**Journal of Neonatal Surgery**
***ISSN(Online): 2226-0439***
***Vol. 14, Issue 32s (2025)***
*https://www.jneonatalsurg.com*

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# Development of Gastro-Retentive Combination Formulation of Montelukast Sodium and Ketotifen Besilate for Allergic Rhinitis and Asthma

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Cite this paper as: Satyawan Singh Dangi, Om Prakash Agrawal, (2025) Development of Gastro-Retentive Combination Formulation of Montelukast Sodium and Ketotifen Besilate for Allergic Rhinitis and Asthma. *Journal of Neonatal Surgery*, 14 (32s), 7462-7472.

## ABSTRACT

**Aim**: The study aimed to develop a once-daily sustained-release gastroretentive combination formulation of ketotifen besilate and montelukast sodium using multilayer tablet technology and gastro-retentive systems for the treatment of allergic rhinitis and asthma.

**Background**: Ketotifen besilate and montelukast sodium are commonly used to manage allergic rhinitis and asthma. However, their conventional formulations often require multiple doses per day, leading to poor patient compliance. A gastro-retentive system allowing once-daily dosing could improve adherence and therapeutic outcomes.

**Materials and Methods**: A multilayer tablet was formulated with montelukast sodium in the immediate-release layer and ketotifen besilate in both the immediate- and sustained-release layers, using calcium silicate as a floating agent for gastric retention. Hydroxypropyl Methylcellulose (HPMC) controlled the sustained release of ketotifen, while the addition of super-disintegrants and a surfactant improved the release of poorly soluble montelukast. The lactose-microcrystalline cellulose ratio was adjusted to meet the target dissolution profile and comparative dissolution tests were conducted to assess similarity to the desired release profile.

**Results**: Comparative dissolution tests demonstrated high similarity between the combination formulation and the target release profile, with similarity factor (f2) values of 58.5 and 65.9. The formulation successfully allowed for different release rates of the two active ingredients, improving drug absorption and extending the duration of action.

**Conclusion**: The developed gastro-retentive formulation enabled a transition from twice-daily to once-daily dosing, enhancing patient compliance. The multilayer tablet design efficiently controlled the release profiles of both active ingredients, addressing limitations associated with the absorption sites of each drug.

***Keywords:*** *Combination Formulation, Floating, Gastro-Retentive, Similarity factor.*

## 1. INTRODUCTION

Allegic rhinitis is a significant and independent risk factor for the onset of asthma.1 Allergic responses are characterized by early and late-phase reactions. The early-phase reaction typically occurs within min to an hour and results from the degranulation of mast cells on the mucosal surface, releasing histamine, tryptase, Prostaglandin D2 and leukotrienes, with histamine being primarily involved. The late-phase reaction generally arises 2 to 4 hr post-exposure, involving T-cell activation, adhesion molecule production and eosinophil infiltration, leading to chronic inflammation. Leukotrienes, metabolites of arachidonic acid, are known to be among the mediators that induce this late-phase response.2 Allergic rhinitis and asthma are chronic inflammatory diseases of the upper and lower respiratory tracts, respectively, often coexisting and sharing a similar pathophysiology, including inflammation and hyper-responsiveness driven by mast cells, eosinophils and T-helper cells. Antihistamines, which primarily block H1 histamine receptors, are effective in reducing immediate allergic symptoms such as itching, sneezing and nasal discharge. Montelukast, a leukotriene receptor antagonist, acts by inhibiting leukotriene D4, a mediator associated with late-phase allergic responses, thus providing prolonged anti-inflammatory effects.3 While the prevalence of asthma is approximately 5% in the general population, asthma is present in 10-40% of rhinitis patients and rhinitis coexists in 70-80% of asthma patients.4,5 Rhinitis exacerbates asthma and leads to increased respiratory symptoms and exacerbations in patients with concomitant asthma and rhinitis.6 These findings underscore the importance of treating rhinitis in the management of asthma.7 When rhinitis and asthma coexist, treatment should be based on guidelines for each condition, addressing both disorders concurrently.1,8

Ketotifen besilate is a second-generation antihistamine with selective histamine H1 receptor antagonist activity. It is used to treat allergic reactions such as allergic rhinitis, urticaria, erythema and pruritus (Figure 1-a).[9,10] Ketotifen besilate, formulated in a dosage form requiring twice-daily administration due to its short half-life in the body, is currently available on the market. However, its rapid elimination kinetics pose challenges in achieving effective plasma concentrations between doses, potentially leading to suboptimal therapeutic outcomes. Moreover, the high systemic exposure of the drug carries the risk of eliciting systemic side effects.[11] In the case of ketotifen besilate, the absorption site of the drug is limited to the upper part of the small intestine, making it impossible to achieve adequate bioavailability with conventional sustained-release formulations.[12] To address these issues, applying a gastro-retentive system capable of delaying passage through the upper part of the small intestine can improve bioavailability by ensuring sustained drug release and demonstrating biological equivalence with the twice-daily dosing regimen.[13]

Montelukast, a leukotriene receptor antagonist, is effective as a first-line treatment for asthma and mild persistent allergic rhinitis. It can be used either as monotherapy or in combination with antihistamines (Figure 1-b). Leukotrienes do not stimulate the sensory nerves in the nasal mucosa; therefore, they do not affect nasal itching or sneezing. In numerous studies, leukotriene receptor antagonists have significantly improved symptoms in patients with both seasonal and perennial allergic rhinitis.[14] When compared to antihistamines, there was no significant difference in efficacy[15-17] and they were found to be less effective than intranasal corticosteroids.[18,19] Patients with allergic rhinitis who require corticosteroid treatment due to comorbid allergic conditions such as asthma or urticaria may experience adverse effects if the dosage is excessive. These effects can include psychiatric disturbances, growth suppression in children and skin abnormalities.[20]

When antihistamines and leukotriene receptor antagonists are used in combination, their efficacy is superior to when each drug is used alone and they demonstrate comparable efficacy to intranasal corticosteroids.[18,21] Considering that approximately 40% of allergic rhinitis patients also have concurrent asthma, leukotriene receptor antagonists, either alone or in combination therapy, can be clinically useful in both upper and lower airway allergic diseases, particularly in patients with allergic rhinitis accompanied by asthma.[22]

In the design of combination formulations, such as those containing montelukast and ketotifen, where different drug release rates are required, the most commonly employed technique is the use of multilayer tablet formulations to achieve distinct release profiles for each drug.[13] However, due to the limited absorption sites of the drugs in the combination formulation, achieving the target release profile solely through conventional multilayer tablet technology poses challenges. Therefore, in this study, we aimed to address this issue by incorporating floating technology into the multilayer tablet formulation (Figure 2).

## 2. MATERIALS AND METHODS

### Materials

The Active Pharmaceutical Ingredients (API), montelukast sodium and ketotifen besilate (Figure 1), were provided by Cadila Pharm (Mumbai) and HL Genomix (India), respectively. For comparison, Talion® tablets from Dong-A Pharmaceutical Co.Ltd. and Singulair® tablets from Lupin Pharmaceutical Co.Ltd. were used as reference drugs.

For the dissolution testing and analysis, Sodium chloride and Potassium phosphate monobasic were sourced from Sigma-Alderic (India) and Hydrochloric acid was obtained from S.D. Dine Chem., Ltd. (India). Sodium acetate trihydrate, Acetic acid, Sodium hydroxide and Trifluoroacetic acid were provided by SamJeonSoon Pharm. Co., Ltd. (India).

### Instruments

The tablet press utilized for manufacturing the tablets was from Dajou (Japan) and the dissolution testing apparatus used was the Vision 8 elite (Hanson Research, USA). High-Performance Liquid Chromatography (HPLC) for analysis was conducted using the UltiMate 3000 system (Thermo Scientific, USA), with Aegispak C18-L (Youngjin Biochrom, Korea) and SunFire® C18 (Waters, USA) columns employed for analysis.

### Evaluation of Tablet Flotation

To achieve immediate tablet floating, calcium silicate, a representative low-density excipient, was selected as the floating agent. The floating behavior was assessed based on varying addition ratios and tablet thicknesses, as shown in Table 1.

Excluding the floating agent, the remaining components were composed of cellactose 80, a commonly used excipient with standard density and excellent compressibility, while magnesium stearate was employed as the lubricant.

To achieve immediate floating, the tablet density must be lower than that of water. Thus, tablets were produced using the same punch while maintaining a constant total tablet weight. This method allowed for the formulation of tablets with varying densities by altering the tablet thickness. Equation (1) illustrates the relationship between the weight and volume of tablets capable of floating in water with a density of 1 g/cm³. It was calculated that, for a 200 mg round-shaped tablet with a radius of 4 mM to float, the tablet must have a thickness of approximately 4 mM or greater.

In the cases of T1 and T2, with 10 mg and 20 mg of calcium silicate added respectively, it was observed that, due to the

influence of cellactose 80 with relatively high density, even when compressed with low pressure, the tablet thickness remained below 4 mM, preventing flotation. However, in the cases of T3 and T4, where 40 mg and 80 mg of calcium silicate were added respectively, it was observed that even with relatively higher compression pressures, the tablet thickness was above 4 mM, allowing for immediate floating. In the case of T4, with the highest concentration of the floating agent, the tablets exhibited insufficient binding strength due to the relatively high ratio of the floating agent, resulting in lower hardness and issues such as sticking during compression. Additionally, in the case of T3, increasing the compression pressure to 3 MPa resulted in a slight decrease in tablet thickness to 4.21 mM, while the tablet hardness was improved. Based on these findings, it was decided that, considering potential future coating processes, the tablets should be compressed to achieve a thickness of approximately 4.2 mM.

**Preparation of Bilayer Tablet**

The manufacturing process of the bilayer tablets, comprising the immediate-release layer and the sustained-release layer, followed the procedure illustrated in Figure 3. The formulation of the sustained-release layer granules for tableting was carried out by mixing the API and excipients, excluding the lubricant and diluent, in a V-type mixer for 100 revolutions. Subsequently, a binding solution was prepared using purified water and HPC and the mixture was subjected to a combined process for 5 min using a high shear mixer under the conditions of agitator 100 rpm and chopper 2,000 rpm. The resulting mixture was then dried at 60ºC until the moisture content reached the desired level before granulation. The dried material was sieved through a 30-mesh sieve and then mixed with a diluent and a lubricant to prepare granules. The preparation of granules for the immediate-release layer involved mixing the active pharmaceutical ingredients and excipients in a V-type mixer for 100 revolutions, followed by an additional mixing of the lubricant for 50 revolutions. The prepared granules were compressed into bilayer tablets using a tablet press. First, the sustained-release layer was pre-compressed, followed by the immediate-release layer, which was subjected to main compression. To assess the potential for layer separation in the bilayer tablets, the tablets were rotated in a friability tester at 25 rpm for 4 min, after which any separation of the layers was examined.

**Dissolution Test**

The dissolution test of ketotifen besilate was conducted reflecting its dosage form as a gastro-retentive formulation using the paddle method (apparatus 2) in 0.1 N hydrochloric acid solution (900 mL), which corresponds to the acid stage of the US Pharmacopeia dissolution test. The test was carried out at a temperature of 37.0±0.5ºC with a rotation speed of 50 rpm. Aliquots of 5 mL each were withdrawn at 5, 10, 15, 30, 45, 60, 180, 360, 480 and 720 min and filtered through a 0.45 µm PTFE syringe filter.

The dissolution of montelukast sodium was insufficiently achieved under pH 1.2, 4.0 and 6.8 buffer conditions in preliminary tests. Consequently, dissolution testing was conducted using a dissolution medium consisting of 900 mL of pH 6.8 buffer solution with the addition of 0.5% Sodium Lauryl Sulfate (SLS) as a solubilizing agent, following the US Pharmacopeia dissolution test method with apparatus 2 (paddle method). The dissolution medium condition of pH 6.8 buffer solution with 0.5% SLS is considered clinically relevant for in vitro evaluation, given that the primary absorption site of montelukast is in the upper small intestine, where drug solubility increases within a pH range of 6.5 to 7.5. This condition also aligns with the pharmacokinetics of oral montelukast tablets, which reach maximum plasma concentration approximately 3 hr post-administration, with a half-life of about 2.7 to 5.5 hr.23 The testing was carried out at a temperature of 37.0±0.5ºC with a rotation speed of 50 rpm. Aliquots of 5 mL each were withdrawn at 5, 10, 15 and 30 min and filtered through a 0.45 µm nylon syringe filter.

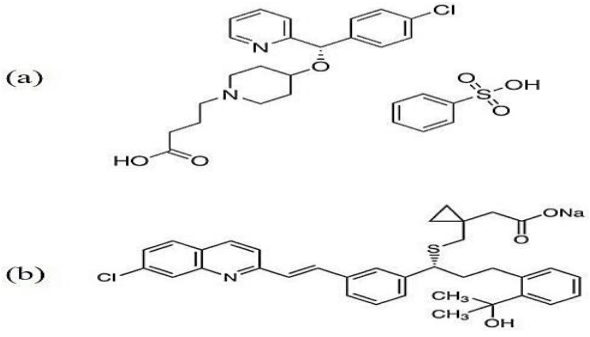


**Figure 1: Chemical structure of ketotifen besilate (a) and montelukast sodium (b).**

**HPLC Analysis**

The analysis of ketotifen besilate standard and test solutions was conducted using a C18-L (5 µm, 4.6x150 mm) column at 40ºC with a flow rate of 1.0 mL/min. The mobile phase consisted of 1-pentanesulfonic acid pH 3.0 buffer and acetonitrile (7:3, v/v). Each sample (20 µL) was injected and the analysis was carried out for 12 min at a wavelength of 260 nm using a

UV detector.

The analysis of montelukast sodium standard and test solutions was conducted using a C18 (5 µm, 4.6x150 mm) column at 30ºC with a flow rate of 1.5 mL/min. The mobile phase was composed of a solution prepared by adding 3% trifluoroacetic acid to 80% acetonitrile, as well as distilled water and acetonitrile (in a 5:200:800 ratio by volume). Each sample (20 µL) was injected and the analysis was performed for 8 min at a wavelength of 225 nm using a UV detector.

## 3. RESULTS AND DISCUSSION

### Target Release Profile Set-up

We aimed to select the target release profile of ketotifen in a combination formulation through dissolution testing of Talion® tablets, the reference drug containing ketotifen besilate. Under pH 1.2 conditions, dissolution testing of Talion® tablets, a twice-daily dosing formulation, exhibited 100% release at the 30 min point. Consequently, for the once-daily formulation to achieve immediate therapeutic effects reaching effective plasma concentrations, it was deemed that approximately 50% of the drug should be rapidly released within 30 min. Subsequently, to maintain appropriate plasma concentrations, the release rate was set to reach 85% at 12 hr following a zero-order kinetics (Figure 4).

As a reference drug for establishing the target release profile of montelukast sodium, once-daily dosing Singulair® tablets were used. According to the requirements of pharmaceutical equivalence testing conditions, dissolution testing of the reference drug was conducted, revealing that the predetermined level of release was not achieved in all dissolution media. Reflecting the unstable characteristics of the active ingredient under acidic conditions and the time taken to reach peak plasma concentration, which is approximately 4 hr, 0.5% SLS was added to the pH 6.8 dissolution medium to ensure suitability for the sink condition of the drug. It was confirmed that the formulation with this dissolution medium would achieve an equivalent drug release rate to that of the reference drug, allowing for the design of the formulation accordingly.

### Ketotifen Besilate Sustained Release Control

In order to implement the designated target release profile of ketotifen besilate in a combination formulation, a bilayer tablet formulation comprising an immediate-release layer and a sustained-release layer was proposed. The sustained-release layer was designed to float in the stomach after the immediate-release layer had been released, ensuring prolonged and steady release in the gastrointestinal tract. Calcium silicate was employed as the floating agent (Table 2).

To achieve the target release profile of ketotifen besilate, prescriptions B1 to B4 were formulated to compare the release rates based on the proportion of ketotifen besilate in the immediate-release layer, while B5 and B6 were formulated to compare the release rates based on the amount of sustained-release agent in the sustained-release layer. In order to ensure buoyancy for the floating system, tablets were manufactured with a lower density than the density of the dissolution medium, at a fixed weight of 200 mg. Calcium sillicate was added as the floating agent in the sustained-release layer, resulting in immediate buoyancy upon contact with the dissolution medium, facilitating gradual drug release from the floating tablets.

**Table 1: Floatation evaluation according to the ratio of calcium silicate and tableting compression pressure.**

| **Function** | **Component** | **T1** | **T2** | **T3** | | **T4** |
|---|---|---|---|---|---|---|
| Floating agent | Calcium silicate | 10 | 20 | 40 | | 80 |
| Diluent | Cellactose 80* | 187 | 177 | 157 | | 117 |
| Lubricant | Mg. stearate | 3 | | | | |
| Total (mg) | | 200 | | | | |
| Compression force (MPa) | | 1 | 1 | 2 | 3 | 2 |
| Thickness (mM) | | 3.08±0.03 | 3.49±0.12 | 4.36±0.04 | 4.21±0.03 | 4.91±0.10 |
| Floating | | X | X | O | O | O |
| Hardness (N) | | 55.33±4.11 | 52.23±8.81 | 48.33±0.47 | 50.00±1.41 | 48.67±0.94 |

*Cellactose 80; lactose 75%+microcrystalline cellulose 25% mixture (spray-drying co-processed).

**Table 2: Formulation list of ketotifen besilate sustained release control.**

| Layer | Function | Component | B1 | B2 | B3 | B4 | B5 | B6 |
|---|---|---|---|---|---|---|---|---|
| Sustained Release (SR) layer | API* | Ketotifen besilate | 18 | 16 | 14 | 12 | 12 | 12 |
| | Binder | HPC** | 10 | 10 | 10 | 10 | 10 | 10 |
| | Diluent | Cellactose 80 | 67 | 67 | 67 | 67 | 47 | 27 |
| | Sustaining agent | HPMC*** 2208 15,000cps | 60 | 60 | 60 | 60 | 80 | 100 |
| | Floating agent | Calcium sillicate | 40 | 40 | 40 | 40 | 40 | 40 |
| | Lubricant | Mg. stearate | 3 | 3 | 3 | 3 | 3 | 3 |
| | SR Layer weight (mg) | | 200 | | | | | |
| Immediate Release (IR) layer | API* | Ketotifen besilate | 2 | 4 | 6 | 8 | 8 | 8 |
| | Diluent | Cellactose 80 | 47.25 | 45.25 | 43.25 | 41.25 | 41.25 | 41.25 |
| | Lubricant | Mg. stearate | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| | IR Layer weight (mg) | | 50 | | | | | |
| Total weight (mg) | | | 250 | | | | | |

*API: Active Pharmaceutical Ingredient, **HPC: Hydroxypropylcelluloce, ***HPMC: Hydroxypropyl Methylcellulose.

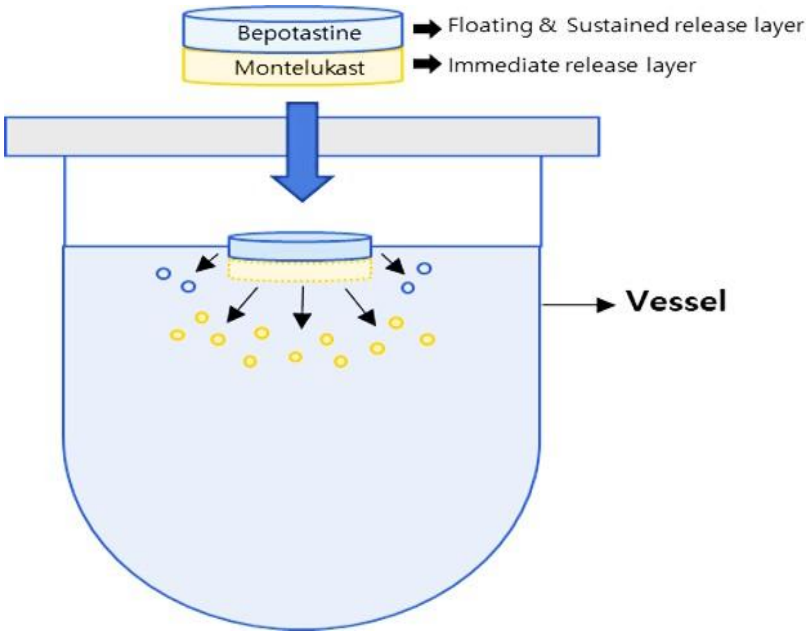


**Figure 2: Schematic diagram of the floating bilayer tablet for gastric retention.**

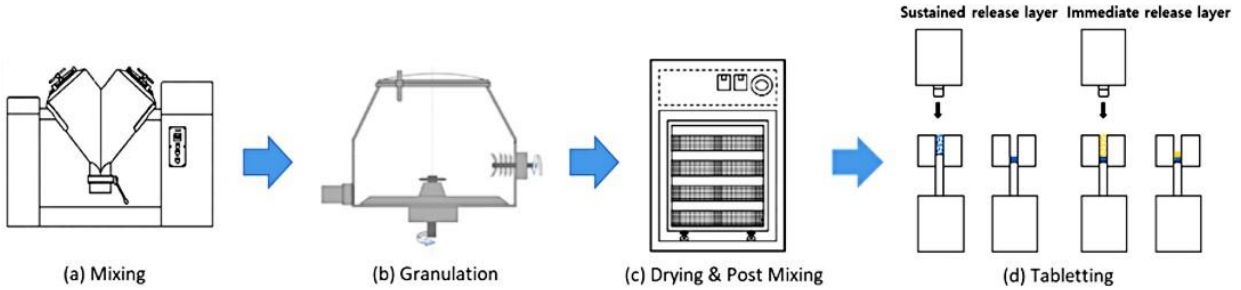


**Figure 3: Preparation process of bilayer tablet.**

**Table 3: Formulation list of immediate release layer.**

| Function | Component | BM1 | BM2 | BM3 | BM4 | BM5 | BM6 | BM7 | BM8 | BM9 |
|---|---|---|---|---|---|---|---|---|---|---|
| API | Ketotifen besilate | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | Montelukast sodium | 10.4 | 10.4 | 10.4 | 10.4 | 10.4 | 10.4 | 10.4 | 10.4 | 10.4 |
| Diluent | Cellactose 80 | 41.25 | 38.22 | 38.22 | 38.22 | 37.62 | 37.01 | 73.1 | 118.85 | 164.60 |
| Disintegrant | Croscamellose sodium | | 3.027 | | | 3.027 | 3.027 | 5 | 7.5 | 10 |
| | Sodium starch glycolate | | | 3.027 | | | | | | |
| | Crospovidon | | | | 3.027 | | | | | |
| Solubilizing agent | Sodium lauryl sulfate | | | | | 0.61 | 1.21 | 2 | 3 | 4 |
| Lubricant | Mg. stearate | 0.89 | 0.89 | 0.89 | 0.89 | 0.89 | 0.89 | 1.5 | 2.25 | 3 |
| Total weight (mg) | | 60.54 | 60.54 | 60.54 | 60.54 | 60.54 | 60.54 | 100 | 150 | 200 |

**Figure 4: Target release profile of ketotifen besilate based on the dissolution results of the reference product.**

The release rates were compared when incorporating ketotifen besilate at ratios of 10% (B1), 20% (B2), 30% (B3) and 40% (B4) in the immediate-release layer. As depicted in Figure 5, it was observed that the release pattern varied depending on the proportion of ketotifen besilate in the immediate-release layer. When 40% was added to the immediate-release layer, the release rate at 30 min met the target; however, the release rate beyond 30 min progressed more rapidly compared to the target release profile. Therefore, an increase in the sustained-release agent content in the sustained-release layer was intended to investigate the changes in the release pattern.

The effect of increasing the amount of Hydroxypropyl Methylcellulose (HPMC), a sustained-release agent included in the sustained-release layer, on the release rate was illustrated in Figure 6. It was observed that as the amount of HPMC in the sustained-release layer was increased from 60 mg (B4) to 80 mg (B5) and 100 mg (B6), the release was effectively controlled. The similarity factor (f2 value) of prescription B6, which contained 100 mg of HPMC, was calculated to be 58.5, indicating equivalence to the target release profile. Therefore, the prescription B6 was chosen for further investigation in the formulation study of combination dosage forms.

**Montelukast Sodium Immediate Release Control**

Table 3 presents the prescription table for the modulation of Montelukast sodium release in the immediate-release layer based on prescription B6. Prescriptions BM1 to BM4 were formulated to compare the effects of different disintegrants on release enhancement depending on their presence and type, while prescriptions BM5 to BM6 aimed to evaluate the effects of varying

the amount of solubilizer on release enhancement. Prescriptions BM7 to BM9 were designed to investigate the changes in release patterns based on the amount of diluent used.

To compare the release patterns of montelukast sodium in the immediate-release layer based on the presence and type of disintegrant, three super disintegrants, sodium croscarmellose,

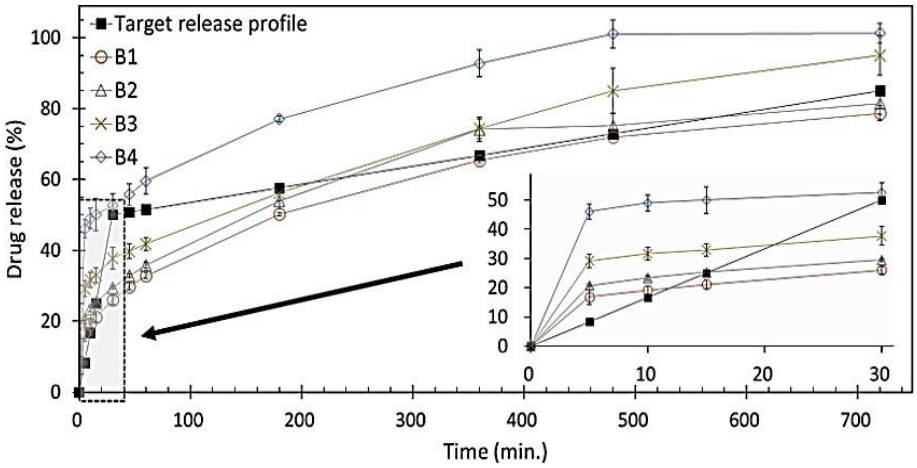


**Figure 5: Dissolution profile based on the proportion of ketotifen besilate in the immediate release layer.**

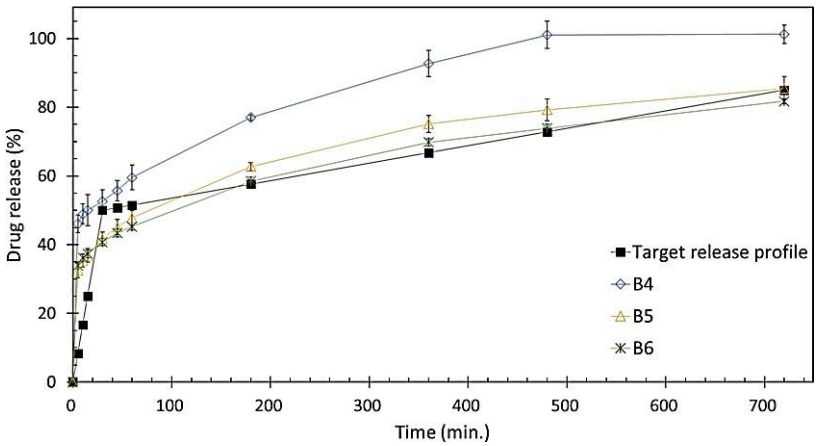


**Figure 6: Dissolution profile of ketotifen besilate based on the ratio of HPMC as a sustaining agent.**

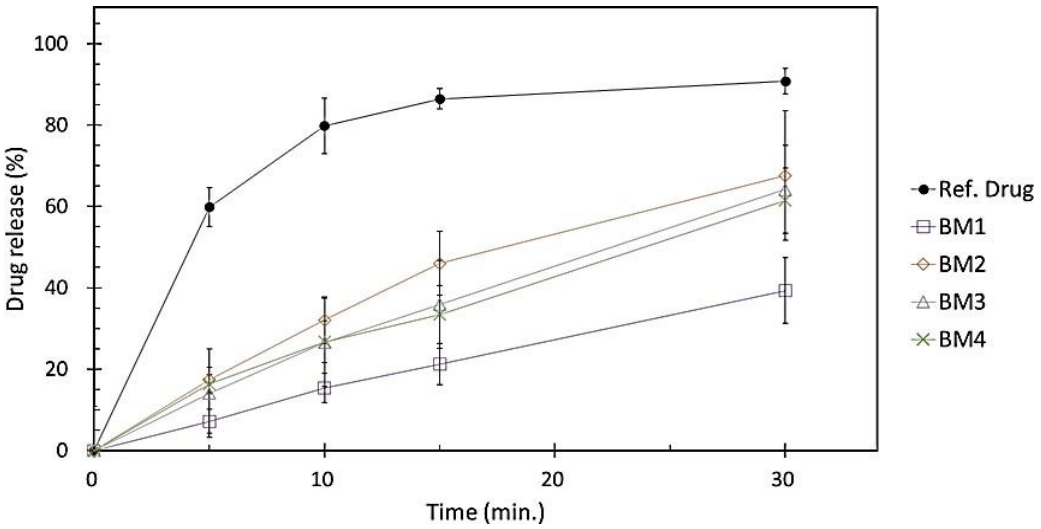


**Figure 7: Dissolution profile of montelukast sodium based on the type of disintegrant.**

sodium starch glycolate and crospovidone, were each added at 5% of the weight of the immediate-release layer. The release rates over time were compared, as depicted in Figure 7. As illustrated in the figure, the addition of disintegrants improved the release rate in all formulations. Sodium croscarmellose exhibited a greater enhancement in release rate compared to sodium starch glycolate and crospovidone; however, it showed significant deviation from the release profile of the reference drug. The reason for this is attributed to the poor solubility of the drug, montelukast sodium, which hindered adequate dissolution within the granules, thereby impeding rapid release. Hence, it was decided to vary the ratio of solubilizer in formulation BM2, which exhibited significant enhancement in release, to investigate its effect on the release pattern, as stated in the experimental results above.

The results comparing the release rates over time with varying solubilizer ratios of 0% (BM2), 1% (BM5) and 2% (BM6) are presented in Figure 8. As depicted in the figure, an increase in the solubilizer ratio led to enhanced release rates; however, BM5 with 1% addition did not show a significant improvement. This was inferred as the 1% addition insufficiently increased the drug's solubility. Moreover, the prescription with the highest release rate, BM6, also exhibited substantial deviation from the reference drug in terms of release profile. Hence, it was postulated that the viscosity properties of montelukast sodium may have acted as a binding agent and therefore, it was decided to enhance dissolution rates by increasing the diluent to improve release through refined disintegration kinetics.

The results comparing the release rates with the addition of the diluent, cellactose 80, to the BM6 prescription, which already contained a solubilizer, are depicted in Figure 9. As illustrated in the figure, an increase in the amount of diluent led to enhanced release rates. This improvement was attributed to Montelukast sodium in the immediate-release layer, which accounted for more than 10% by weight, acting as a binding agent, thereby agglomerating the excipients and impeding the dissolution kinetics of the formulation. However, with the increased amount of diluent, it was observed that the cohesion was weakened, leading to improved drug dissolution. In all formulations with the addition of the diluent cellactose 80, the similarity factor with the reference drug exceeded 50. Particularly, in the BM8 prescription with a diluent quantity of 150 mg, the release rate closely resembled that of the reference drug, thus establishing it as the final prescription for the combination dosage form.

**Equivalence and Reproducibility Assessment Using Similarity Factor**

The dissolution rate equivalence of the final formulation, BM8, containing ketotifen besilate and montelukast sodium, was evaluated against the target release profile using the similarity factor based on the FDA's guidance for industry on dissolution profile comparisons. In the following equation (2), n represents the number of time points used for comparison, Rt denotes the mean dissolution rate of the reference product and Tt denotes the mean dissolution rate of the test product.

A comparative dissolution test was conducted for the B6 formulation, which contains ketotifen in both immediate-release and sustained-release layers, against the target release profile. The similarity factor was found to be 58.5, which is higher than the equivalence threshold of 50, confirming equivalence. Furthermore, a comparative dissolution test for the final combination formulation, BM8, was evaluated using the similarity factor. The similarity factor for ketotifen besilate was 61.4 and for montelukast sodium, it was 65.9, demonstrating equivalence for both components.

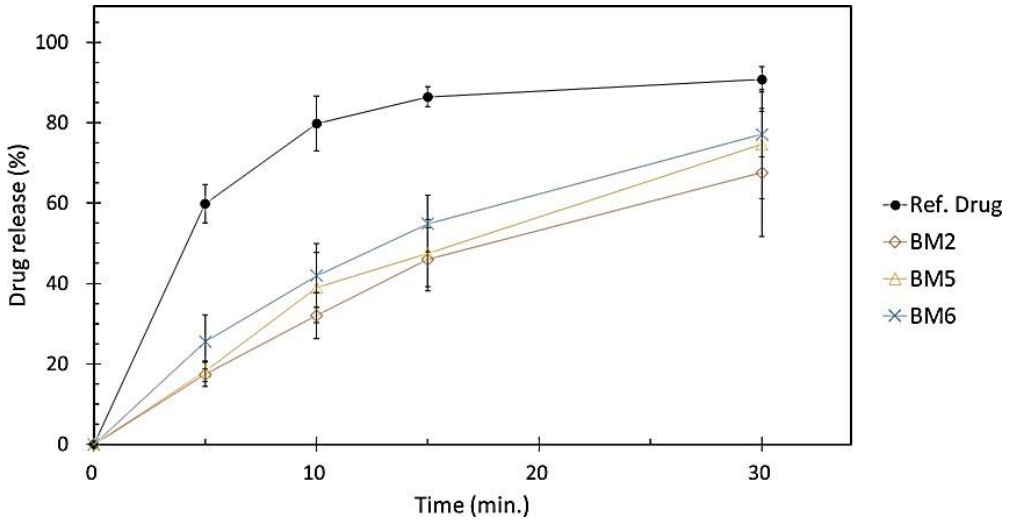


**Figure 8: Dissolution profile of montelukast sodium based on the ratio of solubilizer.**

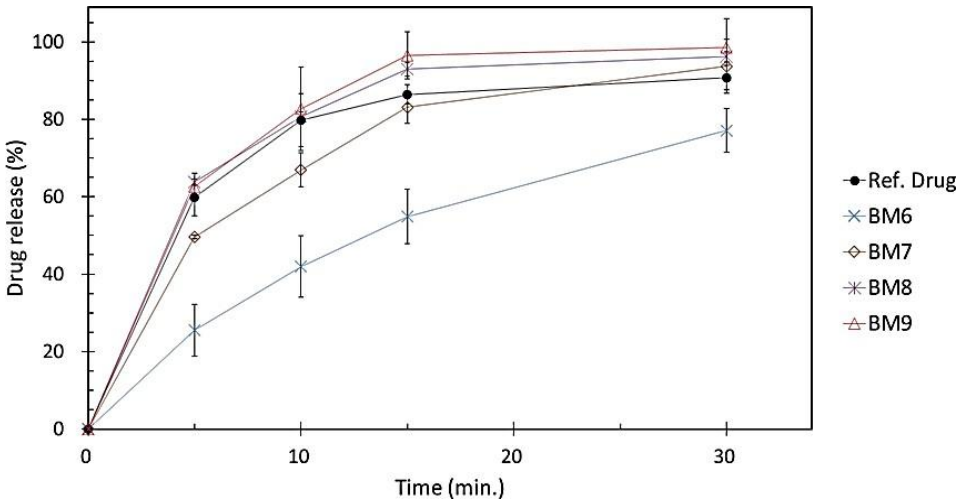


**Figure 9: Dissolution profile of montelukast sodium from immediate layer according to diluent rate.**

To evaluate the reproducibility of the formulation manufacturing process, the BM8-R formulation was prepared using the same composition and manufacturing process as the BM8 formulation. A comparative dissolution test was then conducted using the same method and the similarity factor between BM8 and BM8-R was assessed based on these results. For BM8-R, the similarity factor was 60.5 for ketotifen besilate and 63.7 for montelukast sodium. The similarity factors with the target release profile were 58.3 for ketotifen besilate and 60.8 for montelukast sodium, confirming the reproducibility of the formulation. Notably, the similarity factor values for ketotifen besilate were similar across BM6, BM8 and BM8-R, indicating that the release rate reproducibility was maintained without the influence of montelukast sodium in the immediate-release layer. These findings demonstrate that both active ingredients in the final formulation exhibit pharmaceutical equivalence with the target release profile and the reference product.

## 4. CONCLUSION

In this study, a once-daily dosage form containing ketotifen besilate, which is conventionally administered twice daily and montelukast sodium, which requires rapid release to achieve effective plasma concentrations, was developed. To enable once-daily dosing of ketotifen besilate, a floating system was employed, utilizing calcium silicate as a buoyancy agent with low density to maintain drug buoyancy. Additionally, adjusting the thickness at a fixed weight was implemented to ensure sufficient floating time by reducing the density of the formulation below that of gastric fluid. Increasing the amount of Hydroxypropyl Methylcellulose (HPMC) in the sustained-release layer facilitated achieving equivalent release rates to the target profile. For the rapid absorption demanded by montelukast sodium, super disintegrants were added to ensure rapid dissolution and the addition of a solubilizer at 2% improved drug release rates by enhancing solubility. Furthermore, increasing the diluent amount in the immediate-release layer improved dissolution patterns, securing the concept release profile and equivalence with the reference drug. Additionally, recent studies on combination therapy with antihistamines and leukotriene receptor antagonists in children demonstrated that 76.5% of patients experienced improvements in neuropsychiatric symptoms compared to leukotriene receptor antagonist monotherapy.24 This finding suggests that combination therapy not only enhances symptom relief but also improves patients' quality of life. Based on these results, a fixed-dose combination formulation can be proposed to enhance adherence and provide greater convenience for pediatric patients. This formulation strategy not only shifts the absorption site for once-daily dosing but also enhances the efficacy of the dosage form, overcoming rapid drug clearance. Multilayer tablet formulations offer a way to achieve the distinct release rates required by both active ingredients, creating a new formulation that supports improved medication adherence using existing manufacturing facilities.

## 5. CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

## 6. ABBREVIATIONS

API: Active Pharmaceutical Ingredient;HPLC: High-Performance Liquid Chromatography; HPC: Hydroxypropyl Cellulose; HPMC: Hydroxypropyl Methylcellulose; SLS: Sodium Lauryl Sulfate; IR: Immediate Release; SR: Sustained Release; FGF-2: Fibroblast Growth Factor-2; MMP-1: Matrix Metalloproteinase-1; PTFE: Polytetrafluoroethylene; UV: Ultraviolet; MPa: Megapascal; rpm: Revolutions Per Minute; hr: Hour; min: Minute; mM: Millimeter; mg: Milligram; mL: Milliliter; µm: Micrometer; µL: Microliter; N: Newton; pH: Potential of Hydrogen; ARIA: Allergic Rhinitis and its Impact on Asthma; FDA: Food and Drug Administration; cps: Centipoise; v/v: Volume by Volume.

## 7. SUMMARY

- To achieve different release rates, a bilayer tablet formulation was introduced and a low-density material, Florite R, was used as a buoyancy agent to implement an immediate floating system suitable for each drug's target release profile.
- To develop a once-daily dosage form containing montelukast sodium and ketotifen besilate, a target release profile was established and its compliance was confirmed through comparative dissolution testing.
- By adjusting the ratios of disintegrants, binders, solubilizers and diluents in the drug release from the immediate-release and sustained-release layers, we were able to secure formulations equivalent to the target release profile.
- This implies the potential applicability of this approach in developing combination formulations requiring different absorption sites and release rates in the future

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