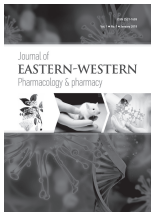

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Development and technology study of combination tablet formulations

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Abstract

Seasonal transitions weaken the human immune system, increasing susceptibility to influenza and influenza-like illnesses. These illnesses are caused by viruses that damage the epithelial cells of the respiratory tract, resulting in symptoms such as fever, sore throat, cough, nasal congestion, rhinorrhea, and headache. Severe cases can lead to complications, including pneumonia, acute bronchitis, otitis media, and sinusitis. Combination drugs containing ibuprofen, phenylephrine hydrochloride, and chlorpheniramine maleate effectively manage these conditions. However, tablet formulations with this combination are not yet available in our country. Consequently, we aimed to develop a manufacturing protocol for such a formulation in a domestic pharmaceutical facility and assess its quality.

The wet granulation method prepared tablets containing the aforementioned combination. Several formulations were developed and evaluated based on quality parameters specified in the Mongolian Pharmacopoeia-National Formulary (MP-NF).

The Hausner ratio and Carr's index for formulations A1 (1.13 and 15, respectively), A3 (1.14 and 14.2), and A5 (1.15 and 15.7) indicated "good" flow properties and high compressibility, enabling successful tableting. Formulations A2 and A4 exhibited Hausner ratios of 1.23 and 1.18 and Carr's indices of 23.5 and 18.9, respectively, reflecting "fair" flow properties and poor compressibility. Tablets could not be compressed from formulation A2 due to granule fragmentation. The successfully compressed formulations (A1, A3, A4, and A5) met all quality criteria stipulated in the Mongolian Pharmacopoeia-National Formulary (MP-NF), including appearance, average weight, weight variation, hardness, and disintegration time.

A2 was unsuitable for compression among the five formulations due to granule breakage. The remaining formulations (A1, A3, A4, and A5) demonstrated

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acceptable compression properties, with formulations A1 and A3 showing the shortest disintegration times (3 and 4 minutes, respectively). These findings suggest that formulations A1 and A3 are the most promising candidates for further development.

INTRODUCTION

According to the World Health Organization (WHO), seasonal influenza affects approximately one billion individuals annually, with 3–5 million cases progressing to severe illness and 290,000–650,000 deaths resulting from respiratory complications.[1] Due to Mongolia's extreme climate, influenza and influenza-like illnesses are common, and recent trends in urbanization and increasing air pollution have further contributed to the spread of these infections.[2] Seasonal transitions weaken the immune system, increasing susceptibility to influenza and related illnesses.[3] The causative viruses damage the epithelial cells of the respiratory tract, leading to symptoms such as fever, sore throat, cough, nasal congestion, rhinorrhea, and headache.[4] In severe cases, complications such as pneumonia, acute bronchitis, otitis media, and sinusitis may develop, posing significant health risks. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), exerts antipyretic and analgesic effects by inhibiting prostaglandin synthesis.[5]

Phenylephrine hydrochloride, a vasoconstrictor, reduces redness and swelling in the upper respiratory tract and paranasal sinuses.[6] Chlorpheniramine maleate, an antihistamine, blocks histamine H1 receptors, alleviating allergic symptoms.[7] This combination of active ingredients is particularly effective for managing the symptoms associated with influenza and influenza-like illnesses. Current symptomatic treatments for influenza and related conditions often rely on combination drugs containing paracetamol. Paracetamol reduces pain by suppressing nociceptor sensitivity through the inhibition of prostaglandin synthesis and lowers fever by normalizing hypothalamic thermoregulatory function through decreased prostaglandin levels in the cerebrospinal fluid.[8] However, paracetamol's typical single dose ranges from 500 to 1000 mg, and excessive dosages are associated with hepatotoxicity.[9] A review of Mongolia's drug registration database indicates the presence of 69 registered combination drugs containing paracetamol for treating influenza and cold symptoms.[10] In contrast, only one ibuprofen-based combination drug, "Total Cold Kunihiro A," manufactured by Japan's Kokando Co., Ltd. and registered by Monos Pharma Trade LLC, was identified. Mongolia's national "Health Policy" emphasizes ensuring an uninterrupted, equitable, and accessible supply of high-quality, safe, and effective medicines to the population, healthcare institutions, and veterinary organizations while promoting rational drug use.[11] Within this policy framework, domestically producing imported drugs and diversifying available therapeutic options represent vital initiatives to improve national healthcare resilience and benefit public health. The U.S. Centers for Disease Control and Prevention (CDC) recommends initiating influenza treatment within the first 48 hours of symptom onset to mitigate the risk of complications, reduce treatment costs, and save time during severe cases.[12] Against this backdrop, this study seeks to develop and evaluate a tablet formulation combining ibuprofen, phenylephrine hydrochloride, and chlorpheniramine maleate, aiming to provide an effective treatment option for alleviating symptoms associated with influenza and influenza-like illnesses.

MATERIALS AND METHODS

Raw Materials and Ingredients:

Ibuprofen (Shandong Xinhua Pharmaceutical Co., Ltd, China CAS No. 15687-27-1), phenylephrine hydrochloride (Sigma-Aldrich Co. LLC, Germany, CAS No. 61-76-7), chlorpheniramine maleate (Sigma-Aldrich Co. LLC, Germany, CAS No. 113-92-8), and excipients were sourced from GMP-certified suppliers to ensure compliance with quality standards and were utilized in this study.

Granulation Process:

The combination tablet formulations were developed using the conventional wet granulation method. Five formulations were prepared based on the composition

and dosage detailed in Table 1. The process involved weighing and dry blending the raw materials, followed by wet granulation using a binder solution.

The granules were then dried at room temperature for 24 hours, sieved to achieve uniform particle size, and blended with glidants and lubricants to produce the final granules suitable for tableting / Table 1. /.

Table 1. Composition and Dosage of Tablet Formulations

№	Material name	Unit	Amount of materials used in a single tablet trial (per batch) in grams				
			A - 1	A - 2	A – 3	A - 4	A - 5
1.	Ibuprofen	g	0.2	-	-	0.2	0.2
2.	Nano ibuprofen	g	-	0.2	0.2	-	-
3.	Phenylephrine hydrochloride	g	0.01	0.01	0.01	0.01	0.01
4.	Chlorpheniramine maleate	g	0.004	0.004	0.004	0.004	0.004
5.	Microcrystal cellulose	g	0.09	0.073	0.143	0.121	0.143
6.	Polevinylprrilidone (PVP)	g	0.02	0.005	0.015	0.011	0.015
7.	Sodium carboxymethyl starch	g	-	-	0.012	0.008	0.012
8.	Sodium croscarmellose	g	0.02	0.02	0.012	0.012	0.012
9.	Colloidal silicon dioxide	g	0.008	0.02	0.002	0.002	0.002
10.	Magnesium stearate	g	0.008	-	0.002	0.002	0.002
11.	Maltodextrin	g	-	-	-	0.03	-
12.	Pregelatinized starch	g	-	40	-	-	-
13.	Corn starch	g	0.04	0.028	-	-	-
14.	Glycerol	ml	-	0.3	-	-	-
15.	Polysorbate 80	ml	-	0.012	-	-	-
16.	Medium-chain triglycerides (MCTs)	ml	-	0.06	-	-	-
17.	Purified water	ml	x	-	X	x	x
18.	**Total**	**g / ml**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**

Assessment of Granule Quality:

The flow properties of the granules were evaluated by determining the bulk. They tapped densities and calculated the Hausner ratio and Carr's index according to the standards outlined in the British Pharmacopoeia 13. Moisture content analysis was performed using the Adam PMB 53 moisture analyzer to ensure compliance with quality parameters / Table 2. /.

Table 2. Flowability Classification Reference

Carr's index	Flowability	Hausner's ratio
≤10	Excellent	1-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Evaluation of Tablet Quality: The S250 SMART tablet press compressed the granules into tablets. The tablets' physical attributes were evaluated per the general specifications for tablet dosage forms as outlined in the Mongolian Pharmacopoeia-National Formulary (MP-NF).14 The tablet appearance was assessed through sensory methods, while the average weight and weight variation were determined using a JX 200 analytical balance. The mechanical strength of the tablets was measured using the THT-3 hardness tester, disintegration time was assessed with the YK-BJ01 disintegration apparatus, and friability was evaluated using the SY-6D friability tester.

Statistical Analysis: Data processing was performed using Microsoft Excel 2016.

RESULTS

Flowability of Granules:

The flow properties of the granules were evaluated based on the bulk density, and the results of the flowability assessment using the Hausner ratio are presented in Table 3.

Table 3. Pre-compression properties of the granules.

Formulation	Bulk density, ml	Tapped density, ml	Hausner's ratio	Flowability
A1	1.55%	1.13	1.13	Good
A2	1.26%	1.22	1.23	Fair
A3	1.79%	1.14	1.14	Good
A4	2.30%	1.18	1.18	Good
A5	1.60%	1.15	1.15	Good

Flowability Assessment Based on Hausner Ratio:

The evaluation of flowability using the Hausner ratio revealed that formulations A1 and A2, with a ratio of 1.23, exhibit medium flowability, while formulations A3 (1.14), A4 (1.18), and A5 (1.15) demonstrate good flowability.

Granule Compressibility Evaluation:

Table 4 presents the compressibility of the granules, assessed based on bulk density, with results determined using Carr's Index.

Table 4. Results of Granule Compressibility Evaluation

Formulation	Bulk density, ml	Tapped density, ml	Carr's index	Flowability
A1	1.55%	1.13	13.1	Good
A2	1.26%	1.22	23.5	Passable
A3	1.79%	1.14	14.2	Good
A4	2.30%	1.18	18.9	Fair
A5	1.60%	1.15	15.7	Fair

Compressibility Evaluation Results:

The findings from the compressibility assessment indicate that formulations A1 and A3 exhibit excellent compressibility, while formulations A4 and A5 display moderate compressibility, and formulation A2 shows acceptable compressibility. Based on these results, formulations A1 and A3 are considered suitable for tablet compression. **Moisture Content of Granules:** Excessive or insufficient moisture content in granules can adversely affect their compressibility, reducing resistance to pressure and friction. Accordingly, the prepared granules' optimal moisture content was determined and presented in Table 5.

Tablet 5. Evaluation Results of Granule Moisture Content

Formulation	Moisture, %
A1	1.55
A2	1.26
A3	1.79
A4	2.30
A5	1.60

Granule Moisture Content Evaluation Results:

The moisture content evaluation results indicate that formulation A1 has a moisture content of 1.55%, formulation A2 has 1.26%, formulation A3 has 1.79%, formulation A4 has 2.30%, and formulation A5 has 1.60%.

Assessment of Tablet Quality:

Appearance: Five granular formulations were compressed into tablets using an S250 SMART automatic tablet press at a 0.4 g. The outcomes are presented in Table 6. Formulations A1, A3, A4, and A5 were successfully molded, whereas formulation A2 failed to form correctly. It is hypothesized that the failure of A2 tablet compression may be attributable to the excipients incorporated in the formulation.

Tablet 6. Post-Compression Appearance Evaluation

Formulation	Color	Shape	Size, mm	
			Thickness	Diameter
A1	White	Oval	15.6±0.1	6.3±0.1
A3	White	Oval	15.4±0.1	6.3±0.1
A4	White	Oval	15.4±0.1	6.3±0.1
A5	White	Oval	15.5±0.1	6.4±0.1

n=5.0

Tablet Quality Evaluation

Post-Compression Appearance of Formulations: The molded formulations exhibit an oval shape, white coloration, intact edges, and smooth surfaces, meeting the established quality standards for tablets.

Average Weight and Weight Variability: The average weight and weight variability are critical parameters for assessing the uniformity of the dosage form. The average weight and weight variability for each formulation were determined by gravimetric analysis and are summarized in Table 7.

The results of the study indicated the following: Formulation A1: Average weight 0.4049 ± 0.002 g, weight variability 1.23%, Formulation A3: Average weight 0.4062 ± 0.007 g, weight variability 1.56%, Formulation A4: Average weight 0.4046 ± 0.002 g, weight variability 1.17%, Formulation A5: Average weight 0.4035 ± 0.002 g, weight variability 0.88%

Table 7. Post-Compression Weight Characteristics

Formulations	Average weight, mg	Weight variability, % <±5	
A1	0.4028±0.003	+1.8	-1.05
A3	0.4022±0.002	+1.5	-1.3
A4	0.4058±0.002	+2.2	-0.2
A5	0.4046±0.001	+2	-0.3

n=20.0

Based on the study results, all formulations comply with the Mongolian Pharmacopoeia-National Formulary (MP-NF) standards, stipulating that the average tablet weight and weight variability must fall within ±5%.

Tablet Resistance to Pressure, Frictional Force, and Disintegration Characteristics:

The tablet's resistance to pressure and friction is determined by the structure, properties, and composition of the raw materials, which significantly influence the tablet's stability and shelf life. Additionally, tablet disintegration plays a critical role in the drug's dissolution rate. In this study, we assessed the tablets' resistance to pressure, frictional forces, and disintegration. The findings in Table 8 demonstrate that the tablet's resistance to pressure meets the Mongolian Pharmacopoeia-National Formulary (MP-NF) requirement of ≥0.45 MPa. In contrast, its resistance to friction meets the Mongolian Pharmacopoeia-National Formulary (MP-NF) standard of ≥97%.

Tablet 8. Physical Properties of the Tablet

Formulations	Pressure, MPa	Friability, %	Disintegration, minute
A1	0.6±0.01	99.6	3
A3	1.2±0.05	99.7	4
A4	1.2±0.02	99.7	13
A5	1.2±0.03	99.65	5

n=3.0

The disintegration times observed for the tablet variants are Variant A1 in 3 minutes, A3 in 4 minutes, A4 in 13 minutes, and A5 in 5 minutes. These results comply with the standards outlined in the Mongolian Pharmacopoeia-National Formulary (MP-NF), which specifies that uncoated tablets should disintegrate within 15 minutes.

DISCUSSION

In this study, we performed technological trials based on the formulation of Advil-coated tablets (Wyeth, USA) utilizing an identical composition. The formulation was adjusted to suit the active pharmaceutical ingredients, and five variations were selected for testing. The granules were prepared using the traditional wet granulation method, followed by sieving through 14 and 20-mesh screens to ensure uniformity. The resulting granules were compressed into 0.4 g tablets using an S 250 SMART automatic tablet press.

This research indicates that no similar products exist in the Mongolian pharmaceutical market. A US Food and Drug Administration study compared the antipyretic and analgesic effects of paracetamol and ibuprofen. The duration of ibuprofen's antipyretic effect ranged from 60 minutes to 6 hours, while paracetamol's effect lasted from 80 minutes to 3.5 hours. [15]

Research conducted by Lailah Nakazibwe et al. (2023) involved the production of ibuprofen-containing tablets using Musa acuminata starch (banana starch) as a binder, employing the wet granulation method to produce five tablet variations for quality analysis. In this study, the Hausner ratio and Carr's index before compression ranged from 1.08 to 1.2 and 6.3 to 16.738, respectively. In contrast, our study found that the Hausner ratio and Carr's index of our tablet formulations ranged from 1.13 to 1.22 and 14.2 to 22, respectively. These differences are attributed to variations in the excipients used in both studies. [16]

Similarly, the research by Kishore Babu et al. (2010) utilized sodium croscarmellose and sodium carboxymethyl starch as disintegrants in ibuprofen-containing tablets, which aligns with the excipients used in our study. [17]

The study conducted by Yandi Syukri et al. (2019) on the formulation of tablets containing chlorpheniramine maleate utilized microcrystalline cellulose at a concentration of 79.63%. In contrast, our study employed microcrystalline cellulose at varying levels across different formulations:

22.5% in A1, 18.25% in A2, 35.75% in A3, 35.75% in A4, and 30.25% in A5. These variations can be attributed to differences in factors such as the average tablet weight and the content of the active pharmaceutical ingredient. Additionally, our formulation incorporated excipients such as magnesium stearate, colloidal silicon dioxide, and polyvinylpyrrolidone (K-30), which are consistent with those reported in the study by Yandi Syukri et al. [18]

CONCLUSION

The technological guidelines for a combined formulation to address the symptoms of influenza and influenza-like illnesses were developed and evaluated for quality. In the pre-tableting stage, the flowability of pellets A1, A3, and A5 was rated as "good," while pellets A2 and A4 demonstrated poor flowability. Upon compression, the A2 variant failed to compress and disintegrated, while the other variants were successfully compressed into tablets. Analysis of the tablets revealed that the A1 and A3 variants had the shortest disintegration times of 3 and 4 minutes, respectively. Based on these results, it is concluded that the formulations of A1 and A3 are the most suitable for further optimization and development. Formulation A1 utilized conventional ibuprofen, while Formulation A3 incorporated nano-ibuprofen. Due to the inherently poor absorption of ibuprofen, nano-ibuprofen was selected to address this limitation, whereas conventional ibuprofen was included for comparative purposes. Further analyses, including quantitative determination, dissolution, and disintegration studies, will be conducted in accordance with international pharmacopoeial standards.

These evaluations will provide a comprehensive understanding of the differences between the two active ingredients and help determine the most effective formulation for future application.

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