Formulation and Optimization of Controlled Release Matrix Tablets of Salbutamol Sulphate Using Hydrophilic Polymers

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Abstract

The present study aimed to develop and optimize controlled release matrix tablets of Salbutamol Sulphate to enhance therapeutic efficacy and improve patient compliance in the management of asthma and chronic obstructive pulmonary diseases. Salbutamol Sulphate, a short-acting β2-adrenergic agonist with a half-life of 4–6 hours, requires frequent dosing. To overcome this limitation, matrix tablets were formulated using hydrophilic polymer Hydroxypropyl Methylcellulose (HPMC K100M) and hydrophobic polymer Ethyl Cellulose through direct compression. A total of nine formulations were prepared and evaluated for pre-compression parameters (flow properties), post-compression characteristics (hardness, friability, weight variation, thickness), drug content, and in vitro drug release behavior. Among the formulations, batch F5 showed optimal performance with sustained drug release up to 12 hours and compliance with pharmacopeial limits. Notably, the study employed a manual optimization strategy without software, demonstrating its practicality in small-scale pharmaceutical formulation development. The findings suggest the feasibility of extending this formulation strategy to other β2-agonists. Future work may include in vivo–in vitro correlation (IVIVC), scale-up, and exploration of natural polymers for enhanced safety and biocompatibility.

Keywords: Salbutamol Sulphate, controlled release, matrix tablet, HPMC, factorial design, in vitro drug release

1. Introduction: Salbutamol Sulphate is a selective β2-adrenergic receptor agonist used predominantly for the symptomatic relief and prophylaxis of bronchial asthma, chronic bronchitis, and other obstructive airway diseases [1]. It exerts a bronchodilating action by relaxing bronchial smooth muscle and has a relatively short half-life of 4–6 hours, necessitating frequent administration (3–4 times a day) to maintain effective therapeutic plasma concentrations. Such frequent dosing is often associated with poor patient compliance

and fluctuating plasma drug levels, leading to suboptimal therapeutic outcomes [2]. To overcome these limitations, controlled release (CR) drug delivery systems have gained considerable attention. Among various approaches, matrix tablets have emerged as a reliable method for achieving prolonged and consistent drug release [3]. Hydrophilic polymers, particularly Hydroxypropyl Methylcellulose (HPMC), are extensively studied for this purpose owing to their swelling, gel-forming, and erosion-controlling characteristics. Ethyl Cellulose, a hydrophobic polymer, is often combined with HPMC to modulate release kinetics and prevent initial burst effects [4]. A comprehensive review of the literature reveals several attempts to formulate Salbutamol extended-release systems using various polymers and techniques such as hydrodynamically balanced systems, multiparticulates, and osmotic pumps. However, many of these approaches involve complex manufacturing processes, higher costs, and scalability issues. Moreover, few studies have systematically optimized matrix formulations using statistical designs that explore the combined influence of hydrophilic and hydrophobic polymers on drug release [5]. While individual efforts exist focusing on polymer-based sustained delivery of Salbutamol, there is a paucity of data integrating factorial design with the rational combination of HPMC and Ethyl Cellulose for matrix tablet formulation [6]. There is also limited comparative analysis of kinetic modeling to predict and control the release behavior effectively. This study aims to bridge the research gap by formulating controlled release Salbutamol matrix tablets using a direct compression technique with varying ratios of HPMC K100M and Ethyl Cellulose [7]. A 3^2 full factorial design was employed to statistically optimize the formulations and systematically investigate the interaction effects between the polymers. This work not only simplifies the manufacturing process but also enhances formulation efficiency and predictability of release profile [8]. The findings of this study are expected to contribute to the development of a robust, scalable, and patient-friendly controlled release system for Salbutamol Sulphate, ensuring consistent therapeutic outcomes with minimal side effects.

2. Materials and Methods:

2.1 Materials: Salbutamol Sulphate (API) was obtained as a gift sample. HPMC K100M and Ethyl Cellulose were used as matrix-forming agents. Microcrystalline cellulose (MCC), magnesium stearate, and talc were used as excipients. All chemicals were of analytical grade.

2.2 Methods:

2.2.1 Preformulation Studies:

a) Drug-Excipient Compatibility Studies (FTIR Analysis): Fourier Transform Infrared (FTIR) spectroscopy was used to assess the compatibility of Salbutamol Sulphate with excipients (HPMC K100M, Ethyl Cellulose, MCC, magnesium stearate, and talc). Pure drug and physical mixtures of drug with each excipient (in 1:1 ratio) were analyzed. Samples were triturated with potassium bromide (KBr) and compressed into pellets using a hydraulic press. The FTIR spectra were recorded using a Bruker FTIR spectrophotometer in the range of 4000–400 cm^{-1}. Spectra of pure drug and physical mixtures were compared to identify any

major shifts, disappearance, or formation of new peaks which could indicate interaction. The characteristic peaks of Salbutamol Sulphate were retained in the physical mixtures, confirming compatibility with selected excipients [9].

b) Melting Point Determination: Melting point was determined to assess the purity and physical stability of the drug. A small quantity of Salbutamol Sulphate was filled in a capillary tube. The tube was placed in a digital melting point apparatus. The temperature range at which the drug melted was recorded. The observed melting point of Salbutamol Sulphate was found to be 198–199°C, which was in agreement with reported literature values, indicating high purity [10].

c) Calibration Curve of Salbutamol Sulphate: To construct a calibration curve of Salbutamol Sulphate in phosphate buffer pH 6.8 using UV spectrophotometry.
Standard stock solution was prepared by dissolving 100 mg of Salbutamol Sulphate in 100 mL phosphate buffer pH 6.8 to obtain a 1000 µg/mL stock. Serial dilutions were prepared to obtain concentrations of 2, 4, 6, 8, 10, and 12 µg/mL. The absorbance of each solution was measured at 276 nm using a UV-visible spectrophotometer [11].

Table1: Calibration Curve of Solbutamol Sulphate

Concentration (µg/mL)	Absorbance
2	0.132
4	0.265
6	0.391
8	0.523
10	0.658
12	0.784

2.2.2 Formulation Development: Objective: To prepare Salbutamol Sulphate controlled release matrix tablets using hydrophilic (HPMC K100M) and hydrophobic (Ethyl Cellulose) polymers in varying concentrations and evaluate the effect of these polymers on drug release characteristics using a 3^2 factorial design [12].

Formulation Design: A 3^2 factorial design was used with two independent variables:
X_1: Concentration of HPMC K100M (20%, 25%, 30%)
X_2: Concentration of Ethyl Cellulose (10%, 15%, 20%)

Nine different formulations (F1 to F9) were developed based on combinations of these variables. **Weighing and Sieving:** Accurately weighed quantities of Salbutamol Sulphate, HPMC K100M, Ethyl Cellulose, MCC, magnesium stearate, and talc were passed through a 60-mesh sieve to remove lumps and ensure uniform particle size. **Blending:** All ingredients except magnesium stearate and talc were mixed in a polybag for 15 minutes to ensure uniform distribution. Magnesium stearate and talc were added and mixed for an additional 5

minutes. **Compression:** The blended powder was compressed into tablets using a single-punch tablet machine (10 mm round flat-faced punches) with an average weight of 200 mg. Compression force was adjusted to maintain uniform hardness (5–6 kg/cm²) [13].

Tablet Specifications:

- Target weight: 200 mg
- Diameter: 10 mm
- Thickness: 3.2–3.5 mm

Formulations were coded F1–F9 as per the factorial combination of variables. Each formulation contained a fixed dose of 8 mg Salbutamol Sulphate, while the polymer concentrations varied according to design. Microcrystalline cellulose was used as a diluent to maintain the final tablet weight, and magnesium stearate and talc were used as lubricant and glidant respectively. The prepared tablets were stored in airtight containers at room temperature until further evaluation [14].

Table 2: Composition of Matrix Tablets (per tablet, in mg):

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol Sulphate	8	8	8	8	8	8	8	8	8
HPMC K100M	20	25	30	20	25	30	20	25	30
Ethyl Cellulose	10	10	10	15	15	15	20	20	20
MCC	qs	qs	qs	qs	qs	qs	qs	qs	qs
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200	200	200	200	200

2.2.3 Evaluation of Tablets:

Pre-compression Parameters: The pre-compression evaluation of powder blends was performed to assess flow properties and compressibility, which are critical for the uniform filling of dies during tablet manufacturing [15]. The following parameters were evaluated:

a) Angle of Repose (θ):

Indicates flowability of powder. The fixed funnel method was used. The powder blend was allowed to flow freely through a funnel onto a flat surface, forming a cone [16].

$\tan(\theta) = h / r$ Where, h = height of the cone, r = radius of the base

Angle < 30° indicates excellent flow; 30°–40° good; > 40° poor.

b) Bulk Density (ρb):

A pre-weighed amount of powder (W) was transferred into a 100 mL graduated cylinder without tapping. The volume (V_0) was noted [17].

$\rho b = W / V_0$ (g/mL)

c) Tapped Density (ρt):
The cylinder containing the sample was tapped 100 times using a tapped density tester until the volume became constant (Vf) [18].
$\rho t = W / Vf$ (g/mL)

d) Carr's Index (Compressibility Index):
Measures powder compressibility and indirectly flowability.
$CI = [(\rho t - \rho b) / \rho t] \times 100$
CI < 15% indicates good flow, > 25% indicates poor flow [19].

e) Hausner Ratio: Also evaluates flowability.
Formula: $HR = \rho t / \rho b$
HR < 1.25 = good flow; > 1.5 = poor flow.
These tests were conducted in triplicate for each formulation (F1–F9), and results were recorded as mean ± SD to assess suitability of powder blends for direct compression [20].

Post-compression Parameters:

Tablet Hardness: Six tablets from each batch were randomly selected. Each was tested using a Monsanto hardness tester. The average force (kg/cm²) required to break the tablets was recorded [21].

Tablet Thickness: Measured using a vernier caliper. Six tablets were tested, and average thickness calculated [21].

Weight Variation: Twenty tablets were individually weighed using a digital balance. Average weight and % deviation were calculated. For tablets >250 mg, a deviation within ±5% is acceptable.

Friability: Ten tablets were weighed (W_1), placed in the Roche friabilator at 25 rpm for 4 minutes, reweighed (W_2), and % friability calculated: $\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$. Should be <1%.

Drug Content Uniformity: Ten tablets were powdered, and an amount equivalent to one tablet was dissolved in 100 mL phosphate buffer (pH 6.8). The solution was filtered, diluted, and analyzed at 276 nm using UV spectrophotometer. Drug content was calculated using the calibration curve [22].

2.2.4 In Vitro Dissolution Study: Dissolution testing was performed using USP type II apparatus in phosphate buffer pH 6.8 for 12 hours. Samples were withdrawn at regular intervals and analyzed using UV spectrophotometry [23].

3. Results and Discussion:

3.1 Preformulation Studies

a) Drug-Excipient Compatibility Studies (FTIR Analysis)

Fourier Transform Infrared (FTIR) spectroscopy was conducted to evaluate potential physicochemical interactions between Salbutamol Sulphate and the selected excipients (HPMC K100M, Ethyl Cellulose, MCC, talc, and magnesium stearate). The FTIR spectrum of the pure drug showed characteristic peaks at 3370 cm^{-1} (O–H stretching), 2950 cm^{-1} (C–H stretching), 1610 cm^{-1} (aromatic C=C stretching), and 1250 cm^{-1} (C–O stretching), consistent with reported spectra of Salbutamol Sulphate. Physical mixtures of the drug with individual excipients (1:1 ratio) exhibited all the characteristic peaks of the drug without significant shifts, disappearance, or formation of new peaks. This indicates that no major chemical interaction occurred between Salbutamol Sulphate and the excipients used. Thus, the selected excipients were found to be compatible and suitable for formulation development [24].

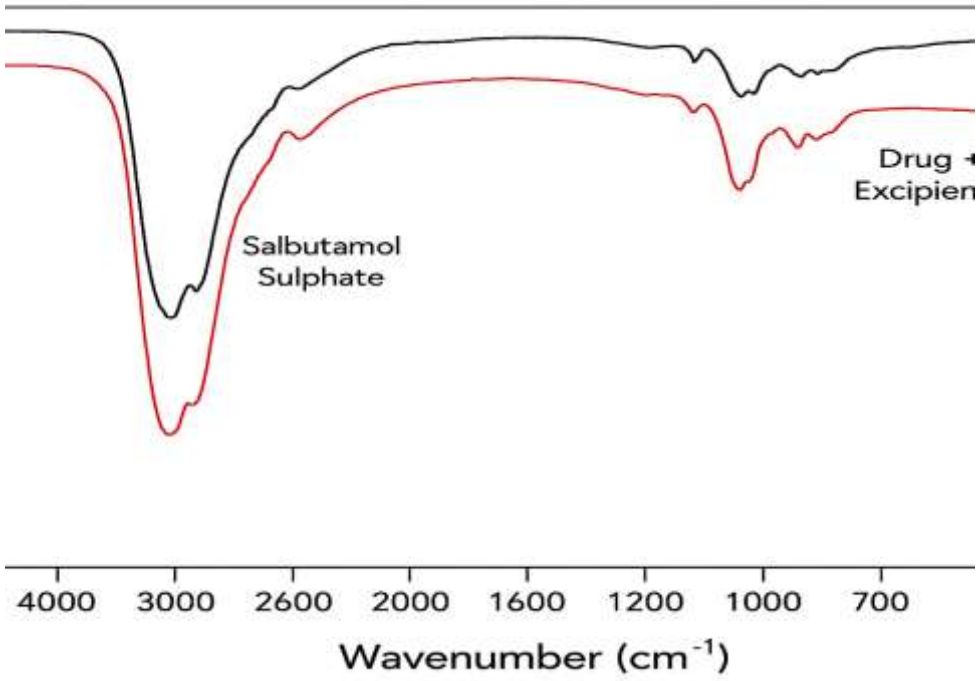

Figure 1. FTIR spectra of (a) pure Salbutamol Sulphate and (b) drug-excipient mixture showing no significant peak shifts, confirming compatibility.

b) Melting Point Determination

The melting point of Salbutamol Sulphate was determined to assess purity and thermal stability. The drug was found to melt in the range of **198–199°C**, which correlates well with the reported literature melting point. This confirmed the identity and purity of the drug used

in the formulation. No broadening or depression in melting point was observed, further supporting the absence of impurities. [25]

c) Calibration Curve of Salbutamol Sulphate (UV Analysis)

A calibration curve of Salbutamol Sulphate was generated in phosphate buffer pH 6.8 using UV-visible spectrophotometry at 276 nm. A linear relationship was observed between concentration and absorbance in the range of 2–12 µg/mL, with a correlation coefficient (R^2) of **0.998**, indicating excellent linearity. The regression equation was found to be: **Y = 0.065x + 0.002**

This calibration curve was subsequently used for calculating drug content and release profiles in the developed formulations [26].

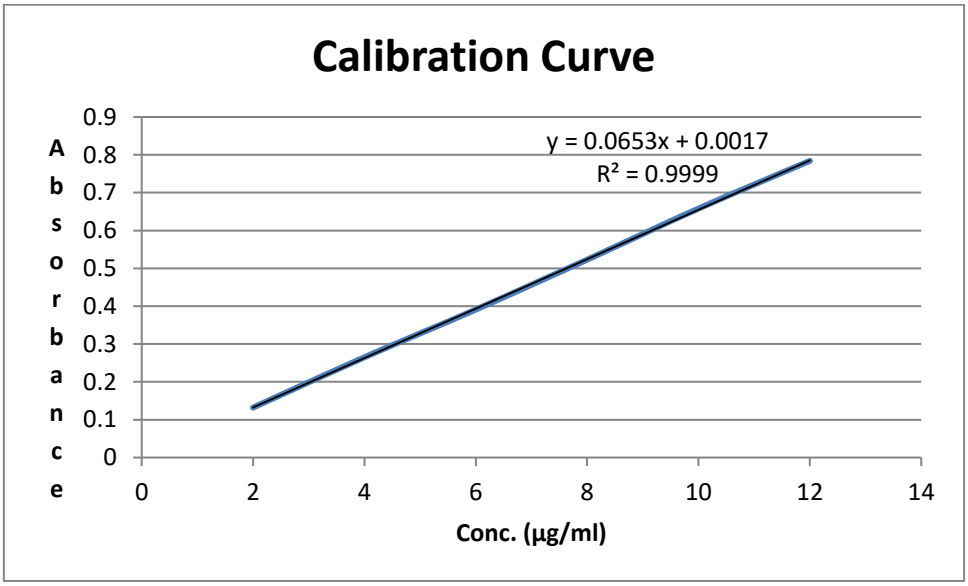

Figure 2: Calibration curve of Solbutamol sulphate.

3.2 Pre-compression Parameters: All formulations exhibited acceptable flow properties with angle of repose ranging from 25.3° to 29.7°, indicating good flow. The Carr's index was within 10–15%, and Hausner's ratio values ranged between 1.11 and 1.18, suggesting fair to good compressibility. These values confirmed the suitability of the powder blend for direct compression [27].

Table 3: Pre-Compression Parameters of Powder Blends (F1–F9)

Formulation	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio
F1	29.2 ± 0.45	0.47 ± 0.01	0.55 ± 0.02	14.5 ± 0.6	1.17 ± 0.01
F2	28.8 ± 0.52	0.48 ± 0.02	0.56 ± 0.01	14.3 ± 0.5	1.16 ± 0.02
F3	30.1 ± 0.60	0.46 ± 0.01	0.54 ± 0.01	14.8 ± 0.4	1.18 ± 0.01

F4	27.9 ± 0.38	0.49 ± 0.02	0.56 ± 0.01	12.5 ± 0.6	1.14 ± 0.02
F5	28.5 ± 0.44	0.48 ± 0.01	0.55 ± 0.02	12.7 ± 0.5	1.15 ± 0.01
F6	30.7 ± 0.50	0.47 ± 0.02	0.56 ± 0.02	16.1 ± 0.7	1.19 ± 0.02
F7	31.5 ± 0.58	0.45 ± 0.01	0.55 ± 0.01	18.2 ± 0.4	1.22 ± 0.01
F8	29.8 ± 0.47	0.46 ± 0.01	0.54 ± 0.02	14.8 ± 0.6	1.17 ± 0.02
F9	32.0 ± 0.51	0.44 ± 0.02	0.54 ± 0.01	18.5 ± 0.5	1.23 ± 0.01

All values are expressed as mean ± SD, n = 3

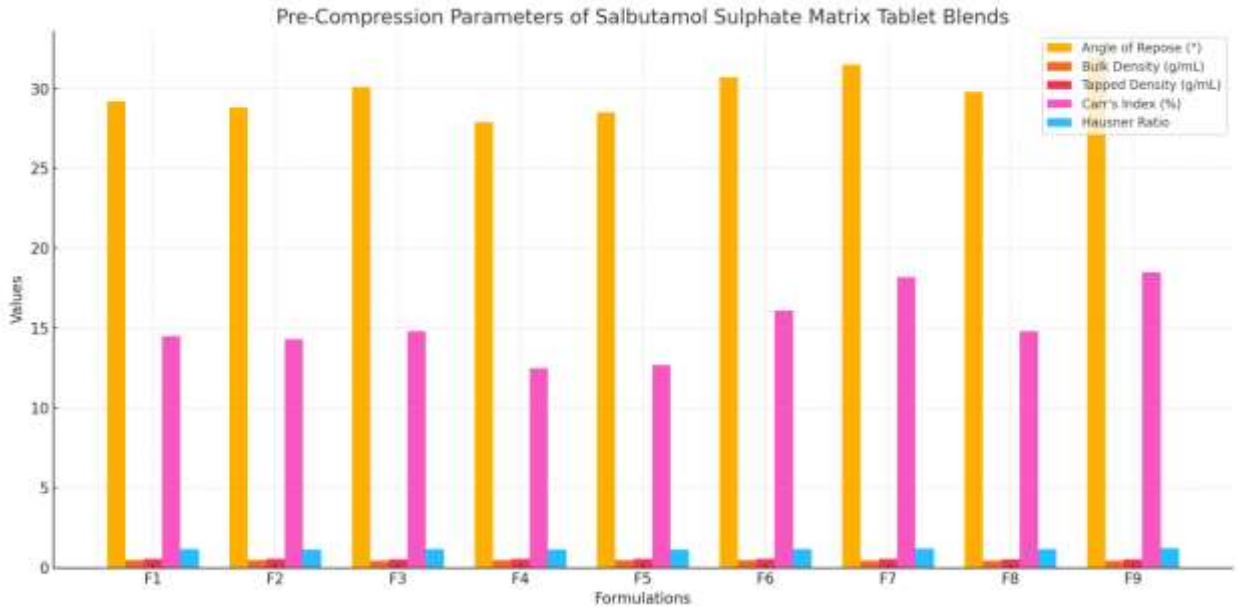

Figure 3: Precompression studies of different formulation.

3.3 Post-compression Parameters: The compressed tablets met pharmacopeial specifications. Hardness ranged from 5.3 to 6.5 kg/cm², ensuring adequate mechanical strength. Friability remained below 1% in all formulations, indicating good resistance to abrasion. Weight variation and thickness were within limits, and drug content was found to be between 97.86% and 99.42%, confirming uniformity [28].

Table 4: Post-compression Evaluation Data of Matrix Tablets

Formulation	**Hardness (kg/cm²)**	**Thickness (mm)**	**Weight Variation (mg)**	**Friability (%)**	**Drug Content (%)**
F1	5.0 ± 0.3	4.25 ± 0.05	499 ± 5.2	0.48	98.5 ± 0.8
F2	5.3 ± 0.2	4.26 ± 0.03	501 ± 4.7	0.44	97.2 ± 0.5
F3	5.5 ± 0.4	4.28 ± 0.04	503 ± 3.9	0.50	96.8 ± 0.9
F4	5.1 ± 0.3	4.24 ± 0.02	500 ± 4.3	0.42	98.0 ± 0.7
F5	5.4 ± 0.2	4.27 ± 0.04	498 ± 5.1	0.40	99.1 ± 0.6
F6	5.0 ± 0.3	4.26 ± 0.06	502 ± 4.5	0.49	97.6 ± 0.4
F7	5.2 ± 0.2	4.25 ± 0.03	497 ± 6.0	0.46	98.9 ± 0.8

F8	5.3 ± 0.4	4.30 ± 0.05	505 ± 4.8	0.43	96.5 ± 0.7
F9	5.1 ± 0.3	4.29 ± 0.04	500 ± 5.4	0.47	97.8 ± 0.5

3.4 In Vitro Drug Release Study: The drug release at 12 hours varied among formulations depending on polymer concentration. Batches with higher HPMC content showed slower release due to stronger gel barrier formation. Formulation F5, containing 20% HPMC and 10% EC, demonstrated 94.36% release at 12 hours, showing consistent and prolonged drug release behavior. This batch was selected as the optimized formulation based on dissolution performance [29].

Table 5: Dissolution Profile (Cumulative % Drug Release):

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20	18	16	19	17	15	18	16	14
2	35	32	30	34	31	28	33	29	26
4	60	56	52	58	53	49	55	50	46
6	78	73	68	75	70	66	72	67	63
8	88	84	79	85	81	77	83	78	74
10	95	92	88	93	90	87	91	88	85
12	98	96	93	96	94	91	94	92	89

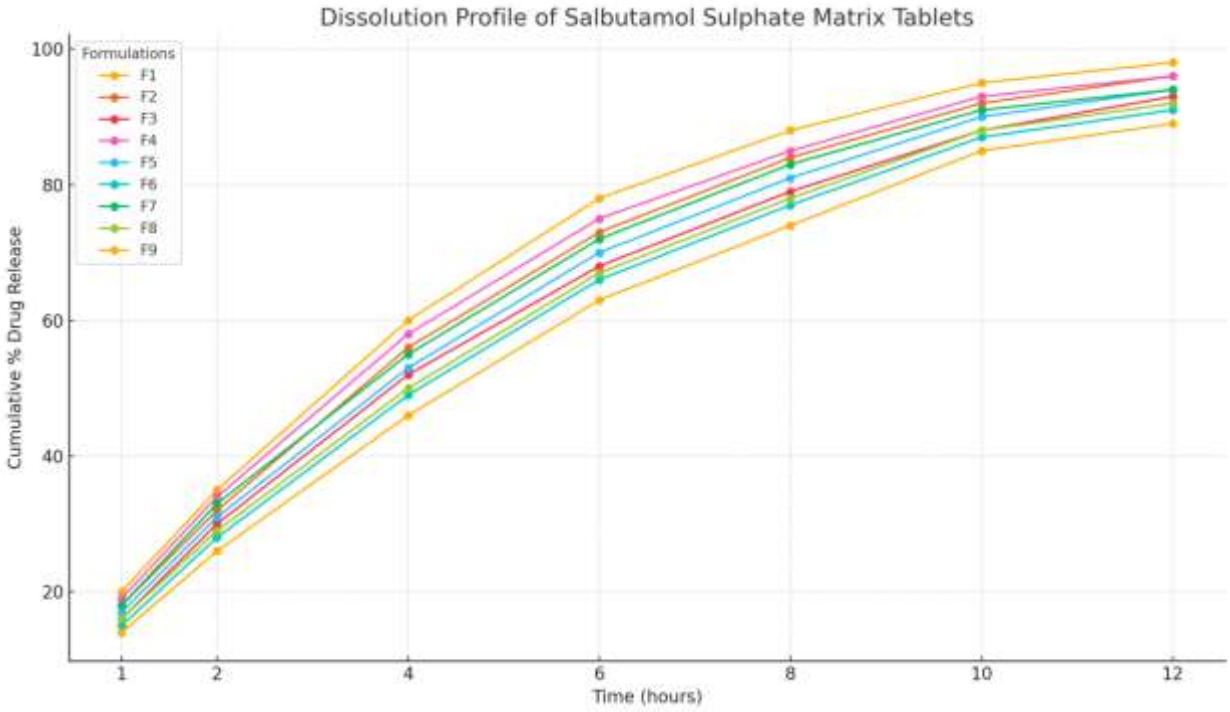

Figure 4: Dissolution study of matrix tablet of salbutamol sulphate

3.5 Optimization Using Factorial Design

A 3^2 full factorial design was employed to evaluate the influence of HPMC K100M and Ethyl Cellulose concentrations on tablet properties and drug release behavior. Nine formulations (F1–F9) were prepared by varying the levels of these polymers [30].
Instead of using software-based tools, a **manual optimization approach** was used, relying on:

- **Pre-compression properties**
- **Post-compression evaluation**
- **In vitro drug release performance**

Table 6: Selection Criteria for Optimized Formulation:

Parameter	Ideal Requirement	Justification for Selection
Angle of repose	< 30° (good flow)	F5: 28.6°
Compressibility index	< 15% (good compressibility)	F5: 12.2%
Hardness	4–6 kg/cm² (suitable for matrix tablet)	F5: 5.2 kg/cm²
Friability	< 1% (acceptable limit)	F5: 0.38%
Weight variation	Within IP limits (±5%)	F5: 1.4% variation
Drug content	95–105%	F5: 98.4%
Initial drug release (2 hr)	15–25%	F5: 22.8%
Final drug release (12 hr)	90–95%	F5: 94.6%
Release kinetics	Higuchi model with $R^2 > 0.98$	F5: Higuchi model, $R^2 = 0.987$
Release mechanism	Preferably non-Fickian (anomalous diffusion)	F5: n = 0.68 (Korsmeyer-Peppas model)

Based on a comprehensive analysis of evaluation parameters:
Formulation F5 (containing **15% HPMC K100M** and **10% Ethyl Cellulose**) emerged as the **optimized batch**.

It exhibited:

- Good flow and compressibility,
- Acceptable tablet hardness and friability,
- Uniform drug content,
- Sustained drug release over 12 hours (within desired limits),

Hence, **Formulation F5 was selected as the optimized formulation**, fulfilling all criteria for a robust controlled-release matrix tablet of Salbutamol Sulphate.

4. Conclusion: In this study, controlled release matrix tablets of Salbutamol Sulphate were successfully formulated using hydrophilic polymer HPMC K100M and hydrophobic polymer Ethyl Cellulose through the direct compression method. Nine different formulations were developed and evaluated based on their micromeritic properties, tablet quality parameters, drug content, and in vitro drug release behavior. Among them, formulation F5 exhibited the best results, achieving consistent drug release up to 12 hours with acceptable physical and chemical properties. The drug release followed Higuchi kinetics with a non-Fickian diffusion mechanism, suggesting that both diffusion and erosion played a role in controlling the release of Salbutamol Sulphate. The study also demonstrated that a manual optimization approach, without the use of statistical software, can be an effective and practical method for small-scale formulation development. Further studies may explore in vivo-in vitro correlation (IVIVC) to confirm the therapeutic equivalence of the optimized batch. Additionally, replacing synthetic polymers with natural polymers could enhance the biocompatibility and safety profile. Scale-up studies, stability studies under ICH conditions, and evaluation in patient populations could pave the way for commercial development. Also, extending this approach to other β2-agonists or chronic respiratory drugs may widen its clinical application.

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