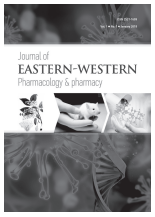

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# Study of technology and standardization of composite medicines with compound ingredients for use in flu and flu-like diseases

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KEYWORDS

*Acetaminophen, Phenylephrine hydrochloride, Chlorpheniramine maleate Caffeine, HPLC*

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ABSTRACT

According to the World Health Organization, seasonal influenza results in approximately one billion cases annually, with 3–5 million severe complications and 290,000–650,000 deaths worldwide. Symptomatic treatments for fever, headache, joint and muscle pain, nasal congestion, and other related symptoms are commonly used.

In our country's pharmaceutical market, traditional medicines, herbal remedies, and generic drugs with expectorant and fever-reducing properties are domestically produced. This study aimed to develop and evaluate the quality of compounded ingredients formulated as tablets for treating influenza and flu-like illnesses.

Tablets containing active ingredients were formulated and compressed to a weight of 600 mg (C1) and 640 mg (C2, C3) using a tablet compression machine. Manufacturing defects, such as capping and cracking, were observed in the C3 tablet. The active ingredient content in C1 was found to be insufficient, failing to meet the established quality requirements. In contrast, the C2 tablet met the quality standards for tablet formulations.

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## INTRODUCTION

Influenza and flu-like diseases infect numerous individuals quickly, often leading to complications and fatalities, making them a significant public health concern [1]. Influenza viruses are categorized into four types: A, B, C, and D, with influenza A and B being the most prevalent[2]. Common symptoms include fever, chills, cough, sore throat, muscle aches, headache, and fatigue. These symptoms can range from mild upper respiratory tract infections to potentially fatal pneumonia and complications involving the heart, central nervous system, and other non-respiratory systems[3]. Influenza-like illnesses are caused by more than 200 types of viruses, most commonly rhinoviruses, adenoviruses, and coronaviruses [4].

The progression of flu and flu-like illnesses depends on the patient's general health, age, and previous exposure to the influenza virus. Clinical manifestations can be categorized into four types: mild, severe, severe, and highly toxic. Treatment involves addressing symptoms such as fever, headache, joint and muscle pain, nasal congestion, and interventions targeting the underlying cause 5. Adults typically experience colds 2–4 times annually, while children are affected 6–8 times yearly[6].

Mongolia's pharmaceutical market offers traditional medicines, herbal remedies, and generic drugs with expectorant and fever-reducing effects. This study aims to develop tablet technology utilizing high-quality, certified raw materials to create a fixed-dose combination of acetaminophen, phenylephrine hydrochloride, chlorpheniramine maleate, and caffeine. This formulation is intended to alleviate the pain and pathological symptoms of acute upper respiratory tract inflammation[7].

Acetaminophen alleviates pain by reducing the sensitivity of nociceptors through the inhibition of prostaglandin synthesis and by normalizing the thermoregulation center in the hypothalamus [8]. Chlorpheniramine maleate exerts its effects by blocking histamine H1 receptors, thereby mitigating allergic reactions and reducing vascular permeability 9. Phenylephrine hydrochloride acts on α-adrenergic receptors to reduce nasal and throat mucosal swelling and redness, thereby facilitating nasal breathing 10. Caffeine helps alleviate drowsiness and fatigue, enhancing mental and physical performance [11]. Tablets with this composition are registered under the brand names Nolcold and Rinza in Russia and India within the Mongolian drug registration system.

## MATERIALS AND METHODS

### Materials

In the development of tablet technology, several tests were conducted using wet granulation technology with Acetaminophen (103-90-2), Phenylephrine hydrochloride (61-76-7), Chlorpheniramine maleate (113-92-8), Caffeine (58-08-2), and suitable auxiliary substances as active ingredients. Chlorpheniramine maleate (Sigma-Aldrich Co LLC Germany), Phenylephrine hydrochloride (Sigma-Aldrich Co LLC, Germany), Acetaminophen (Shanghai Macklin Biochemical Co., Ltd, Shanghai, China), Caffeine (Sigma-Aldrich Co LLC Germany) RST were used.

### *PRE-COMPRESSION EVALUATION OF GRANULES*

#### Moisture

1 g of granules was weighed with an accuracy of 0.001 g and dried at 100-105ºC to a constant weight[12].

#### Tapped density

The tapped densities (TD) of granules were determined by gently 25 gm sample mixture through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from a height of 2 inches until a constant volume was obtained, and then the average value of all formulations was reported. The final volume occupied by the sample after tapping was recorded, and tapped density was calculated by using the formula [13].

$$\text{Tapped density} = \frac{\text{Weight of the powder (g)}}{\text{Tapped volume occupied by granules (ml)}}$$

#### Compressibility

Carr's compressibility provides a valuable empirical guide. The compressibility of the polyherbal powder mixture was calculated by comparing the bulk density and tapped density. The percentage compressibility of all formulations was calculated [14].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{X100}$$

**Hausner's ratio**

It also shows the densification of the herbal powder mixture, which may result from the vibration of the feed hopper, which was calculated using the formula [14].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

**Bulk density**

The granules' bulk density (BD) was determined by gently 25 gm sample mixture through a glass funnel into a 100 ml graduated cylinder. The initial volumes occupied by the sample were recorded. The bulk density was calculated using the following formula [14].

$$\text{Bulk density} = \frac{\text{Weight of the powder (g)}}{\text{Volume occupied by granules (ml)}}$$

***POST COMPRESSION EVALUATION OF TABLET***

**Weight Variation**

Weight variation was calculated by using 20 tablets. Weigh 20 tablets individually and calculate the average weight of 20 tablets. Then, calculate the upper and lower limits using the formula [13].

**Weight variation = (Iw − Aw)/Aw Ч 100%**
**Where Iw=Individual weight of the tablet and**
**Aw = Average weight of the tablet.**

**Hardness**

Hardness is defined as the force required to break the tablet. It is used to determine the strength of the tablet. A Monsanto hardness tester is used to determine the tablet's hardness. Hardness is measured in mPa [15].

**Friability** 10 tablets are required to calculate the friability. For friability, pre-weighted 10 tablets, then rotated at 25 rpm for 4 minutes. After the removal of fine particles, re-weight the tablets. The percentage of weight loss will be calculated by using the following formula [15]:

**% Friability = W1 – W2/W1 * 100**

**W1 = Initial weight of tablets**

**W2 = Final weight of tablets**

**Disintegration test**

For the test, one tablet was placed in each tube, and the basket risk was positioned in a 1000 ml vessel containing 900 ml of water maintained at 37 ± 0.5 °C so that the tablets remained 2 cm below the surface of the liquid on their upward movement and descent not closer than 2 cm from the bottom of the beaker. The apparatus was operated for 15 min. The disintegration time was taken to be the time when no particle remained on the basket [13].

**Dissolution test**

Dissolution test for this test, a USP dissolution apparatus was used. One tablet was placed in each vessel (6 vessels) to test for dissolution, containing 900 ml of water maintained at 37 ± 0.5 °C. The rotational speed of the apparatus was held constant at 50 rpm. A sample of 5 ml was withdrawn at fixed time intervals (30min), and this was immediately replaced with the same volume of fresh test media. The analysis was performed under HPLC conditions [13].

**Assay**

For drug content, weigh 20 tablets accurately and crush all the tablets into fine powder. Weigh the sample equivalent to the active drug (in mg) and dissolve it in methanol. Filter the sample through 0. 45 µm millipore filters and analyze under HPLC [13].

**Statistical analysis**

The results are expressed as the mean standard deviation (SD). All statistical analyses were performed using the Excel 2016 software.

**RESULTS**

**Pre-compression evaluation of granules**

All values are reported as mean±SD, n=3 measurements.

**Table 1. The basic characterization of granule formulation**

| Granules code | Moisture, % | Bulk density, g/ml | Tapped density, g/ml | Hausner's ratio | Carr's index |
|---|---|---|---|---|---|
| C1 | 1.7±0.046 | 0.70±0.0124 | 0.63±0.016 | 1.11±0.014 | 11.6±1.069 |
| C2 | 2.15±0.061 | 0.57±0.012 | 0.51±0.009 | 1.12±0.004 | 12.84±0.617 |
| C3 | 1.02±0.038 | 0.62±0.037 | 0.55±0.032 | 1.12±0.004 | 13.38± 0.08 |

The moisture content of the granules in formulations C1, C2, and C3 was 1.7%, 2.15%, and 1.02%, respectively. The Hausner's ratio for the C1 granules was 1.11, indicating excellent flowability, while the Hausner's ratios for the C2 and C3 granules were 1.12, suggesting good flowability. Regarding compressibility, the tablets exhibited values ranging from 11 to 13, indicating good compressibility for all the granules.

**Formulation and characterization of tablets**

**Table 2. Composition for compound tablets**

| Ingredients | Unit | Tablets code | | |
|---|---|---|---|---|
| | | C1 | C2 | C3 |
| Acetaminophen | mg | 500 | 500 | 500 |
| Caffeine | mg | 30 | 30 | 30 |
| Phenylephrine hydrochloride | mg | 5 | 5 | 5 |
| Chlorpheniramine maleate | mg | 2 | 2 | 2 |
| Corn starch | mg | 23.6 | - | 69.9 |
| Povidone K-30 | mg | 12 | 22.5 | 4.1 |
| Sodium starch glycolate | mg | 15 | 18 | 10.3 |
| Talc | mg | 7 | - | - |
| Magnesium stearate | mg | 3 | 3 | 6.2 |
| Colloidal silicon dioxide | mg | 0.5 | 3 | 7.2 |
| FD&C Yellow No5 | mg | 0.9 | - | 5.2 |
| FD&C Yellow No1 | mg | - | 0.48 | - |
| Microcrystalline cellulose | mg | - | 46.42 | - |
| Stearic acid | mg | - | 5.1 | - |
| Croscarmellose sodium | mg | - | 4.5 | - |
| Purified water | ml | q.s | q.s | q.s |
| Total weight | | 600 | 640 | 640 |

Based on the dosage and formulation specified in Table 2, three formulations were prepared using appropriate excipients in different ratios, with the C1 granules based on Agicold, C2 granules based on Nolcold, and C3 granules based on Rinza. The 600 mg (C1) and 640 mg (C2, C3) tablets were prepared using a Kilian-S250 rotary tablet press machine with 16.6 mm punches.

**Table 3. Physical description of tablets**

| Parameter | C1 | C2 | C3 |
|---|---|---|---|
| Color | Yellowish orange | Yellowish | Yellowish orange |
| Shape | Oval | Oval | Oval |
| Size in mm | | | |
| -Thickness | 5.2 | 5.4 | * |
| -Diameter | 16.6 | 16.6 | * |

As presented in Table 3, manufacturing defects such as capping and cracking were observed in the C3 tablets. These defects were attributed to the lower moisture content of the C3 tablets than those of C1 and C2, resulting in inadequate compaction during manufacturing. Consequently, it was concluded that further investigation of this formulation could not proceed.

As illustrated in Figure 1, the C1 and C2 models satisfied the quality criteria for tablet appearance, demonstrating characteristics consistent with oval-shaped tablets, including well-defined edges, smooth surfaces, and a uniform yellow color. In contrast, due to physical damage, Model C3 failed to meet the established criteria.

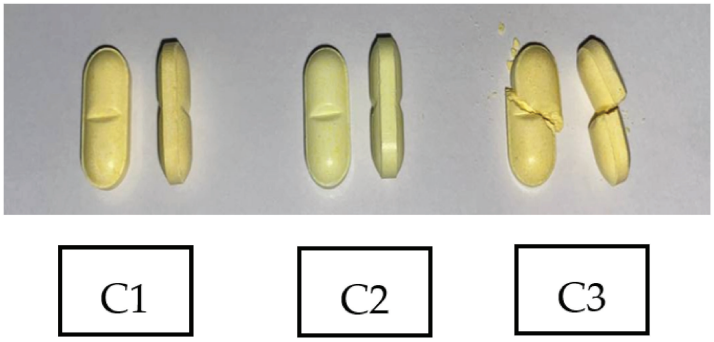


**Figure 1. Physical appearance of tablets**

**Table 4. Physical properties of tablets (n=20 Mean±SD)**

| Tablets code | Average weight, mg | Weight variation, , % ±5% | | Hardness, mPA | Frability, % |
|---|---|---|---|---|---|
| C1 | 0.59±0.0092 | +2.79 | -3.63 | 1.17±0.0031 | 99.6±0.0011 |
| C2 | 0.64±0.007 | +1.87 | -2.23 | 0.86±0.0051 | 99.4±0.0023 |

All values are reported as mean±SD, n=20 measurements.

In Table 4, the C1 tablet has an average weight of 0.59g, a hardness of 1.17 MPa, and a friability of 99.6%. The C2 tablet has an average weight of 0.64g, a hardness of 0.86 MPa, and a friability of 99.4%. Based on these results, both C1 and C2 tablets meet the quality requirements for tablet dosage forms.

**Table 5. Quality control test for tablets**

| | Specifications | Tablet quality | C1 | C2 |
|---|---|---|---|---|
| | Disintegration | No more than 15 minutes | 4 | 5 |
| Dissolution | Acetaminophen | Not less than 80.0% in 30 minutes | 85.45 | 89.94 |
| | Caffeine | | 97.44 | 99.43 |
| | Phenylephrine hydrochloride | | 92.94 | 94.35 |
| | Chlorpheniramine maleate | | 101.44 | 95.26 |
| Assay | Acetaminophen | 5% (475-525mg) | 471.249 | 477.661 |
| | Caffeine | 7.5% (27.75-32.25mg) | 28.898 | 29.065 |
| | Phenylephrine hydrochloride | 10% (4.5-5.5mg) | 4.688 | 4.727 |
| | Chlorpheniramine maleate | 10% (1.8-2.2mg) | 1.684 | 1.967 |

The content of the active ingredients in the tablets was evaluated using the HPLC method, compared to the respective standard substances. The results for each tablet are presented in Table 5 /Figure 2, 3./. The caffeine and phenylephrine hydrochloride content in the C1 tablet complied with the required standards.

However, the content of chlorpheniramine maleate (1.684 mg) and acetaminophen (471.249 mg) did not meet the established standards. In contrast, the content of all active ingredients in the C2 tablet was within the acceptable range. Additionally, the disintegration times of the tablets were 4 minutes for C1 and 5 minutes for C2, both of which meet the requirement of being less than 15 minutes. The dissolution results for the C1 and C2 tablets, as shown in Table 5, also complied with the quality requirements for tablet dosage forms.

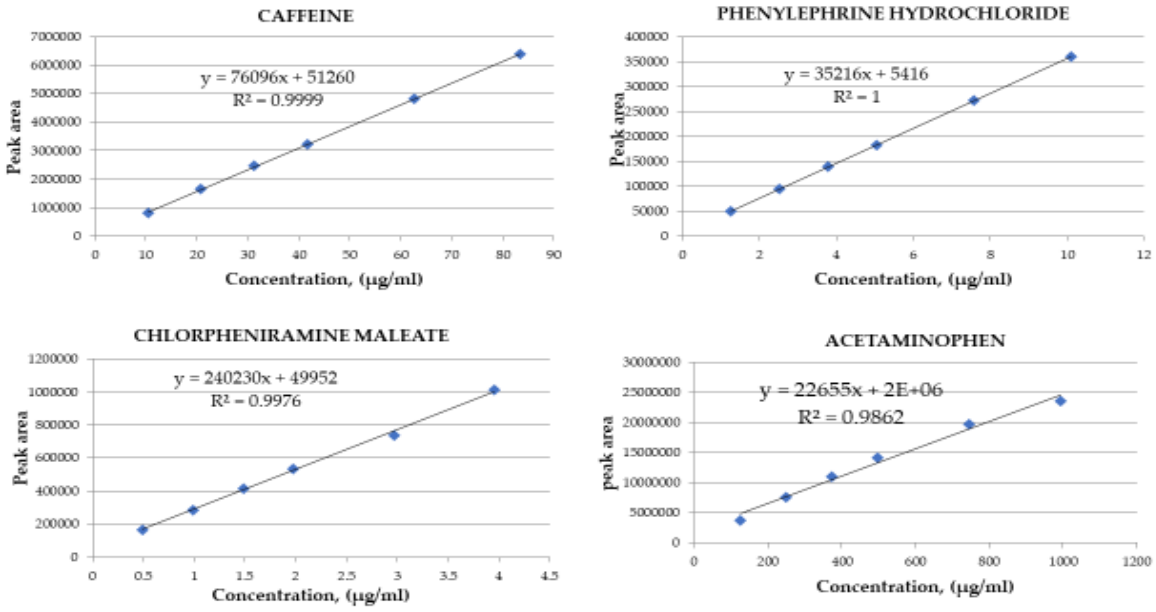


**Figure 2**. Standard curves of active ingredients

According to Figure 1, the correlation coefficient is 1.0000 for phenylephrine hydrochloride, 0.9976 for chlorpheniramine maleate, 0.9976 for acetaminophen, and 0.9999 for caffeine.

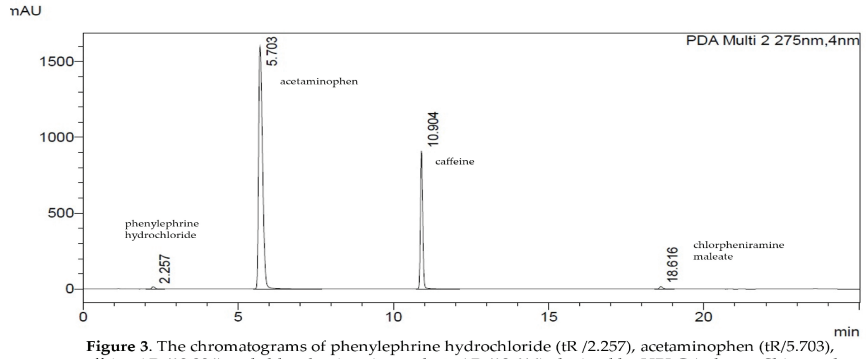


**Figure 3**. The chromatograms of phenylephrine hydrochloride (tR /2.257), acetaminophen (tR/5.703), caffeine (tR /10.904) and chlorpheniramine maleate (tR /18.616) obtained by HPLC (column: Shim-pack GIST C18, 150/3 mm; mobile phase ,0.05 M potassium dihydrogen phosphate /pH=3.0/: acetonitrile, 95:5 v/v).

## DISCUSSION AND CONCLUSION

The quality of tablets containing acetaminophen, phenylephrine hydrochloride, chlorpheniramine maleate, and Caffeine for the combined symptoms of cold and flu was tested according to the methods of the Mongolian Pharmacopoeia–National Formulary (MP–NF) 2011 and the British Pharmacopoeia 2013. The World Health Organization (WHO) and the Society for Infectious Diseases guidelines recommend the combination of an analgesic (acetaminophen) and an antihistamine (chlorpheniramine) for the treatment of seasonal influenza A given respiratory

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Based on experience from other countries, the effectiveness of fixed-dose combination therapy for treating common cold symptoms in Indian adults was investigated. This study found that a combination dose of acetaminophen 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg was effective and safe[17].

Pharmaceutical excipients significantly improve the drug's physical properties and bioavailability, making the dosage form more suitable. The choice of excipients plays an essential role in the preparation of dosage forms [18].

Researchers Michal Szumilo, Piotr Belniak, Katarzyna Swiader, Ewelina Holody, and Ewa Poleszak conducted a study titled "Evaluation of the Physical Properties of Granules Containing Acetaminophen and Caffeine." They used mannitol as a filler, calcium hydrogen phosphate as a lubricant, corn starch as a disintegrant, and polyvinylpyrrolidone K30 as a binding agent. Our research employed the same binding agent, demonstrating its versatility in pharmaceutical formulations[19].

In a study conducted in India by scientists V.K. Redasani, A.P. Gorle, and R.A. Badhan, an experiment was performed to simultaneously determine acetaminophen, phenylephrine hydrochloride, chlorpheniramine maleate, and Caffeine using a C18 column in HPLC. The correlation coefficients reported were 0.9999 for Caffeine, 0.9998 for phenylephrine hydrochloride, 0.9998 for chlorpheniramine maleate, and 0.9996 for acetaminophen[20]. In our study, the correlation coefficients were 0.9999 for Caffeine, 1.0 for phenylephrine hydrochloride, 0.9976 for chlorpheniramine maleate, and 0.9976 for acetaminophen. These results affirm the precision and reliability of our analytical methods.

As a result of our research, we have developed suitable excipients, an appropriate formulation, and preparation technology methods for tablets with complex ingredients intended to treat influenza and flu-like diseases. We established quality criteria and demonstrated the quality of the tablets through parameters such as strength, dissolution, disintegration, and dosage uniformity. This research highlights the feasibility of replacing imported products with modern pharmaceutical forms that can be utilized in therapeutic practice and contribute to the diversity of domestic medicines. The quality parameters of the experimental tablet models met the standards set by the Mongolian Pharmacopoeia–National Formulary (MP–NF) for pharmaceutical tablets. C1 tablets failed to meet the quality requirements due to the low content of the main active ingredients, acetaminophen, and chlorpheniramine. C3 tablets could not be compressed due to their low moisture content. However, the C2 tablet met the requirements set for tablet formulations. In conclusion, this study demonstrates the potential to produce high-quality, effective pharmaceutical tablets for treating influenza and flu-like diseases using locally sourced materials and advanced formulation techniques. The results pave the way for reducing dependency on imported medications and expanding the scope of domestic pharmaceutical production.

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