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Research Paper

Development of Pharmaceutical Equivalent Montelukast Sodium Immediate-Release, Film-Coated Tablets

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Abstract
Montelukast tablets are sold under the brand name Singulair and are used to control and prevent asthma symptoms. In this study, 10 mg film-coated montelukast tablets were developed as a generic drug in order to evaluate the pharmaceutical equivalent of the innovator's products. The primary formulation ingredients used in all developed formulations (F1-F5) were the same as those described in the Singulair tablet package insert, except for formulations F3, F4, and F5, to which solubilizing enhancers were added to increase montelukast solubility. The core tablets were produced using the wet granulation method before being coated with HPMC polymer. FT-IR and DSC were used to determine drug and excipient compatibility. The micromeritic properties of the granules were assessed. The physicochemical properties of generated montelukast tablets and Singulair tablets were also investigated. The dissolution profiles of the tested drug and the innovator were assessed in a variety of pH mediums (pH 1.2, 4.5, 6.8, and water). The similarity (f_2) and difference (f_1) factors were computed. The accelerated and long-term stability of the tested drug in hot and humid climate zones was evaluated. The analytical method validation used in this study was ICH-acceptable for 8 parameters including specificity, range, linearity, accuracy, precision, limit of detection, limit of quantitation, and robustness. F1-F5 granules had similar properties, such as a pale-yellow color and excellent flow properties. There were no chemical interactions between montelukast and the excipients according to FT-IR and DSC analyses. The physical properties of all developed montelukast film-coated tablets were similar (average weight 212-218 mg; thickness 3.02-3.07 mm; assay 101-102% LA; disintegration time 3-4 min), except that the disintegration time of F3 was 8.10 min and that of F5 was 5.90 min, which was caused by the addition of poloxamer 188 to the formulation. In all mediums, only the F1 formula produced acceptable comparison dissolution profiles to Singulair. After 6 months of storage under accelerated and long-term conditions, the results showed the F1 formulation remained physically and chemically stable.

Keywords
Montelukast Sodium, Immediate-Release Tablet, Dissolution Profile Comparison, Pharmaceutical Equivalent, Stability

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1. INTRODUCTION

In Thailand, new generic drug development follows the Association of Southeast Asian Nations (ASEAN) harmonization and the ASEAN common technical requirement (ACTR), which states that pharmacists must develop new generic drugs with a pharmaceutical equivalent, quality control of raw materials, product, and packaging, and evidence of product interchangeability equivalence. Developing a new generic drug product in the pharmaceutical industry requires a scientific and technical approach that is distinct from developing an innovative product (Hasan et al., 2021). The goal of developing a new generic drug should be to have the same pharmaceutical properties, treatment efficacy, and safety as the original product (Davit et al., 2016).

Montelukast sodium (Figure 1) is an orally administered selective cysteinyl leukotriene 1 receptor inhibitor. This medication is approved for the prevention and treatment of symptoms including asthma, exercise-induced bronchoconstriction, and allergic rhinitis. Currently, granules, chewable tablets, and film-coated tablets are available in the market today (Barbosa

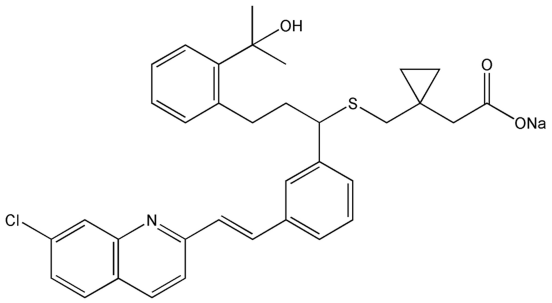

Figure 1. Chemical Structure of Montelukast Sodium

et al., 2016; Chen et al., 2017). The physicochemical properties of montelukast sodium include low solubility; pKa1 is 3.3 and pKa2 was found to be 4.4 (Singh et al., 2022) or other literature reported 2.7 and 5.8 (Okumu et al., 2008; Martir et al., 2020) and classified in BCS class 2 (Okumu et al., 2008; Martir et al., 2020). Singulair, the trade name for montelukast sodium manufactured by Merck (USA), has been FDA approved since February 20, 1998. Even after more than 25 years on the market, montelukast remains a popular and effective well-tolerated prophylactic treatment for both adults and children with asthma and allergic rhinitis (Nayak, 2004; Lee and Kim, 2020). Several different research groups have prepared montelukast sodium tablets over the past few years in orally disintegrating tablets (ODT) or fast-dissolving tablets (Mahesh et al., 2012; Jain and Mundada, 2015; Chen et al., 2017; Mahant et al., 2020). However, ODT is categorized as a new drug because the release profiles and bioavailability are not equivalent to an innovation (World Health Organization, 2016). The preparation of chewable tablets of montelukast sodium was carried out to ensure immediate release (Shruthi and Thahera, 2013; Rajesh et al., 2019). In addition, inclusion complexes of montelukast with hydroxypropyl-β-cyclodextrin were also developed to increase drug solubility (Barbosa et al., 2016; Kim et al., 2015). Because the solubility of montelukast sodium is pH-dependent (Chen et al., 2017), dissolution profile evaluation tests in a range of buffer solutions with varying pH values are necessary to accurately evaluate *in vitro* montelukast sodium performance and pharmaceutical equivalence. The pharmaceutical industry continues to perform and investigate generic drug research and development, and the procedures are not systematically disclosed. However, there is a report of a montelukast sodium film-coated tablet being developed on an industrial scale, but there is a lack of information during the research and development process in research and development by pharmaceutical industries (Zaid et al., 2013). It is interesting to develop a generic montelukast sodium film-coated tablet formulation which is similar and equivalent to the original product and ensures that the final bioequivalence studies will be equivalent.

The objectives of this study were to create film-coated tablets of montelukast sodium that are pharmaceutically equivalent and evaluate dissolution profiles similar to those of commercially available film-coated tablets (Singulair). The principal screening tools for each formulation were dissolution profiles in various media. Dissolution profile comparison experiments were then used to evaluate the optimized formulation. Evaluations were also conducted on the granule flow properties, tablet physical property characteristics, disintegration time and stability.

2. EXPERIMENTAL SECTION

2.1 Materials

Pharmaceutical-grade montelukast sodium (batch no. 0065, bulk batch no. HG021) was purchased from Silom Medical Co., Ltd. (Pra Nakhon Si Ayutthaya, Thailand). Standard montelukast sodium hydrate (≥98% HPLC) was obtained from Sigma-Aldrich, St. Louis, MO, USA. The inactive ingredients including microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium lauryl sulfate (SLS) and carnauba wax were obtained from S. Tong Chemical (1985) Co., Ltd, Bangkok, Thailand. The color lakes (red ferric oxide and yellow ferric oxide) were used from raw materials at the Pharmaceutical Technology Laboratory for pharmacy students and they were not identified for origin. Poloxamer 188, dibasic sodium sulfate was purchased from BASF (Ludwigshafen, Germany). Acetonitrile, trifluoroacetic acid, methanol, hydrochloric acid, sodium acetate, glacial acetic acid and other reagents were analytical grade and purchased from Labscan (Bangkok, Thailand).

The innovator montelukast sodium tablet is Singulair, and 10 mg film-coated tablets were used to compare the pharmaceutical equivalent test lot no. N029366 (Mfg. 26/09/2017 Exp. 25/09/2020).

2.2 Preparation of Montelukast Tablets

2.2.1 Core Tablets

All montelukast sodium core tablets were produced using the formulations listed in Table 1. All formulations are based on the wet granulation method to improve the flow properties and strength of the tablet to film coat it in the final step. The composition of F1 and F2 was designed roughly based on the original excipients described in formulations created with the innovator. The F3–F5 formulations, on the other hand, were prepared by wet granulation with a solubilizing agent. Due to the stability of the montelukast sodium (Chen et al., 2017), every tablet formulation was manufactured in a dark environment to minimize exposure to light.

All ingredients were sieved through mesh no. 18 (sieve aperture 1 mm) to reduce powder aggregates and agglomerates and make them easier to mix with other ingredients. The batch size of this research and development laboratory scale was 500 tablets (100 g). The montelukast sodium and intragranular components were weighed precisely and blended thoroughly for 15 minutes. Using a hydroxypropyl cellulose solution to wet the intragranular mixture, a wet coherent mass was then passed through a 12-mesh sieve with a sieve aperture of 1.25

Table 1. Composition of Immediate-Release Montelukast Sodium Tablets

Ingredients	Formulation Codes / Amount of Ingredients (mg)					Function
	F1	F2	F3	F4	F5	
Montelukast sodium (equivalent to montelukast 10 mg)	10.4	10.4	10.4	10.4	10.4	Active ingredient
Microcrystalline cellulose	60.0	60.0	60.0	60.0	60.0	Diluent
Lactose monohydrate	61.6	71.6	87.6	87.6	87.6	Diluent
Croscarmellose sodium	60.0	50.0	30.0	30.0	30.0	Disintegrant
Hydroxypropyl cellulose	6.0	6.0	6.0	6.0	6.0	Binder
Sodium lauryl sulphate	-	-	4.0	-	2.0	Solubility enhancer
Poloxamer 188	-	-	-	4.0	2.0	Solubility enhancer
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	Lubricant
Purified water*	0.5	0.5	0.5	0.5	0.5	Granulating solvent
Total weight	200	200	200	200	200	

* will evaporate during the manufacturing process

mm to create wet granules. Wet granules were dried at 60 °C in a hot-air oven (FFD Binder, Tuttlingen, Germany) for 45 minutes. Subsequently, an 18-mesh sieve was used to remove any aggregated or lumps from the dried granules. A 40-mesh sieve with a sieve aperture of 0.45 mm was used to sieve the extra-granular excipients. Extra-granular disintegrant was mixed thoroughly with dried granules for five minutes, and magnesium stearate was mixed thoroughly for three minutes. The obtained granules were compressed into 8 mm diameter tablets with a flat surface punch using an electric single punch tableting machine (Charatchai Machinery Ltd., Bangkok, Thailand).

2.2.2 Film Coating Process

The montelukast sodium tablet coating material formulation is displayed in Table 2. Hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) 6000 were weighed and dissolved in purified water to produce a transparent solution. Titanium dioxide, red ferric oxide, and yellow ferric oxide lakes were sieved through an 80-mesh sieve with a 180 mm sieve aperture before being mixed vigorously for 30 minutes in a polymer solution. Throughout the coating process, the dispersion was stirred constantly. In the Thai Coater automatic coating pan (model FC 15; Pharmaceuticals and Medical Supply Limited Partnership (PMS), Bangkok, Thailand) using one spray gun, tablet coating was done. Table 3 provides an overview of the coating process conditions and parameters. The coating pan was cleaned with water and 95% ethanol before being loaded with 100 montelukast sodium tablets with placebo tablets weighing about 1.5 kg (different tablet shapes to be separated later) to reduce the amount of drug required. A drier and a high-pressure air spray gun were used to pre-heat the tablet cores to approximately 40 °C. Warm air, between 45 and 55 °C, was blown into the coating pan for the entire coating procedure. The aqueous coating dispersion was loaded into the spray gun by a peristaltic pump and utilized at the flow rate suggested by the manufacturer. The pan coating speed was set at 12 rpm. The seal-coating dispersion was sprayed over the tablet bed cores at the proper air pressure of 1.7–2.0 bar. In the coating pan, tablets were air-dried for 20 to 25 minutes after the air heater was turned off. The weight of the core tablets increased by about 10 mg after the coating procedure. The film-coated tablets were then polished for 3 minutes using carnauba wax that had been dissolved in acetone at a concentration of 10% w/w and poured into the coating pan for 200 mL. For further assessment, the coated tablets were stored in an amber glass bottle with silica gel.

2.3 Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR instrument (Bruker Corporation, Bremen, Germany) was used to conduct compatibility studies on montelukast sodium and all excipients. Prior to measurement, the raw material of montelukast sodium was mixed with KBr and hydraulically pressed to obtain a KBr disc. All ingredients with montelukast sodium including solubilizing agents were mixed and then pressed with KBr to obtain the KBr disc. The disc samples were analyzed by FT-IR instrument. The FTIR spectra were recorded between 4000 and 400 cm^{-1} with a resolution of 4 cm^{-1} using 16 scans per sample.

2.4 Differential Scanning Colorimetry (DSC)

Montelukast sodium powder and the physical mixing of montelukast sodium with lactose monohydrate, and montelukast sodium with croscarmellose sodium were carried out on a differential scanning calorimeter (DSC 800, Perkin Elmer Inc., USA). Each sample (4-5 mg) was heated at a rate of 10 °C/min from 50 to 300 °C under a flowing nitrogen atmosphere (flow rate: 20 mL/min) in an aluminum pan.

2.5 Physical and Mechanical Properties of Granules

2.5.1 Moisture Content

The moisture contents of granules, after being obtained from a hot air oven, were determined by a moisture analyzer (model

Table 2. Film Coating Materials of Immediate-Release Montelukast Sodium Tablets

Coating materials	Amount for 1 Tablet (mg)	Amount for Batch Size (g)	Function
Hydroxypropyl methylcellulose (E15)	6.0	60.0	Film forming agent
Polyethylene glycol 6000	0.6	6.0	Plasticizer
Titanium dioxide	2.5	25.0	Opacifying agent
Red ferric oxide	0.2	2.0	Coloring agent
Yellow ferric oxide	0.7	7.0	Coloring agent
Purified water*	-	1 kg	Solvent
Carnauba wax	qs	qs	Polishing wax
Total weight	10 mg	1.1 kg	

* will evaporate during the manufacturing process

Table 3. Film Coating Process Parameter and Conditions

Film Coating Parameters	Conditions
Pan coating model and specification	Thai coater (perforated pan with baffles) model FC 15" (15-inch pan diameter) with dust collector
Tablet loading	100 tablets of montelukast sodium tablets loaded with 12 mm diameter placebo tablets (1.5 kg)
Tablet bed temperature (°C)	45 °C-55 °C
Pan rotation speed (rpm)	12 rpm
Air inlet temperature (°C)	75 °C-85 °C
Spray rate	20 rpm of peristaltic pump
Atomizing air pressure	1.7 – 2.0 bar
Spray gun	Low pressure air atomized system,
Distance between gun spray tip and tablet bed surface	5 inches from tablet bed and set angle of 45°
Total coating times	40 min

HR83, Mettler Toledo, Greifensee, Switzerland). The moisture content of finished granules after mixing with an extra-granular excipient was also measured.

2.5.2 Angle of Repose

The montelukast sodium granule formulations (F1–F5) were placed in a funnel and allowed to fall into a heap on graph paper. The funnel was suspended from a burette stand at a fixed height. Using the formula in Equations (1) and (2), the height and radius of the heap were measured, and the angle of repose (θ) was computed.

$$\tan\theta = \frac{\text{Height of the heap formed (h)}}{\text{Radius of the heap (r)}} \quad (1)$$

$$\theta = \tan^{-1}\frac{h}{r} \quad (2)$$

2.5.3 Compressibility Index

According to the general chapter <616> of the United States Pharmacopoeia, bulk and tap densities were calculated using method I, which involved measuring in a graduated cylinder (United States Pharmacopeial, 2023). About 100 g of the granule formulations F1–F5 were placed in a graduated 250–mL cylinder, and the unsettled apparent volume was read to determine the bulk density in g/mL. Using the Jolting Apparatus (Pharma Test, model PT-TD, Hainburg, Germany) described in USP, the tapped volume determination was continued from

bulk density (United States Pharmacopeial, 2023). The cylinder containing granules was tapped, and the volume corresponded to the number of taps. If the difference in volume between 500^{th} taps and $1{,}250^{th}$ taps is less than or equal to 2 mL, the volume of $1{,}250^{th}$ taps is a tapped volume. If the difference between 500^{th} taps and $1{,}250^{th}$ taps is more than 2 mL, repeat every $1{,}250^{th}$ tap until the measurement is less than or equal to 1 mL. The tapped density is calculated from the mass and tapped volume of the granule in g/mL. The compressibility index was computed from tapped density (ρ_{tapped}) and bulk density (ρ_{bulk}) using Equation (3), as described in general chapter <1174> powder flow (United States Pharmacopeial, 2023).

$$\text{Compressibility index} = \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right) \times 100 \qquad (3)$$

2.5.4 Hausner's Ratio

This Hausner's ratio was calculated from tapped density (ρ_{tapped}) and bulk density (ρ_{bulk}) according to general chapter <1174> powder flow using the following Equation (4) (United States Pharmacopeial, 2023).

$$\text{Hausner's Ratio} = \frac{\rho_{tapped}}{\rho_{bulk}} \qquad (4)$$

2.5.5 Particle Size Analysis of Granules

Sieve analysis for particle size distribution of montelukast sodium granule formulations was performed using a sieve shaker analyzer (AS200, Retsch, Retsch-Allee, Germany). The 100 g of each granule was placed on the top of stack sieves with the larger sieve on top, from #20 to #120 sieves, at power 5, starting for 5 minutes. Each sieve, along with the retained particles, was weighed individually after shaking. The particle size distributions were plotted with retained particle mass vs. sieve diameter. The average particle size of granules was calculated.

2.6 Evaluation of Mechanical and Physical Properties of Tablets

2.6.1 Appearance and Dimension of Tablets

The appearance of montelukast sodium core and coated tablets with defects were organoleptically observed when tableting. The diameter of the tablets was measured with a Vernier caliper. Data were expressed as mean value ± standard deviation and repeated 6 times.

2.6.2 Thickness Test

The thickness of montelukast sodium tablet formulations F1–F5 were measured using a dial thickness gauge (Mitutoyo model 7301A, Tokyo, Japan). A mean value ± standard deviation was obtained from six measurements and expressed in mm.

2.6.3 Hardness Test

Six tablets of each montelukast sodium tablet formulation F1–F5 were randomly chosen. Tablet hardness was measured using a PTB311E model (Pharma Test, Hainburg, Germany) and expressed as a mean value ± standard deviation. The average value of six independent tests was used in data analyses.

2.6.4 Average Weight Measurement

The weight of the coated and core tablets was measured frequently to verify that the right amount of active ingredient was present in each tablet. Twenty tablets of each montelukast sodium tablet formulation F1–F5 were randomly chosen and weighed by analytical balance. A mean value ± standard deviation was reported.

2.6.5 Friability Test

Following USP guidelines, approximately 6.5 g (or around 33 tablets) of each montelukast sodium formulation were precisely weighed and then placed in a plastic chambered friability apparatus (Erweka, model TA220, Heusenstamm, Germany). The chamber was connected to a motor that rotated at 25 rpm for 4 minutes. The obtained tablets were dusted for cleanliness and weighed again. The braking, capping, or laminating of tablets should not be found. The tablets were weighed afterwards, and the following Equation (5) was used to determine the % weight loss (friability):

$$\text{Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \qquad (5)$$

2.6.6 Disintegration Test

The disintegration test for the montelukast sodium tablets (F1–F5) was carried out in compliance with USP United States Pharmacopeial (2023) using a disc-based disintegration apparatus (Pharma Test, model DIST3, Hainburg, Germany) with six duplicates for each tablet group. The tablets were kept at 37 ± 2 °C and were individually put in each tube within a 900 mL beaker of distilled water. The mean disintegration time and standard deviation values were calculated. To ensure that the montelukast sodium tablet dissolved entirely within 30 minutes, a disintegration time of less than 15 minutes was considered acceptable.

2.7 Analytical Validation of Montelukast Sodium

2.7.1 Chromatographic System

The HPLC system used to determine the content of montelukast sodium is a Dionex Ultimate 3000 HPLC system (Thermo Scientific, USA). An HPLC system consists of a temperature control device, an inline degasser, an auto-sampler, and a UV/VIS absorbance detector. The Chromeleon operating software was used during the study. A C18 column (250 × 4.6 mm, 5 μm particle size) was used as the stationary phase. The mobile phase was optimized with 60% methanol, 30% acetonitrile, and 10% water. The injection volume of the sample was 20 μL. They were carried out by a UV/VIS detector at 254 nm. A flow rate of 1 mL/min and a runtime of 5 min.

2.7.2 Preparation of Standard Solution and Calibration Curve

A stock solution of standard montelukast sodium with a concentration of 1,000 μg/mL was prepared by accurately weighing and adding 100 mg of the standard montelukast sodium to a 100-mL volumetric flask and then adjusting the volume with the mobile phase. To get the montelukast sodium concentration in the range of 1–800 μg/mL, further dilutions were done. Appropriate aliquots of montelukast sodium standard stock solution (1,000 μg/mL) were diluted in an appropriate volumetric flask with mobile phase to create subsequent dilutions, yielding final concentrations of 1, 3.125, 6.25, 12.5, 25, 50, 100, 200, 400, and 800 μg/mL. Before HPLC analysis, the sample was filtered via a 0.45-μm nylon membrane filter. The peak area ratio of the obtained chromatogram vs. the applied montelukast concentration was plotted to create the calibration curve, and a regression equation was calculated.

2.7.3 Method Validation

To determine whether there were any interfering components, the specificity of the test was examined. The total separation of montelukast sodium in the presence of its degradation products, as well as other factors like retention time, capacity factor, tailing or asymmetry factor, were used to determine the specificity of the HPLC method. Additionally, the degradant sample was analyzed in triplicate under various circumstances using a mobile phase with varying selectivity to determine the specificity.

The linearity of the method was evaluated between 50% and 210% of the desired assay concentration range for the analyte. There were 1-800 μg/mL of montelukast sodium in standard solutions. Three duplicates of the linearity solutions were injected into the HPLC system.

The percentage recovery of montelukast sodium was computed to indicate accuracy. Placebo powdered were mixed and then diluted with mobile phase. A quantity of montelukast sodium equal to 50%, 100%, and 150% of the labeled claimed was added to the sample. The amount of montelukast sodium in each combination was measured using a calibration equation after each sample was examined in triplicate. The acceptability criteria for the percentage of recovery in this investigation were established at 95% - 105%.

Montelukast sodium samples were prepared following the test protocol and injected six times into the HPLC system. Repeatability was determined by measuring the montelukast sodium concentrations six times. Intermediate precision was performed by different pharmacy students to analyze the samples on different days. A precision study indicates the method is reliable when %RSD < 2.

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in the analytical procedure parameters. To evaluate the robustness of the HPLC method, a few parameters were deliberately varied. The parameters included variation of columns C8 (old & new), percentage of methanol in the mobile phase, percentage of acetonitrile in the mobile phase and methanol or acetonitrile of different lots. In addition, change in wavelength ± 2 nm and change in flow rate ± 0.2 mL/min were performed.

The limit of detection (LOD) and limit of quantitation (LOQ) of an analytical method may be defined as the concentration, which gives rise to an instrument signal that is significantly different from the blank. For analytical techniques that rely upon a calibration curve for quantitative measurements, the standard deviation (SD) of the response and the slope (S) of the calibration curve were calculated for LOD and LOQ based on Equations (6) and (7) as follows.

$$\text{LOD} = 3.3\ (\text{SD}/\text{S}) \tag{6}$$

$$\text{LOQ} = 10\ (\text{SD}/\text{S}) \tag{7}$$

2.8 Assay Content of Montelukast Sodium and Content Uniformity

Twenty tablets were weighed and finely milled. The powder containing 10 mg of montelukast was weighed accurately and added into a 100 mL volumetric flask. The drug powder was dissolved in the mobile phase to prepare 100 μg/mL of montelukast concentration and then diluted to obtain 10 μg/mL of concentration. The sample solution was filtered through a 0.45 μm nylon membrane filter before analysis. System suitability was performed by injecting 20 μL of standard solution, and the results should be found to be within the range. Twenty microliters of the sample and standard solutions were individually injected into the HPLC system. The concentration of montelukast sodium in the sample was evaluated according to the procedures mentioned previously. The assay analysis was performed in triplicate.

The uniformity of the dosage unit of film-coated tablets was determined according to the general chapter <905> of USP, which indicated that the dose of an active drug less than 25 mg or less than 25% of the total tablet weight must be performed by content uniformity (United States Pharmacopeial, 2023). Ten tablets were weighed separately and transferred directly to a 100 mL volumetric flask. Seventy milliliters of mobile phase were added to each flask for dissolving. The sample solution was sonicated for 30 min, adjusted to 100 mL with the mobile phase, and then filtered through a 0.45-mm nylon membrane filter. The montelukast sodium concentration was analyzed by the HPLC method, as described above. The acceptance criteria for content uniformity were calculated using the formula provided in the USP, and the maximum allowed acceptance value was considered at 15 (United States Pharmacopeial, 2023).

2.9 *In Vitro* Dissolution Profile Studies

A USP dissolution test apparatus II (Varian, Vankel VK7010, CA, USA) was used for an in vitro dissolution study in 900 mL of different medium types at 37 ± 0.5 °C with a stirring speed of 50 rpm (United States Pharmacopeial, 2023). The dissolution media that were examined were 0.5% SLS in water,

0.2% SLS in phosphate buffer (pH 6.8), 0.2% SLS in phosphate buffer (pH 4.5), and 0.1% SLS in a solution of 0.1 M HCl (pH 1.2). One coated tablet of developed montelukast sodium or Singulair was placed in each basket, and aliquots of 5 mL were taken out and replaced with an equal volume of fresh media that was kept at the same temperature at specified intervals (0, 1, 5, 10, 15, 20, 30, 45, and 60 min). Twelve replicates were employed in the experiment. Aliquots of the sampling substance were filtered using a 0.45-μm membrane filter. The concentration of montelukast sodium in the aliquot was assessed using the previously indicated HPLC method at a wavelength of 254 nm. The dissolution profiles of developed montelukast sodium and Singulair were compared employing an independent mathematical model by calculating a difference factor (f_1) and a similarity factor (f_2) using Equations (8) and (9), respectively.

$$f_1 = [\{\frac{\Sigma_{t=1}^{n} |R_t\text{-}T_t|}{\Sigma_{t=1}^{n} R_t}\} \times 100] \quad (8)$$

$$f_2 = 50 \times [log[\{1 + \frac{1}{n}\Sigma_{t=1}^{n}(R_t\text{-}T_t)^2\}^{-0.5}] \times 100 \quad (9)$$

where n is the number of withdrawal points, Rt and Tt are the percentages of dissolved substance in the tested product (developed montelukast sodium tablets) and the reference product (Singulair tablets), respectively, at time t. When the two dissolution profiles under comparison had f_2 values between 50 and 100, they were comparable. However, they were different when they had f_1 values between 1 and 15 (Shah et al., 1998).

2.10 Stability Studies

Following the ICH climatic zone IVb, the optimized formulations of the montelukast sodium tablets were packed in Alu-PVC blister covered with aluminum foil, to protect moisture and light. The tablets were then kept under accelerated and long-term conditions in Thailand (Kopp, 2006; Malik et al., 2011; González-González et al., 2022). The accelerate condition was performed at a temperature of 40°C ± 2°C and relative humidity (RH) of 75% ± 5%. The test interval is sampling at 1, 2, 3 and 6 months. The long-term stability condition was performed at a temperature of 30°C ± 2°C and 75% ± 5% RH in a stability chamber, and the samples were sampled every 3 months. The appearance of tablets, montelukast content expressed in % labeled claim (%LA), and disintegration time were evaluated at stability period intervals.

2.11 Statistical Analysis

Microsoft Excel (Redmond, Washington, USA) was used to conduct the statistical analysis. The results are demonstrated as means ± standard deviation. The independent student's t-test was utilized to compare the means of the two groups. Statistical significance was acceptable at a P-value < 0.05.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation and Formulation Development of Generic Drug Montelukast Sodium

The composition of Singulair 10 mg film-coated tablet, as confirmed by Merck & Co., Inc., included microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax. To prevent drug incompatibility with any excipients and ensure the same dissolution profile, this information from the innovator was used for the initial proposed formulation of montelukast tablets and can be manufactured similarly. Testing Singulair 10 mg film-coated tablets for physical properties is the first step in developing a generic version of a drug. The findings revealed that Singulair tablets weighed 204.83 ± 3.15 mg, and had a thickness of 3.78 ± 0.01 mm, a length of 8.96 ± 0.02 mm, and a hardness of 3.77 ± 0.15 kP. The disintegration times for Singulair were 3.93 ± 1.65 min, with values ranging from 2.26 to 6.86 min (n = 6 of all tests). Determining the release profiles of Singulair 10 mg film-coated tablets by dissolution test was the second stage of the preparation for the montelukast sodium generic drug according to United States Pharmacopeial (2023). The dissolution test medium was 0.1% w/v SLS in water (900 mL). The preliminary test aimed to determine the dissolution pattern for formulation development, even though the recommended dissolution profile test for product development is three mediums at different pH levels of 1.2, 4.5, and 6.8. The findings demonstrated that montelukast released from the tablet at over 60% at 5 minutes and at 90% at 10 minutes. Within 20 minutes, 100% of the Singulair was released. Results showed that Singulair is a tablet with an immediate release. When examining the excipient list for Singulair in the literature, formula F1 and F2, which is depicted in Table 1, is the suggested formulation. Since the innovator's product is film-coated tablets, the direct compression method cannot be used to prepare tablets. Hydroxypropyl cellulose is used as a tablet binder, and croscarmellose sodium is used as a super disintegrant (Dürig and Karan, 2019; Hiremath et al., 2019; Paul J. Sheskey, 2020). Based on the characteristics of each substance, excipient amounts were predicted and varied, as shown in Table 1. At 25°C, the aqueous solubility of montelukast sodium was reported to be between 0.2 and 0.5 μg/mL (Thibert et al., 1996; Okumu et al., 2008). It is a highly lipophilic drug, with pKa values between 2.7 and 5.8, and an estimated log P of 8.79 (Okumu et al., 2008; Martir et al., 2020). Montelukast is a weak acid drug with low solubility in the pH range of 1.2 to 4.5, which may result in dissolution-limited absorption. Since montelukast is a BCS class II drug and has a pH-dependent solubility range of 0.18 μg/mL at pH 1.2 to 0.24 mg/mL at pH 7.5, its solubility is crucial to the drug's effectiveness (Martir et al., 2020; Prieto-Escolar et al., 2021). To increase the solubility and make it comparable to the dissolution profiles of Singulair, the solubility enhancers

SLS and poloxamer 188, or a combination of the two, were added to formulations F3-F5. It is necessary to modify the formulation's excipient content if the results of the dissolution profile tests are not comparable.

3.2 Analytical Validation Results

Even though there are official methods for analyzing montelukast sodium in pharmacopoeias or research articles, we have an expedient in-house procedure that we employ for this study (Singh et al., 2010; Rashmitha et al., 2010; United States Pharmacopeial, 2023). The analytical method of montelukast sodium using HPLC was validated according to the ICH guidelines (Eldin et al., 2011; Singh et al., 2010; Ethiraj et al., 2011). Figure 2 displays the chromatogram of montelukast sodium in the standard solution, tablet sample, and excipient signal. To evaluate specificity, the peak of montelukast sodium in the standard and sample had a high resolution at a retention time of about 2.4 min, and the excipients did not affect the signal. Table 4 displays the parameters of the validation results. The calibration curve of the montelukast sodium standard at concentrations ranging from 3.125 to 800 μg/mL showed good linearity with r^2 of 0.9999. The accuracy was determined by the %recovery, which was 96.7% ± 1.0%. The intra- and inter-day precisions were evaluated as %RSD, which were 0.23% and 0.17%, respectively. The calculation of LOD and LOQ were 0.5 and 1.6 μg/mL, respectively. The robustness was found to be in an acceptable range (%recovery = 95%–105%) in the variation of the HPLC column, ratios of the mobile phase, wavelength of the detector, and the flow rate (Table 4). These outcomes confirmed the suitability of this analytical technique by HPLC for measuring the montelukast sodium in tablet formulation.

3.3 Montelukast Sodium Granules Characteristics

Figure 3 depicts the granule form of montelukast sodium and the finished tablet. The pale-yellow color is caused by the color of the excipient and active substance. In Table 5, a summary of the granule micromeritics tests is provided. The bulk and tapped densities of various developed formulations ranged from 0.41 to 0.42 g/mL and 0.45 to 0.46 g/mL, respectively. Even though the formulation contained a different amount of solubilizing or disintegrant enhancers, the same density values were obtained. This is because the primary ingredients in both formulations are the same. The flow characteristics of the granules were revealed by the compressibility index, angle of repose, and Hausner's Ratio. It proved that the difference between the calculated bulk and tapped densities was what determined the compressibility index, which ranged from 6.67 to 10.87. The range of the Hausner's ratio was 1.09 to 1.12. The angle of repose was between 18.43 and 20.52 degrees. The compressibility index was 10, while Hausner's Ratio was between 1.00 and 1.11, and the angle of repose was between 25 and 30. These results demonstrated excellent flow characteristics for both powder and granules, eliminating the need for a glidant in the formula (United States Pharmacopeial, 2023).

The particle size distribution of all granules revealed D50 to be in the 845–920 μm range, which is an ideal granule size for an 8 mm die diameter. High granule density, large particle size, smooth surface, and sphere shape could enhance the ability of granules to flow (Sinko, 2016; Goh et al., 2018; Šantl et al., 2012). For good flow and tableting properties, the moisture content of the dried granules was set at 1% to 3%. However, more research into process validation is required. Since the tableting process depends on the flow characteristics of the pharmaceutical granules filling into the cavity of the die, the results of the development of montelukast sodium granules by wet granulation show that all formulations do not have flow characteristics problems. This guarantees that the pharmaceutical production of tablets, whether on a lab or commercial scale, is consistent.

Figure 4(a) displays the FT-IR spectrum of montelukast sodium and tablet with all excipients. The tertiary hydroxyl groups in the pure drug montelukast sodium displayed a broad peak around 3300 cm^{-1}, and the carboxylic acid peak, which is in the form of a salt, displayed a strong asymmetric stretch peak near 1600 cm^{-1} and a strong symmetric stretch peak near 1400 cm^{-1}. Aromatic C-H peaks are also observed between 2900 cm^{-1} and 3000 cm^{-1}. The stretch absorptions for the C=C ring often occur in pairs at 1600 cm^{-1} and 1475 cm^{-1} (Donald et al., 2001; Hadi et al., 2012; Rao et al., 2012). The physical mixing of montelukast sodium and excipients revealed the montelukast sodium characteristic peak at the same wavenumber as pure montelukast sodium. The results indicated that none of the functional groups of either the drug or polymers underwent any chemical reaction in the excipients of the core tablet, which are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, SLS and poloxamer 188. All functional groups remained intact. Therefore, it can be proven that none of the ingredients in the formulation underwent any chemical reactions.

The thermogram of montelukast sodium and montelukast sodium mixed with lactose monohydrate or croscarmellose sodium is shown in Figure 4(b). From the literature, the melting point of montelukast sodium is varied including 275.9 F (=135.5 °C) (Reddy et al., 2023), 138.6-139.8 °C (Hadi et al., 2012; Shruthi and Thahera, 2013). However, the DSC thermogram result showed that the melting point of montelukast in this study is 154 °C (see Figure 4b). When the physical mixture of montelukast sodium had lactose monohydrate, the melting peak was found at 154 °C, corresponding with montelukast sodium. However, no endothermic peak was observed from 50 to 300 °C in the physical mixture of montelukast sodium and croscarmellose sodium. This result may indicate that the montelukast formed the amorphous phase with croscarmellose sodium. This result is in agreement with a previous study that indicated montelukast sodium is compatible with common excipients in tablet dosage form (Sahu and Jain, 2020).

The melting point of lactose monohydrate, croscarmellose sodium to melt or decompose over 200 °C showed a broad

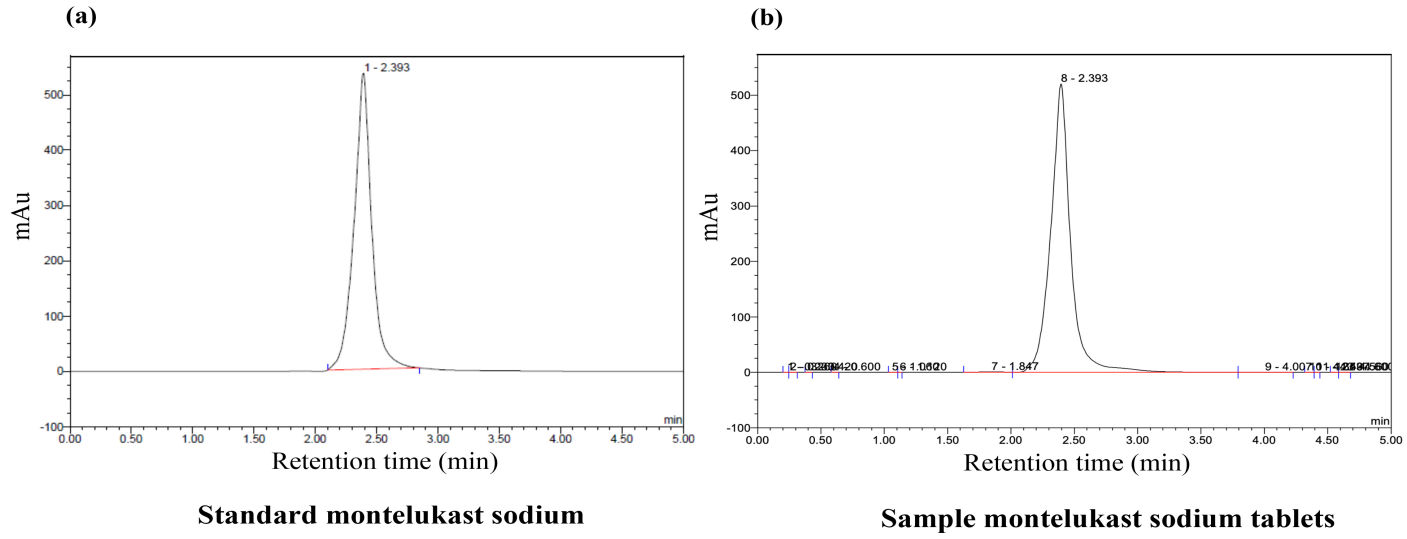

Figure 2. Chromatogram of Standard Montelukast Sodium at a Concentration of 200 μg/mL (a), Sample of Montelukast Sodium Tablets at a Concentration of 200 μg/mL (b)

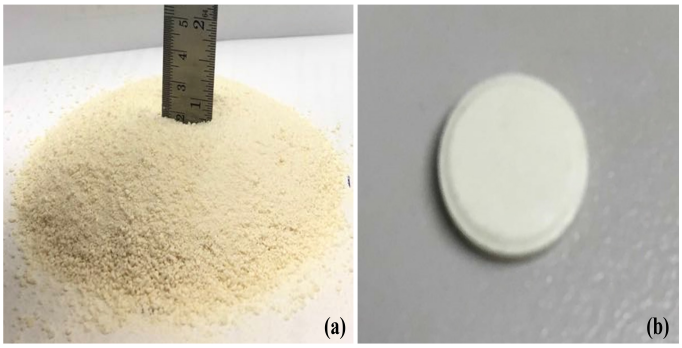

Figure 3. The Appearance of Montelukast Sodium Granules (a) and Core Tablets (b) (Example of Formulation F1)

peak around 200-220 °C of the thermogram (Gombas et al., 2002; Torrado-Salmerón et al., 2019). The results of FT-IR and DSC confirmed that not all excipients interact with montelukast sodium.

3.4 Physicochemical Properties of Montelukast Sodium Tablets

The physical properties of tablets are shown in Table 6. Granules are easily compacted into tablets using an automatic single-punch tableting machine without the need to use excessive pressure. Because of plastic deformation, the appearance of all core tablet formulations is smooth and shiny. The average weight of a compressed tablet produced by an automatic single punch tableting machine is between 201.2 and 205.5 mg, with a maximum deviation from the target weight of 3%. This indicates that the granule flow properties of all formulas are acceptable, and no defects were discovered in the tableting process or after it had been finished, such as capping, laminating, binding, or sticking. The tablet diameter is 8.10 mm, which corresponds to the punch and die used in these studies (die-punch set diameter of 8 mm). There are minimal differences in the thickness and hardness of all formulas. However, the hardness of the tablet is very low for the film coating process; the core tablets must be sufficiently strong to withstand the tremendous mechanical stress that occurs throughout the coating process. Because the tablet cores constantly collide with one another and the coating of the pan's surface is metallic, the coating process was done slowly at first. This may result from the fact that the tablet's total weight is 200 mg, which is a relatively small quantity. In addition, the placebo tablets were used as an auxiliary coating due to the amount of montelukast tablets, which was much less than the minimum volume of the coating pan. The tablets' friability was found to be between 0.35 and 0.52

Formulation F1 disintegrated quickly compared to other formulations because it contains the highest amount of super disintegrant (30%). The quantity of super disintegrant used has a significant impact on the disintegration time of the formulation. SLS and poloxamer were added to formulations F3-F5 to serve as a solubility enhancer, but they also had an impact on the tablet's ability to disintegrate. In formulations F3-F5, the amount of croscarmellose sodium disintegrant per tablet was 30 mg, compared to 60 mg in formulation F1. However, formulation F4 with poloxamer (4 mg/tablet) and less disintegrant gave a disintegration time that was not significantly different from F1 (p-value > 0.05). Thus, the combination of super disintegrant and poloxamer 188 demonstrated the

Table 4. Validation Results of HPLC Analytical Method of Montelukast Sodium Tablets

Parameters	Results Obtained
Specificity	pass
Accuracy (%Recovery)	96.7% ± 1.0%
Precision	
Intra-day precision (%RSD)	0.23%
Inter-day precision (%RSD)	0.17%
Linearity (r^2)	0.9999
Robustness (%Recovery)	
HPLC column old	95.5% ± 0.4%
HPLC column new	97.1% ± 0.4%
Methanol: Acetonitrile: Water (50:40:10)	98.4% ± 1.2%
Methanol: Acetonitrile: Water (70:20:10)	96.8% ± 0.9%
Flow rate 0.8 mL/min	95.3% ± 0.3%
Flow rate 1.2 mL/min	96.8% ± 1.1%
Wavelength 252 nm	95.5% ± 0.5%
Wavelength 256 nm	99.7% ± 0.7%
Limit of detection (LOD)	0.5 µg/mL
Limit of quantitative (LOQ)	1.6 µg/mL

Table 5. Micromeritics results of montelukast sodium granules (Mean ± SD, n = 3)

Test	F1	F2	F3	F4	F5
Bulk volume (mL)	123 ± 0.1	123 ± 0.0	120 ± 0.0	122 ± 0.0	121 ± 0.0
Bulk density (g/mL)	0.41 ± 0.00	0.41 ± 0.00	0.42 ± 0.00	0.41 ± 0.00	0.41 ± 0.00
Tapped volume (mL)	112 ± 0.0	111 ± 0.2	110 ± 0.0	112 ± 0.0	109 ± 0.1
Tapped density (g/mL)	0.45 ± 0.00	0.45 ± 0.00	0.45 ± 0.00	0.45 ± 0.00	0.46 ± 0.00
Compressibility index	8.89	8.89	6.67	8.89	10.87
Angle of repose (°)	20.52	19.89	20.52	20.12	18.43
Hausner's Ratio	1.09	1.11	1.09	1.09	1.12
D50 (sieve method)* (μm)	920	843	830	845	888
Moisture content (after drying) (%)*	2.20	2.22	2.05	2.40	2.00
Moisture content (after mixed with extra-granular excipients) (%)*	2.26	2.30	1.98	2.20	2.14

* All values show P-value > 0.05, * n = 1,

fastest disintegration that resulted from solubilizing, enhancing the possibility of polymeric micelles. Furthermore, poloxamer may affect disintegration time by swelling and being easily disintegrated. The disintegration of the tablet was delayed by SLS, resulting in the slowest disintegration time. Formulation F3 containing SLS (4 mg/tablet) exhibited a very long disintegration time (7.47 minutes), whereas formulation F5 containing a combination of SLS and poloxamer exhibited a moderate disintegration time of 5.43 minutes. This demonstrated that poloxamer increases disintegration time, whereas SLS decreases it. This is due to the absorption of SLS during wet granulation and the increased aggregation of granules before tableting. However, the dissolution test results must be observed again because it is more related to the effect of the drug action.

The coating process of montelukast sodium tablets in a laboratory was used in the perforate pan systems. Physical characteristics of coated tablets, such as thickness and time of disintegration, were comparable to those of the core tablets in each formulation. Because HPMC dissolves quickly in water, film-coating material does not affect disintegration time.

3.5 Drug Content and Content Uniformity of Montelukast Sodium Tablets

The content of all developed formulations F1-F5 ranged between 101 and 103% of the labeled amount. This met the requirements for USP montelukast sodium tablets, which states that the active ingredient must make up between 92.5% and 107.5% of the amount demonstrated on the label (United States Pharmacopeial, 2023). The major impurities of montelukast

Table 6. Physical Properties of Montelukast Sodium Tablets (Mean ± SD, n = 6-10)

Test	F1	F2	F3	F4	F5
			Core tablets		
Appearance			Light yellow colored, round flat bevel-edged tablets and plain on both sides		
Average weight (mg)	201.2 ± 0.9	203.2 ± 3.7	203.8 ± 3.1	205.5 ± 3.0	204.3 ± 3.8
Diameter (mm)	8.10 ± 0.05	8.10 ± 0.05	8.10 ± 0.05	8.10 ± 0.05	8.10 ± 0.05
Thickness (mm)	2.93 ± 0.15	2.98 ± 0.08	3.02 ± 0.04	2.99 ± 0.03	2.98 ± 0.12
Hardness (kp)	4.25 ± 0.25	4.48 ± 0.43	3.67 ± 0.51	4.02 ± 0.17	3.95 ± 0.25
Disintegration time (min)	3.36 ± 0.72	3.93 ± 1.68	7.47 ± 1.13	3.35 ± 1.64	5.43 ± 0.22
Friability (%)	0.35 ± 0.02	0.45 ± 0.40	0.52 ± 0.10	0.43 ± 0.03	0.42 ± 0.02
			Coated tablets		
Appearance			Beige to yellow colored, round flat bevel-edged film coated tablets and plain on both sides		
Average weight (mg)	212.4 ± 2.5	214.5 ± 3.3	214.3 ± 4.1	215.6 ± 2.4	218.2 ± 3.2
Thickness (mm)	3.02 ± 0.09	3.07 ± 0.21	3.09 ± 0.30	3.07 ± 0.06	3.06 ± 0.12
Disintegration time (min)	3.40 ± 0.68	4.14 ± 2.02	8.10 ± 0.68	3.45 ± 0.50	5.90 ± 0.55
Assay (%Labeled claim)	101.34 ± 0.64	102.55 ± 1.33	101.09 ± 0.76	102.43 ± 0.03	101.55 ± 1.32
Content uniformity*	Pass	Pass	Pass	Pass	Pass

* Complied according to USP criteria

tablets are also listed in the USP, and they are as follows: sulfoxide impurity not to exceed 2.0%, montelukast ketone impurity not to exceed 0.2%, cis-isomer not to exceed 0.2%, and any other individual degradation product not to exceed 0.2%. The total impurities combined must not exceed 3.0% (United States Pharmacopeial, 2023). In the current study, however, we did not perform this because we focused on the dissolution profiles compared with the innovator. Many studies have found that the total amount of impurities in generic formulations is greater than that of innovator formulations by more than 3% (Gallelli et al., 2013). As a result, it is critical to note that impurities should be investigated and reported during the development process. All formulations met the acceptance criteria for performance following the USP method of content uniformity and were uniform in terms of drug content for the dosage unit (United States Pharmacopeial, 2023).

3.6 Dissolution Profile Comparison

Dissolution studies were conducted in different pH media, including 0.1% SLS in 0.1M HCl (pH 1.2), 0.2% SLS in phosphate buffer (pH 4.5), and 0.2% SLS in phosphate buffer (pH 6.8) to replicate the pH range of the gastrointestinal system from the stomach to the duodenum, respectively. In addition, 0.5% SLS in water was investigated as part of the quality control component of the dissolution test recommended in the USP monograph for montelukast sodium tablets (United States Pharmacopeial Convention, 2023). SLS significantly increases the dissolution of montelukast sodium tablets when compared to 1.5 and 0.2% SLS in the dissolution medium (Prieto-Escolar et al., 2021).

The dissolution profiles of montelukast released from montelukast tablets formula F1-F5 and innovator Singulair tablets in different mediums are shown in Figure 5(a-d). At the same time, acidic medium tablets had a lower rate of montelukast dissolution than other media. The dissolution of montelukast may depend on pKa. The pKa of montelukast is 3.3 and 4.4, resulting in reduced solubility at low pH (Singh et al., 2022). Montelukast sodium dissolves almost entirely in 20 minutes at the higher pH media (0.2% in phosphate buffer pH 6.8 and 0.2% SLS in water). Except for 0.1 M HCl (pH 1.2), the sodium montelukast solution is dissolved at over 85% only in formulation F3. This agrees with a previous report that showed SLS may increase the rate at which acidic drugs (such as aspirin and simvastatin) dissolve (Alshora et al., 2022). Disintegration time and dissolution may not be directly related because slow disintegration time shows high drug release. However, the disintegration times for all formulations were remarkably similar (between 3 and 7 minutes). The best dissolution is formulation F3 (green line) in all mediums, which dissolved faster than other formulations, possibly due to the presence of SLS as the solubilizing agent in the formulation (4 mg/tab). However, the pharmaceutical equivalent of the developed drug should have the same dissolution profiles as the innovator drug (red line). The calculation of f1 and f2 for F3 is not acceptable (see Table 7). The dissolution of formulation F3 is significantly impacted by SLS, an additional excipient added to the excipients already present in innovator products. The mechanism of SLS after dissolving in the medium may form a polymeric micelle and increase the solubility of montelukast sodium. F4 used poloxamer 188 as a solubilizing agent, but the slower dissolution time than others may be caused by the properties of

Table 7. Dissolution Profile Comparison by Difference Factor (f_1) and Similarity Factor (f_2) of Montelukast Sodium Tablets with Reference product Singulair tablets

Dissolution Medium		F1	F2	F3	F4	F5
0.5% (w/v) SLS in water	f_1	1.43	1.77	3.25	6.25	5.55
	f_2	85.80	79.88	71.11	53.28	56.27
0.1% SLS in a 0.1 M HCl solution	f_1	1.82	9.55	26.79	31.23	26.62
	f_2	84.61	55.35	31.40	31.39	34.89
0.2% SLS in phosphate buffer (pH 4.5)	f_1	2.42	5.73	8.56	12.87	9.90
	f_2	75.34	59.89	49.21	42.86	48.75
0.2% SLS in phosphate buffer (pH 6.8)	f_1	1.59	2.89	6.78	10.53	6.78
	f_2	86.79	72.58	53.00	46.13	54.74

Table 8. Stability Results of Selected Montelukast Sodium Tablets (Formula F1) Compared with Innovator Singulair Tablets Faster Storage at Accelerated and Long-Term Conditions (Mean ± SD, n = 6)

Products	Storage Conditions	Test Interval (month)	Test		
			Appearance	Assay (%Labeled Claim)	Disintegration Time (min)
Montelukast sodium tablet (formula F1)	30°C ± 2°C 75% ± 5%RH	1	Conforms	102.80 ± 0.20	3.45 ± 0.12
		3	Conforms	101.02 ± 1.02	3.22 ± 0.67
		6	Conforms	101.93 ± 1.56	3.40 ± 0.22
	40°C ± 2°C 75% ± 5%RH	1	Conforms	100.04 ± 0.48	3.55 ± 0.87
		3	Conforms	101.22 ± 1.59	4.01 ± 0.30
		6	Conforms	100.33 ± 0.30	4.12 ± 0.53
Singulair tablet	30°C ± 2°C 75% ± 5%RH	1	Conforms	102.63 ± 1.04	3.90 ± 0.34
		3	Conforms	101.98 ± 2.02	4.05 ± 0.76
		6	Conforms	100.89 ± 0.26	4.20 ± 0.20
	40°C ± 2°C 75% ± 5%RH	1	Conforms	101.82 ± 0.86	3.80 ± 0.50
		3	Conforms	101.85 ± 1.45	4.56 ± 0.38
		6	Conforms	101.50 ± 1.63	4.65 ± 0.20

poloxamer forming a matrix in tablets when wet granulation was performed, resulting in controlled release of the dissolution (Jannin et al., 2006; Lee et al., 2008). The dissolution result of F5 is the same as F4. It consists of a half amount of poloxamer 188 compared with F4, and its SLS was included in the formula. The dissolution results of F5 are between F2 and F4. As shown in Figure 5, the formula most similar to the original product is the F1 formula after calculating f1 and f2 values (Table 7). The f1 are 1.43, 1.82, 2.42, 1.59 and f2 are 85.80, 84.61, 75.34, and 86.79 when performed in the medium pH 1.2, 4.5, 6.8 and water, respectively. According to FDA recommendations, f1 should be between 0 and 15, and f2 should be between 50 and 100, so the results are acceptable (Shah et al., 1998; World Health Organization, 2016W). The dissolution test can be used as a biowaiver for bioequivalent (BE) study if the drug is dissolved > 85% within 15 minutes and BCS class I but montelukast sodium is BCS class II, which requires BE study (World Health Organization, 2016). The dissolution profile of F1 is very similar to that of Singulair, which led us to select it for the stability study in the following step. When formulation F1 is applied to BE studies, it is guaranteed that they are equivalent to Singulair to reduce the risk of high study costs. Additionally, the physical characteristics of the granule and tablet are acceptable. The accelerated and long-term stability (short period) were tested before pilot batch manufacturing and the full option of stability test in the future. However, formulation F3 has the potential to be studied further to improve drug dissolution, but it was not chosen for generic drug development because it did not meet the regulations for generic drug requirements.

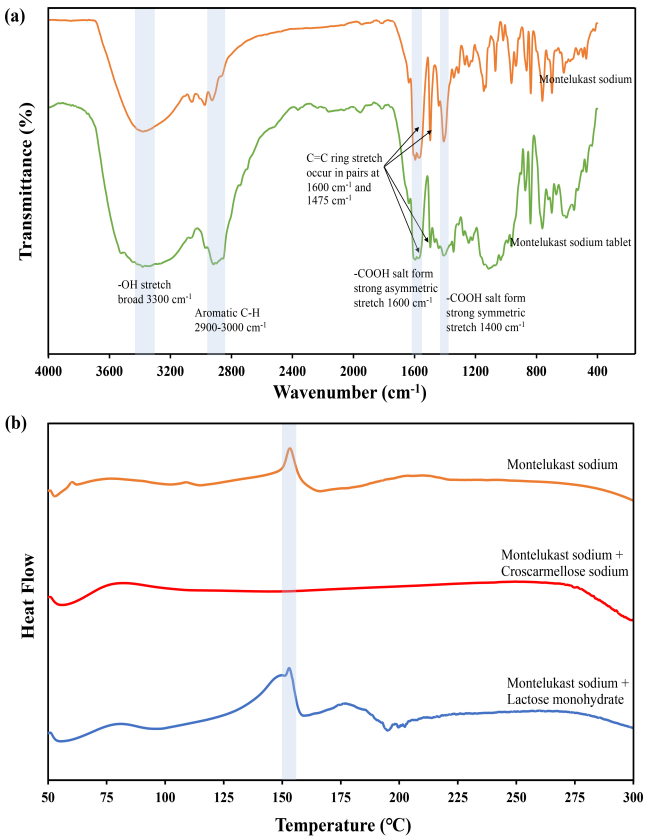

Figure 4. (a) FT-IR Spectrum of Montelukast Sodium and Montelukast Tablet (with All Excipients). (b) Differential Scanning Calorimetry (DSC) Thermograms of Montelukast Sodium and Montelukast Sodium with Lactose Monohydrate and Croscarmellose Sodium

3.7 Stability of Montelukast Sodium Tablets

The USP advises that montelukast sodium tablets be stored at a constant room temperature, protected from light, and stored in airtight containers. As a result, the chosen montelukast sodium formulation F1 was kept in amber glass containers with silica gel. The stability results are shown in Table 8. The stability data at accelerated conditions for 6 months and long-term conditions for 12 months should be reported as the climate zone of IVb for drug registration in ASEAN countries (Kopp, 2006; González-González et al., 2022). The results demonstrated that the innovator product or formulation F1 complied with the same appearances as the initial. These studies, though, have been carried out since October 2017, and the innovator batch that was purchased was the one that was produced within six months of the present study. Consequently, it is unlikely that the production period differences between developed F1 and the innovator affected the stability results. However, compared to the initial assay, the drug content is within 2% under both accelerated and long-term conditions. The high humidity may have resulted in slightly longer disintegration times because the

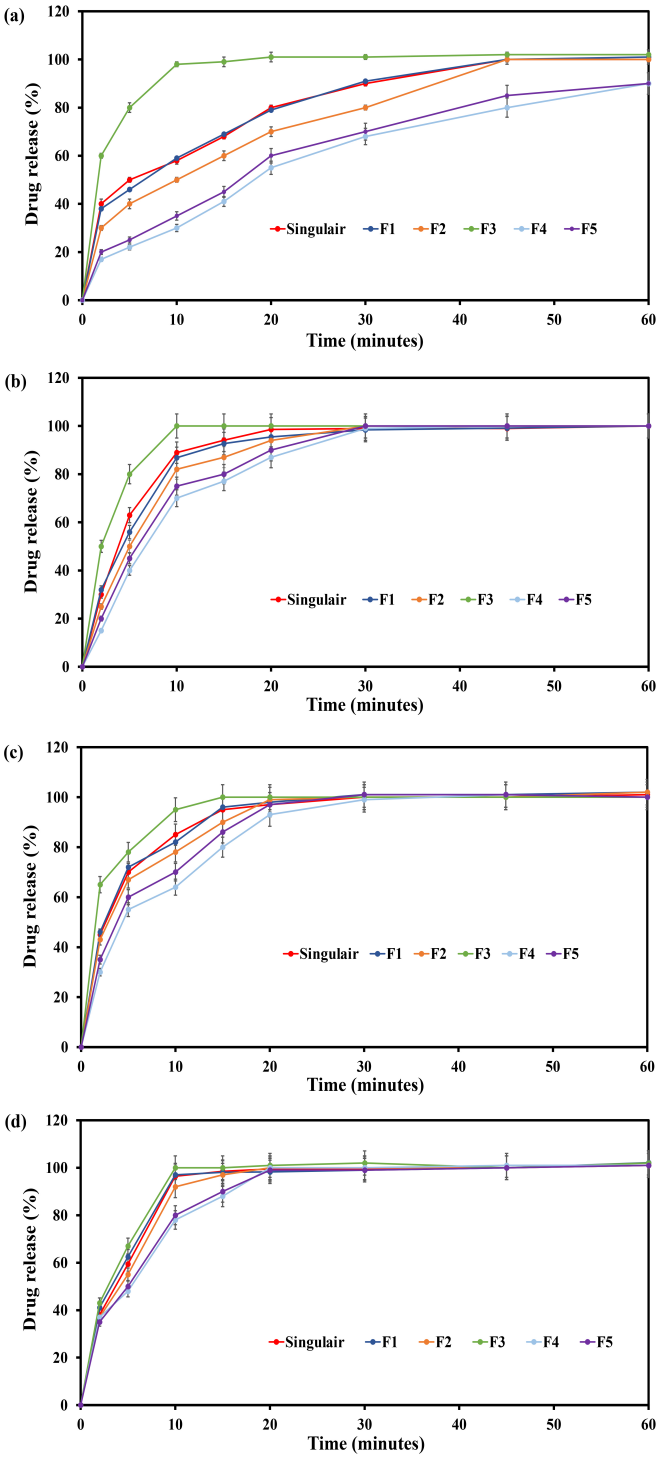

Figure 5. Dissolution Profile of Montelukast Released from Montelukast Tablets Formula F1-F5 and Innovator Singulair Tablets in Difference Medium: 0.1% SLS in 0.1 N HCl (a), 0.2% SLS in Phosphate Buffer pH 4.5 (b), 0.2% SLS in Phosphate Buffer pH 6.8 (c), and 0.2% SLS in Water (d). The Data Expressed in Mean ± Standard Deviation, n = 12)

powder particles became harder and more agglomerated.

3.8 Limitations

Pharmaceutical companies develop generic drug products using a scientific and technical methodology that is entirely distinct from the methodology used to create innovator or reference products (Hasan et al., 2021). The main difference is that generic drugs should have a BE test result to confirm the efficacy equivalent of two products. When active ingredients are present in the same proportion, in the same dosage form, and when they are administered using the same route of administration, generic products must meet the FDA's basic requirements for pharmaceutical equivalence to innovator products. Generic products have the same biological properties when potential bio-involution issues are absent. They have enough labels and have been deemed safe and efficient. They are identical in terms of identity, power, purity, and quality. According to the FDA's good manufacturing practice regulations, they are manufactured to the same exacting standards as innovator products (Jain and Mundada, 2015). However, these studies do have some limitations.

1. Lack of patent information on original claims. If the innovator claims some point regarding this study, the manufacturer cannot implement it.

2. The quality control of products and all raw materials used in generic drugs should be developed and validated.

3. Manufacturing in a pilot batch is necessary after a successful lab-scale process. The feasibility of manufacturing and equipment used when the scale-up process should be clearly stated.

4. The process validation of pilot batch manufacturing with monitoring of the long-term stability until the end of shelf-life or equivalent to original claims needs to be studied.

5. BE study should be performed by using pilot batch manufacturing to represent the drug that will be produced, such as the study reported in the literature (Muñoz et al., 2014; Ratanajamit et al., 2017).

6. All regulatory requirements and documents should be confirmed be sure of the regulations for drug registration and related document requirements for the country of the drug registry.

4. CONCLUSION

The generic 10 mg montelukast sodium film-coated tablet was found to be appropriate for the wet granulation production process. When compared to the innovator in the dissolving profile test, the optimized formulation was developed successfully, and they were pharmaceutically equivalent. The lab-scale production of film-coated tablets containing montelukast sodium results in granules, core tablets, and film-coated tablets with the developed formulation F1-F5 that have the appropriate physical and chemical properties. Only formulation F1 with no solubility enhancer and the highest amount of super disintegrant demonstrated a dissolution profile comparable to the innovator. It was concluded that the desired montelukast sodium 10 mg film-coated tablets in this study were pharmaceutically equivalent to Singulair.

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