Antitussive Quantity: 0.15 g/100 mL

Dextromethorphan HBr was selected as the cough suppressant due to its effectiveness in controlling dry and irritating cough. It acts centrally on the cough center in the medulla and helps reduce excessive coughing without causing significant respiratory depression. Its compatibility with other cold medications makes it suitable for multi-symptomatic formulations.

#### 4. Cetirizine Hydrochloride

Category: Antihistamine Quantity: 0.05 g/100 mL

Cetirizine HCl was included to manage allergy-related symptoms such as sneezing, watery eyes, nasal discharge, and throat irritation. It is a second-generation antihistamine with comparatively less sedative effect, making it more suitable for daytime administration. The drug effectively blocks histamine receptors and improves patient comfort during allergic manifestations associated with cold.

Excipient	Category	Quantity	Rational Selection/Function
Xanthan Gum	Suspending Agent	0.4g	Selected to maintain uniform suspension of insoluble drug particles like ibuprofen and paracetamol. It prevents sedimentation and improves physical stability of the formulation.
Sodium CMC	Viscosity Enhancer	0.3g	Used to increase viscosity and improve consistency, ensuring better mouthfeel, uniform drug distribution, and easy pouring of the oral liquid.
Tween 80	Wetting Agent	0.2mL	Incorporated to improve wetting and dispersion of hydrophobic drug particles, especially ibuprofen, thereby enhancing formulation uniformity and stability.
Sodium Benzoate	Preservative	0.1 g	Selected to inhibit microbial growth and enhance shelf life and microbiological stability of the oral liquid preparation.
Sodium Citrate	Buffering Agent	0.2 g	Used to maintain pH stability of the formulation, which is essential for drug stability and preservative effectiveness.
Citric Acid	pH Adjuster	0.1g	Added to adjust and maintain optimum pH, improve taste, and support stability of the formulation.
Glycerin	Co-solvent/ Humectant	10 mL	Included to improve solubility of ingredients, enhance viscosity, provide sweetness, and improve mouthfeel.
Sorbitol Solution	Sweetening Agent	20 mL	Used to improve palatability, mask bitter taste of drugs, and contribute to formulation viscosity and stability.
Sucrose Syrup	Vehicle / Sweetener	25 mL	Selected as the primary vehicle to provide sweetness, improve flavor masking, and enhance patient acceptability.
Flavor	Flavoring Agent	q.s.	Added to improve taste and overall sensory acceptance, especially for pediatric and geriatric patients.
Color	Coloring Agent	q.s.	Incorporated to enhance aesthetic appearance and improve patient appeal and identification of the formulation.
Purified Water	Vehicle/ Solvent	Upto 100 mL	Used as the solvent system for dissolving and dispersing all ingredients uniformly in the formulation.

This synergistic combination of antipyretic, analgesic, antitussive, anti-inflammatory, and antihistaminic agents provides comprehensive therapeutic management of cough, cold, and fever while minimizing the need for multiple medications.

## II. METHODOLOGY

### Step 1: Preparation of Polymer Base

Accurately weighed quantities of xanthan gum and sodium CMC were dispersed slowly in a portion of purified water with

continuous stirring to avoid lump formation. The mixture was allowed to hydrate completely for approximately 30 minutes to obtain a smooth and uniform polymeric base.

### Step 2: Preparation of Drug Solution

Paracetamol, dextromethorphan HBr, and cetirizine HCl were dissolved separately in purified water under continuous stirring.

Ibuprofen, being poorly water-soluble, was dispersed separately using Tween 80 as a wetting agent. Glycerin was added to improve dispersion and solubility of ibuprofen particles.

### **Step3: Incorporation of Sweetening and Buffering Agents**

Sorbitol solution and sucrose syrup were added gradually into the hydrated polymer base with continuous stirring. Sodium citrate and citric acid were then incorporated to maintain the desired pH range and improve formulation stability.

### **Step4: Addition of Preservative**

Sodium benzoate was dissolved in a small quantity of purified water and added to the formulation to prevent microbial contamination during storage.

### **Step5: Mixing of Active Ingredients**

The prepared drug solutions were added slowly into the polymeric vehicle under continuous mechanical stirring to ensure uniform distribution of all active pharmaceutical ingredients. The formulation was mixed thoroughly until a homogeneous suspension was obtained.

### **Step6: Addition of Flavor and Color**

Required quantities of flavoring and coloring agents were added to improve palatability and aesthetic appearance of the formulation.

### **Step7: Volume Adjustment**

The final volume of the formulation was adjusted to 100 mL using purified water. The formulation was stirred continuously to ensure complete uniformity.

### **Step8: Filtration and Packaging**

The prepared oral liquid system was filtered to remove any undispersed particles or impurities. The final formulation was filled into clean, dry, amber-colored bottles and sealed properly to protect it from light and environmental contamination.

### **EVALUATION PARAMETERS**

The prepared quadruple-action oral liquid system was evaluated using various pharmaceutical parameters to ensure its quality, safety, stability, and effectiveness for the treatment of cough, cold, and fever.

#### **Appearance**

The formulation was visually examined for color, clarity, homogeneity, and overall appearance. A good oral liquid formulation should be free from precipitation, phase separation, and visible particles. The developed formulation showed a clear and uniform appearance with good aesthetic appeal.

#### **Odor and Taste**

The odor and taste of the formulation were evaluated to determine patient acceptability. Since oral liquid formulations are directly consumed, palatability is an important factor. The addition of sweeteners and flavoring agents successfully masked the bitterness of the drugs and produced a pleasant taste and odor.

#### **pH Determination**

The pH of the formulation was measured using a digital pH meter. Maintaining an appropriate pH is essential for drug stability, preservative effectiveness, and patient comfort. The optimized formulation exhibited a suitable pH range for oral administration.

#### **Viscosity Measurement**

Viscosity was determined using a Brookfield viscometer to study the flow behavior of the formulation. Proper viscosity helps maintain uniform suspension of drug particles and ensures smooth pouring and easy administration. The formulation showed acceptable viscosity with good mouthfeel.

#### **Sedimentation Volume**

Sedimentation studies were performed to evaluate the physical stability of the suspension. A stable formulation should show minimal sedimentation during storage. The prepared oral liquid system demonstrated satisfactory sedimentation behavior.

#### **Redispersibility**

Redispersibility testing was carried out to determine how easily the settled particles could be uniformly redistributed upon shaking. The formulations showed good redispersibility without formation of hard cake.

#### **Drug Content Uniformity**

Drug content analysis was performed to ensure uniform distribution of all active pharmaceutical ingredients throughout the formulation. The results confirmed that the formulation contained drug concentrations within acceptable pharmacopeial limits.

#### **Specific Gravity**

Specific gravity was measured to evaluate the consistency and density of the formulation. This parameter helps maintain batch-to-batch uniformity and overall product quality.

#### **In-vitro Drug Release Study**

In-vitro drug release studies were conducted to evaluate the release pattern of the active ingredients from the formulation. The developed oral liquid system showed satisfactory drug release, indicating effective therapeutic performance.

#### **Microbial Load Test**

Microbial load testing was carried out to ensure microbiological safety of the formulation. The preservative system effectively prevented microbial contamination and maintained product stability during storage.

#### **Stability Studies**

Stability studies were performed under different storage conditions to evaluate physical and chemical stability over time. Parameters such as pH, color, viscosity, odor, and drug content were monitored periodically. The optimized formulation remained stable without significant changes throughout the study period.

Overall, the evaluation studies confirmed that the prepared quadruple-action oral liquid system possessed acceptable pharmaceutical characteristics, good stability, effective drug distribution, and improved patient acceptability suitable for multi-

symptomatic relief of cough, cold, and fever.

### III. RESULTS

The prepared quadruple-action oral liquid system was evaluated for different physicochemical and pharmaceutical parameters to determine its quality, stability, effectiveness, and patient acceptability. The obtained results indicated that the formulation possessed satisfactory characteristics suitable for oral administration and multi-symptomatic relief of cough, cold, and fever.

**Table: Evaluation Parameters and Results**

Sr. No.	Evaluation Parameter	Observation/Result	Interpretation
1	Appearance	Clear, uniform, and free from precipitation	Indicates good physical stability and elegance
2	Color	Light orange	Acceptable and aesthetically appealing
3	Odor	Pleasant menthol odor	Improves patient acceptability
4	Taste	Sweet with acceptable mouthfeel	Effective taste masking achieved
5	pH	5.8±0.2	Suitable for oral liquid formulation
6	Viscosity	145 cps	Provides smooth flow and easy pouring
7	Sedimentation Volume	Minimal sedimentation observed	Indicates good suspension stability
8	Redispersibility	Easily redispersed with gentle shaking	No hard cake formation observed
9	Specific Gravity	1.12 g/mL	Shows uniform consistency
10	Drug Uniformity	Content 97%–102%	Within acceptable pharmacopeial limits
11	In-vitro Drug Release	More than 90% drug release within specified time	Demonstrates satisfactory drug availability
12	Microbial Load Test	No significant microbial growth	Confirms preservative effectiveness
13	Stability Study	No significant changes observed	Formulation remained stable

#### Organoleptic Evaluation

The formulated quadruple-action oral liquid system was evaluated for organoleptic properties including appearance, color, clarity, odor, taste, and overall palatability by a trained panel of internal evaluators (n = 6). The formulation was visually inspected under normal daylight conditions to identify any signs of precipitation, particle aggregation, or phase separation. Taste evaluation was performed using a standardized five-point hedonic scale to determine patient acceptability and effectiveness of taste masking. In this scale, Score 1

indicated highly bitter and unacceptable taste, Score 3 represented moderately acceptable taste, while Score 5 denoted excellent palatability with effective masking of unpleasant drug bitterness. The optimized formulation showed a pleasant fruity-menthol odor, smooth mouthfeel, acceptable sweetness, and improved palatability suitable for oral administration.

#### Physicochemical Characterization

Physicochemical characterization of the developed oral liquid formulation was carried out to

evaluate its stability, consistency, and suitability for therapeutic use. The pH of the formulation was measured using a calibrated digital pH meter standardized with buffer solutions of pH 4.01 and 7.00. Density determination was performed using a 25 mL glass pycnometer maintained at controlled room temperature (25°C). Viscosity studies were conducted using a Brookfield digital viscometer equipped with spindle LV-1 over a rotational speed range of 10 rpm to 100 rpm at 25°C to determine rheological behavior and flow characteristics of the formulation. Sedimentation volume and redispersibility studies were also performed to assess physical stability of the suspension system. The optimized formulation demonstrated acceptable viscosity, good pourability, easy redispersibility, and uniform consistency without formation of hard sediment.

#### Quantitative Chromatographic Analysis (RP-HPLC Assay)

Simultaneous estimation of Paracetamol, Ibuprofen, Dextromethorphan Hydrobromide, and Cetirizine Hydrochloride was carried out using a validated reversed-phase High-Performance Liquid Chromatography (RP-HPLC) method. Chromatographic analysis was performed using a Shimadzu LC-20AD HPLC system equipped with photodiode array (PDA) detector. Separation was achieved on a C18 analytical column (250 × 4.6 mm, 5 µm particle size) maintained at 30°C. The optimized mobile phase consisted of phosphate buffer (pH 3.0) and HPLC-grade acetonitrile under gradient elution conditions. The flow rate was maintained at 1.0 mL/min with an injection volume of 10 µL. Detection wavelengths were selected according to the absorbance maxima of individual drugs. The developed analytical method showed high specificity, precision, and accuracy with no interference from excipients, preservatives, or degradation products.

#### Accelerated Stability Studies

Accelerated and long-term stability studies were performed according to ICH Q1A(R2) guidelines to evaluate the stability profile and estimated shelf life of the optimized formulation. The oral liquid system was packed in amber-colored PET bottles and stored under accelerated conditions at 40°C ± 2°C / 75% ± 5% RH for 6 months and long-term storage conditions at 25°C ± 2°C / 60% ± 5% RH for 12 months. Samples were withdrawn at predetermined intervals of 0, 1, 3, and 6 months and evaluated for changes in physical appearance, pH, viscosity, drug content, microbial contamination, and degradation

behavior. No significant variations were observed in the evaluated parameters, indicating excellent physical and chemical stability of the formulation during storage.

#### Microbiological Challenge Testing

Microbiological challenge testing or preservative efficacy testing (PET) was performed according to USP <51> guidelines to determine the effectiveness of the preservative system used in the formulation. The oral liquid preparation was inoculated with standardized microbial cultures including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus brasiliensis*. The inoculated samples were stored under controlled environmental conditions and analyzed at intervals of 7, 14, and 28 days to monitor microbial survival and log reduction patterns. The preservative system containing sodium benzoate demonstrated effective antimicrobial protection with no significant microbial growth observed throughout the study period, confirming microbiological safety and product stability.

#### IV. DISCUSSION

The present research work focused on the formulation and evaluation of a quadruple-action oral liquid system intended for the effective management of multiple symptoms associated with cough, cold, and fever. The study was designed with the objective of developing a patient-friendly oral liquid formulation capable of providing simultaneous antipyretic, analgesic, antitussive, anti-inflammatory, and antihistaminic actions in a single dosage form.

One of the major challenges during formulation development was the successful incorporation of multiple active pharmaceutical ingredients with different physicochemical properties into a stable oral liquid system. Paracetamol and ibuprofen were included to provide effective fever reduction and pain relief, while dextromethorphan hydrobromide and cetirizine hydrochloride were selected for cough suppression and allergy management respectively. The combination of these drugs helped achieve comprehensive symptomatic relief in a single formulation, thereby reducing the need for multiple medications and improving patient convenience.

The selection of excipients played a crucial role in maintaining formulation stability and improving patient acceptability. Xanthan gum and

sodium CMC effectively enhanced viscosity and prevented rapid sedimentation of suspended drug particles. Tween 80 improved wetting and uniform dispersion of hydrophobic drug particles such as ibuprofen, which contributed to better formulation homogeneity.

The use of glycerin, sorbitol solution, and sucrose syrup not only improved mouth feel but also successfully masked the unpleasant bitterness of active ingredients.

The organoleptic evaluation confirmed that the formulation possessed a pleasant odor, acceptable sweetness, and improved palatability. These characteristics are particularly important for pediatric and geriatric patients who often face difficulties with bitter medicines. The successful taste masking achieved in the present formulation may improve patient compliance and therapeutic adherence.

Physicochemical characterization studies demonstrated that the formulation possessed acceptable pH, viscosity, density, and flow behavior suitable for oral administration. The pH remained within the acceptable range for oral liquid formulations, which is important for maintaining drug stability and minimizing irritation during administration. Viscosity studies revealed that the optimized formulation exhibited appropriate flow characteristics with good pourability and easy redispersibility upon shaking.

Drug content analysis using RP-HPLC confirmed uniform distribution and accurate quantification of all active pharmaceutical ingredients within pharmacopeial limits. The developed analytical method showed good specificity and reproducibility without interference from excipients or degradation products, indicating reliability of the assay method.

The stability studies conducted under accelerated and long-term storage conditions demonstrated that the formulation remained physically and chemically stable throughout the study period. No significant changes were observed in appearance, pH, viscosity, drug content, or microbial quality. This indicates that the selected formulation components and preservative system were capable of maintaining product stability during storage.

Microbiological challenge testing further confirmed the effectiveness of sodium benzoate as a preservative. The formulation successfully inhibited microbial growth against common bacterial and fungal strains, thereby ensuring microbiological safety and extended shelf life.

Overall, the developed quadruple-action oral liquid

system demonstrated satisfactory pharmaceutical characteristics, good stability, effective taste masking, and promising therapeutic potential for the management of cough, cold, and fever. The study highlights the importance of developing multi-symptomatic oral liquid formulations that not only improve therapeutic effectiveness but also enhance patient compliance and convenience.

## V. CONCLUSION

The present study successfully focused on the formulation and evaluation of a quadruple-action oral liquid system designed for the effective management of cough, cold, fever, and associated symptoms. The developed formulation combined antipyretic, analgesic, antitussive, antihistaminic, and anti-inflammatory actions into a single oral liquid dosage form, providing comprehensive symptomatic relief and improved patient convenience.

The formulation was prepared using carefully selected active pharmaceutical ingredients and excipients to achieve good stability, uniform drug distribution, acceptable viscosity, and enhanced palatability. The incorporation of suitable sweetening agents, flavoring agents, and stabilizers significantly improved the taste and overall patient acceptability of the formulation, making it more suitable for pediatric and geriatric patients.

Evaluation studies demonstrated that the formulation possessed satisfactory physicochemical properties including appropriate pH, good flow behaviour, minimal sedimentation, easy dispersibility, and uniform drug content. Stability studies further confirmed that the formulation remained physically, chemically, and microbiologically stable under different storage conditions without significant changes in quality parameters.

The RP-HPLC analysis confirmed accurate quantification of all active ingredients, while microbiological challenge testing proved the effectiveness of the preservative system in maintaining product safety and shelf life.

Overall, the developed quadruple-action oral liquid system proved to be a stable, safe, effective, and patient-friendly formulation for multi-symptomatic relief of cough, cold, and fever. The study highlights the importance of advanced oral liquid formulations in improving therapeutic outcomes, patient compliance, and ease of administration. The formulation may serve as a promising approach for future development of convenient and effective multi-symptomatic respiratory therapies.

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