Formulation and In-vitro Evaluation of Metolazone 10 mg Immediate-Release Tablets Using Direct Compression Method

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Abstract

Metolazone, a thiazide-like diuretic, is widely used for hypertension and edema management but shows poor aqueous solubility and variable bioavailability. To develop and evaluate an immediate-release (IR) tablet formulation of Metolazone 10 mg by the direct compression method to achieve faster disintegration and improved dissolution. Metolazone IR tablets were formulated using microcrystalline cellulose (MCC), sodium starch glycolate (SSG), colloidal silicon dioxide, and magnesium stearate. The powder blends were assessed for flow properties (bulk/tapped density, Carr's index, Hausner's ratio, and angle of repose). Compressed tablets were evaluated for hardness, friability, disintegration, assay, and in-vitro dissolution. The optimized batch was compared with a marketed product and subjected to stability studies under ICH Q1A(R2) guidelines. Optimized tablets showed good flow (Carr's index < 15%, Hausner's ratio < 1.25), adequate hardness (4.2–5.0 kg/cm²), friability < 1%, disintegration within 2 minutes, and >95% drug release in 30 minutes—comparable to the marketed product. Accelerated stability testing confirmed product stability. Immediate-release Metolazone tablets prepared by direct compression demonstrated rapid disintegration, excellent dissolution, and robust stability, providing a cost-effective and scalable formulation strategy.

Keywords:
Metolazone, Immediate-release tablet, Direct compression, Dissolution, Disintegration, Stability studies.

Introduction

Oral drug administration remains the most preferred route for systemic therapy due to its convenience, safety profile, and cost-effectiveness [1]. Immediate-release (IR) formulations are designed to provide a rapid onset of therapeutic action, which is particularly essential for drugs requiring prompt diuretic or antihypertensive effects [2]. Metolazone, a thiazide-like

diuretic, exerts its action by inhibiting sodium reabsorption in the distal tubules and is widely used in the management of hypertension and edema associated with cardiac or renal conditions [3,4]. Although Metolazone demonstrates high permeability, it is classified as a BCS Class II drug due to its poor solubility, which restricts absorption and contributes to variability in plasma concentrations [5,6]. Therefore, improving its dissolution profile is a key focus in the development of an optimized formulation [7]. The direct compression method provides multiple benefits, including fewer manufacturing steps, minimal exposure to moisture, reduced processing time, and improved product stability [8]. However, successful direct compression depends on selecting excipients that impart sufficient compressibility and rapid disintegration [9]. Microcrystalline cellulose (MCC) provides excellent compressibility and promotes uniform distribution of the drug [10]. Sodium starch glycolate (SSG) functions as a super disintegrant, facilitating rapid tablet breakup upon contact with gastric fluid [11,12]. Colloidal silicon dioxide acts as a glidant improving powder flow, while magnesium stearate serves as a lubricant [13]. Recent studies show that optimizing ratios of MCC and SSG significantly enhances dissolution of poorly soluble drugs [14–16]. Therefore, the present study focuses on the formulation and evaluation of Metolazone 10 mg immediate-release tablets using the direct compression method, aiming to achieve rapid disintegration, improved dissolution, and acceptable stability comparable to the marketed product [17–20].

Materials and Methods

Materials

Metolazone was procured from an authorized source, and the excipients—including microcrystalline cellulose (MCC), sodium starch glycolate (SSG), colloidal silicon dioxide, and magnesium stearate—were of analytical grade and used as received.

Formulation Development

Immediate-release tablets of Metolazone 10 mg were formulated using the direct compression method. Six batches (F1–F6) were designed by adjusting the proportions of MCC and SSG while maintaining a constant amount of drug and lubricant. All components were sifted through a #40 mesh, mixed thoroughly, and then lubricated with magnesium stearate. The final powder blends were compressed into tablets using an 8 mm flat-faced punch on a rotary tablet press.

Table 1: Composition of Metolazone IR Tablets (F1 F3)

Ingredient	Formulation 1 (F1)	Formulation 2 (F2)	Formulation 3 (F3)
Metolazone 10 mg	10 mg	10 mg	10 mg
MCC PH 102 (mg)	89	87	-
Colloidal Silicon Dioxide (mg)	-	2	-

Prosolv SMCC HD90 (mg)	-	-	89
Magnesium Stearate (mg)	1	1	1
Core Tablet Weight (mg)	100	100	100

Pre-compression Evaluation

Powder blends were evaluated for flow and compressibility characteristics, including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose.

Post-compression Evaluation

The compressed tablets were evaluated for weight variation, hardness, thickness, friability, disintegration time, drug content, and in-vitro dissolution. Dissolution studies were performed using USP Type II (paddle) apparatus with 900 mL of 0.1 N HCl as the dissolution medium, maintained at 37 ± 0.5°C and stirred at 50 rpm.

Stability Studies

The optimized formulation was subjected to accelerated stability testing under conditions of 40 ± 2°C and 75 ± 5% RH for three months, following ICH Q1A(R2) guidelines.

Results and Discussion

All powder blends demonstrated good flow properties, with Carr's index values below 15% and Hausner's ratios under 1.25, confirming their suitability for direct compression [21].

Table 2: Result for Bulk Density, Tapped Density, Angle of Repose, Loss on Drying, Carr's Index and Hausner's Ratio for the Trial Batches

Parameter	F1	F2	F3
Bulk Density (g/mL)	0.63	0.64	0.65
Tapped Density (g/mL)	0.68	0.68	0.69
Angle of Repose (°)	32.3	29.4	20.1
Loss on Drying (%)	4.2	3.82	4.74
Carr's Index (%)	5.6	5.4	5.8
Hausner's Ratio	1.02	1.04	1.06

The tablets showed consistent weight, adequate hardness (4.2–5.0 kg/cm²), and friability within acceptable limits (<1%). Disintegration times ranged from 90 to 150 seconds, influenced by the concentration of sodium starch glycolate. The optimized formulation (F3) exhibited the fastest disintegration at 90 seconds, indicating rapid disintegration [22]. In-vitro dissolution studies revealed that batch F3 achieved 95% drug release within 30 minutes, demonstrating performance comparable to the marketed formulation [23]. The enhanced dissolution can be attributed to the wicking and swelling mechanisms of SSG, which promote rapid water uptake and tablet disintegration [24].

Table 3: Post-compression Evaluation Results

Parameter	F1	F2	F3	Marketed
Hardness (Kg/cm2)	6.5	6.4	6.7	6.0
Friability (%)	0.089	0.079	0.071	0.085
Disintegration Time (s	132.0	51.0	96.0	84.0
Dissolution @30 min (	87.0	89.0	90.0	89.8

The combined use of MCC and SSG played a key role, where MCC provided good compressibility and mechanical strength, while SSG ensured prompt disintegration, resulting in a synergistic improvement in overall tablet performance [25]. Accelerated stability studies conducted over three months showed no notable changes in appearance, assay values, or dissolution profiles. The f_2 similarity factor remained above 50, indicating that the stored tablets maintained performance comparable to the initial samples [26]. Overall, the findings confirm that the direct compression approach, utilizing an optimized blend of MCC, SSG, and colloidal silicon dioxide, yields a robust, stable, and scalable formulation of Metolazone immediate-release tablets [27-30].

Limitations and Future Scope

This study successfully formulated an immediate-release Metolazone tablet using direct compression; however, the evaluation was limited to in-vitro testing. Future investigations should include in-vivo pharmacokinetic and bioavailability assessments to establish clinical equivalence with the marketed product. Additionally, further research could explore the use of co-processed excipients, nanocrystalline drug forms, and Quality-by-Design (QbD) strategies to improve solubility and support large-scale manufacturing.

Conclusion

Immediate-release Metolazone 10 mg tablets were successfully developed using the direct compression technique. The optimized batch demonstrated rapid disintegration in under 2

minutes, strong mechanical integrity, and more than 95% drug release within 30 minutes. Stability studies further confirmed that the formulation remained robust under accelerated conditions for three months. Overall, this formulation strategy provides a cost-effective and industrially practical solution for achieving a rapid therapeutic effect.

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