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Research Paper**FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER MATRIX TABLETS OF DOXOFYLLINE****Sourav Sharma*, Dilip Agrawal, Mohit Khandelwal**

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Oral administration remains the gold standard route for executing drug delivery across global pharmaceutical manufacturing due to its manufacturing efficiency, flexible dosing precision, extended chemical stability, and high patient compliance. To solve these drawbacks, Controlled Release Oral Drug Delivery Systems (CRDDS) have been engineered to maintain a steady therapeutic plasma concentration within a narrow window, minimizing dangerous peak-and-valley drug levels.

The optimized bilayer formulation provides a predictable biphasic delivery profile that reduces dosing frequency and minimizes extra-pulmonary side effects, demonstrating a highly viable alternative to current single-phase commercial therapies. The primary goal of this research was to design, formulate, and optimize an innovative bilayer sustained-release matrix tablet of Doxofylline. The dosage form features a biphasic release profile consisting of an immediate-release (IR) loading dose layer and a sustained-release (SR) maintenance layer to provide effective round-the-clock management for bronchial asthma and chronic obstructive pulmonary disease (COPD)

Key words: Bronchial asthma, Doxofylline, Bilayer tablets, superdisintegrants.

INTRODUCTION

Bilayer tableting represents a highly advanced facet of CRDDS, serving as an optimal platform for establishing biphasic release kinetics from a single monolithic unit.¹⁻² In a homogeneous bilayer delivery engine, the architecture splits into two distinct operational chambers:

The Immediate Release (IR) Layer: Releases a definitive loading dose within minutes of ingestion to rapidly elicit immediate bronchodilation during acute asthma attacks.

The Sustained Release (SR) Layer: Progressively diffuses the maintenance dose through an engineering polymeric matrix to sustain therapeutic drug concentrations over a 12-hour period.³⁻⁴

Bronchial asthma is a chronic inflammatory disorder characterized by profound airway hyper-responsiveness, mucosal edema, smooth muscle spasms, and excessive mucus plug formation across the tracheobronchial tree.⁵ Methylxanthine bronchodilators form a core foundation of asthma maintenance therapy. Traditional derivatives like Theophylline possess narrow therapeutic indices and produce severe cardiovascular and central nervous system toxicities through unintended interactions with adenosine.⁶⁻⁷

Doxofylline [7-(1,3-dioxolan-2-ylmethyl) theophylline] represents a next-generation methylxanthine derivative. By replacing the traditional structure with a dioxolane group at



the 7th position, Doxofylline retains strong phosphodiesterase IV (PDE-IV) inhibition while exhibiting significantly reduced affinity for adenosine receptors.⁸ This structural alteration delivers a superior pulmonary safety profile with fewer extra-pulmonary side effects. However, because Doxofylline possesses an elimination half-life of 6–7 hours and faces intensive systemic metabolism, it requires a carefully balanced delivery mechanism to prevent initial dose dumping while ensuring continuous action.⁹⁻¹⁰

The primary objective of this investigation was to design, execute, and evaluate a synchronized bilayer matrix tablet containing Doxofylline in both functional segments. This configuration aims to achieve a rapid therapeutic onset within 60 minutes, followed by an extended mathematical release over 12 hours, using an optimized blend of hydrophilic and hydrophobic rate-controlling polymers.

MATERIALS AND METHODS

Materials

Doxofylline was obtained as a gift sample from Dr. Reddy private Laboratories Ltd.

Preparation of standard curve

Estimation of the amount of Doxofylline present in the formulations during in vitro studies were carried out using UV-spectroscopic analytical techniques. For this technique scanning of the pure drug and standard curve were carried out.

For preparation of standard curves, both

phosphate buffer pH 6.8 (at 274 nm) and HCl buffer pH 1.2 (at 273 nm) were used.

Preparation of Tablets

Bilayer matrix tablets of Doxofylline contains two types of granules i.e. first layer will consist of the optimized immediate release tablet granules and second layer, the sustained release layer. Based on the different concentration of disintegrant and superdisintegrants, 16 different immediate release formulations were prepared. The dissolution profiles of all the immediate release formulations will be compared with dissolution profiles of standard marketed formulation and the optimised formulation will be used as an immediate release layer for the bilayer tablet with different sustained release layer. The sustained release layers was prepared by using different proportion of hydrophilic polymer and hydrophobic polymer. Wet granulation methods were adopted for the preparation of both immediate release and sustained release layer granules.

Preparation of Immediate Release (IR) Granules

Formulations were prepared by altering the concentrations of Starch, Ac-Di-Sol, and Polyplasdone XL-10. Doxofylline (361 mg per tablet) was systematically blended with Avicel 101, Lactose Monohydrate, and PVP K30. Distilled water was incorporated to form a cohesive damp mass, which was dried in a hot



air oven (40°C) raised to get a target moisture content of 2–5%. The granules were subsequently lubricated with 1% Magnesium Stearate and 2% Talc.

Preparation of Sustained Release (SR) Granules

The SR maintenance formulation segment (439 mg Doxofylline per tablet) was prepared using varying ratios of HPMC (K4M/K15M) and Eudragit (RSPO/RLPO) along with Lactose and Insoluble Starch. Wet mass binding was facilitated through an aqueous solution of PVP K30, processed through a #20 mesh sieve, dried, and lubricated identically to the IR step.

Evaluation parameters of the tablet Physical characterization⁹⁻¹⁰

- **Hardness**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^2 . Five tablets were randomly picked and hardness of the tablet was determined.

- **Weight variation test**

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. Twenty tablets were randomly selected and accurately weighed, in grams on an analytical balance

- **Disintegration Time**

The test is carried out on the 6 tablets using the

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apparatus specified in IP distilled water at $37^\circ\text{C} \pm 2^\circ\text{C}$ was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

- **In vitro dissolution studies**

For the in vitro release studies of Doxofylline bilayer tablets, a proper simulation of gastrointestinal (GIT) condition was maintained by altering the pH of dissolution medium at different time intervals succeeding two step dissolution conditions. To simulate the physiological conditions of GIT, first 2 hours of dissolution was conducted in 900 ml of HCl buffer (0.05 M HCl, pH 1.2) and the rest of the time in 900 ml of phosphate buffer (pH 6.8). At each hourly interval, the aliquots were withdrawn and analyzed for drug using the UV-Visible spectrophotometer (Spectro 2080, Analytical Technologies Ltd.) at 273 nm. After each sampling, an equal volume of fresh dissolution fluid was replaced to the dissolution medium.

RESULTS AND DISCUSSION

Post-compression parameters of Tablets

The results of in vitro disintegration of all the tablets were found to be within the prescribed limits and satisfying the criteria of fast dissolving tablets.

Formulation DBMF10 that contained 12.5% of HPMC K15M and 8% of eudragit RSPO in

sustained release layer with super disintegrant concentration of 6% (2% ACDi-Sol™ and 4% Polyplasdone-XL) in immediate release layer showed 44% of drug release within first hour as a loading dose and has shown prolonged

release effect upto 12 hours with almost complete release (99%) has emerged as best formulation. Increase in proportion of hydrophilic polymer caused initial burst release effect.

Table 1: Evaluation of Post-compression parameters of Tablets

F. code	Average hardness (kg/cm ²)	Average weight variation (%)	Average friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)
DBMF1	7.54±0.8	3.24±0.23	0.57±0.071	5.82±0.17	99.45±1.5
DBMF2	7.48±0.7	3.45±0.18	0.49±0.093	5.88±0.13	101.67±1.4
DBMF3	7.88±0.8	3.65±0.27	0.61±0.054	5.85±0.16	102.38±1.7
DBMF4	7.75±0.5	3.41±0.09	0.58±0.085	5.76±0.18	98.79±1.5
DBMF5	7.97±0.6	3.56±0.22	0.63±0.056	5.89±0.12	102.42±1.2
DBMF6	7.54±0.7	3.73±0.24	0.64±0.062	5.90±0.14	98.39±1.4
DBMF7	7.89±0.9	3.65±0.27	0.51±0.073	5.89±0.18	99.75±1.6
DBMF8	7.95±0.8	3.84±0.21	0.47±0.084	5.82±0.16	100.95±1.2
DBMF9	8.02±0.6	3.32±0.22	0.63±0.062	5.84±0.12	101.48±1.1
DBMF10	8.01±0.8	3.67±0.23	0.48±0.041	5.82±0.11	101.54±1.5
DBMF11	8.00±0.7	3.84±0.36	0.41±0.052	5.84±0.15	98.84±1.4
DBMF12	8.91±0.9	3.58±0.22	0.46±0.063	5.83±0.14	99.36±1.6
DBMF13	8.98±0.6	3.36±0.33	0.42±0.082	5.85±0.15	99.68±1.2
DBMF14	8.97±0.6	3.52±0.34	0.44±0.083	5.84±0.16	100.19±1.6
DBMF15	7.78±0.9	3.52±0.25	0.54±0.072	5.79±0.14	101.43±1.8
DBMF16	7.96±0.7	3.49±0.36	0.62±0.052	5.81±0.15	98.54±1.5

Table 2: *In vitro* dissolution studies of Tablets

Time (h)	DBM F1	DBM F2	DBM F3	DBM F4	DBM F5	DBM F6	DBM F7	DBM F8	MF
1	65.43 ±2.32	63.55 ±2.44	61.32 ±2.13	59.63 ±2.41	57.21 ±1.44	51.40 ±1.78	60.45 ±1.29	54.21 ±1.52	16.46 ±1.69
2	72.38 ±2.89	68.29 ±2.62	68.41 ±2.27	65.41 ±2.53	63.48 ±1.38	58.62 ±1.49	67.34± 1.37	60.53 ±1.67	24.58 ±1.93
3	79.62 ±2.96	75.45 ±2.71	74.65 ±2.39	70.71 ±2.68	69.75 ±1.51	63.72 ±1.66	73.51± 1.46	67.59 ±2.19	31.72 ±2.13
4	85.71 ±3.05	82.47 ±2.84	81.77 ±2.52	76.83 ±2.82	75.60 ±1.62	70.62 ±1.74	79.83± 1.68	73.68 ±2.32	39.37 ±2.47
5	91.55 ±3.13	89.32 ±2.93	87.53 ±2.63	82.26 ±2.90	81.34 ±1.55	76.47 ±1.19	84.44± 1.81	79.45 ±2.63	47.53 ±2.65
6	97.84 ±3.28	95.46 ±3.06	92.90 ±2.78	88.18 ±3.09	86.42 ±1.26	81.58 ±1.86	89.51± 2.64	84.67 ±2.48	56.74 ±2.87
7	99.46 ±3.35	99.42 ±3.15	98.25 ±2.92	94.39 ±3.24	90.97 ±1.46	86.27 ±2.42	93.46± 2.68	88.31 ±2.85	64.38 ±2.95
8	99.46 ±3.42	99.42 ±3.24	99.32 ±3.16	99.62 ±3.32	95.95 ±1.88	91.45 ±2.72	98.22± 2.82	92.29 ±3.76	72.27 ±3.13
9	-	-	99.32 ±3.44	99.62 ±3.21	99.45 ±2.04	97.23 ±2.46	99.63± 3.14	96.28 ±3.92	81.45 ±3.43
10	-	-	-	-	99.45 ±2.84	99.22 ±3.37	99.63± 2.29	99.27 ±3.91	88.39 ±3.65
11	-	-	-	-	-	99.22 ±3.37	-	-	94.58 ±3.72
12	-	-	-	-	-	-	-	-	99.35 ±3.77



Time (h)	DBM F9	DBM F10	DBM F11	DBM F12	DBM F13	DBM F14	DBM F15	DBM F16	MF
1	48.65 ±1.79	44.91 ±1.58	39.49 ±1.06	42.43 ±1.25	50.85 ±1.45	52.14 ±1.64	47.57 ±1.37	43.95 ±1.43	16.46 ±1.69
2	56.46 ±1.92	49.57 ±1.81	44.57 ±1.57	47.61 ±1.68	56.73 ±1.95	59.41 ±1.72	52.38 ±1.62	48.47 ±1.62	24.58 ±1.93
3	60.71 ±1.64	54.81 ±1.84	49.59 ±1.22	52.59 ±1.77	61.39 ±1.82	66.76 ±1.88	58.62 ±1.74	54.28 ±1.78	31.72 ±2.13
4	64.82 ±1.81	59.52 ±1.73	56.72 ±1.62	58.66 ±1.80	68.63 ±1.95	73.92 ±1.97	63.54 ±1.92	59.63 ±2.16	39.37 ±2.47
5	69.77 ±1.18	64.75 ±1.67	61.91 ±1.75	63.82 ±1.84	75.97 ±1.64	79.24 ±2.16	68.39 ±2.10	63.56 ±2.23	47.53 ±2.65
6	74.42 ±1.36	70.42 ±1.57	67.78 ±1.26	69.59 ±1.64	81.50 ±1.24	85.46 ±2.18	73.28 ±2.26	68.61 ±2.34	56.74 ±2.87
7	80.97 ±1.85	76.82 ±1.66	72.40 ±1.71	73.26 ±1.47	87.97 ±2.20	89.97 ±2.42	78.83 ±2.36	74.67 ±2.45	64.38 ±2.95
8	85.75 ±1.64	81.60 ±1.45	77.81 ±1.29	78.18 ±1.38	92.95 ±1.32	94.55 ±2.60	83.61 ±2.72	80.82 ±2.53	72.27 ±3.13
9	89.40 ±1.72	86.72 ±2.71	82.52 ±1.48	84.45 ±1.64	96.38 ±1.55	98.23 ±2.85	87.55 ±2.82	85.54 ±2.68	81.45 ±3.43
10	94.74 ±2.81	91.38 ±2.84	86.49 ±2.17	89.72 ±2.72	99.74 ±3.49	99.89 ±2.34	92.42 ±2.91	90.45 ±2.82	88.39 ±3.65
11	97.41 ±3.15	96.16 ±3.20	91.57 ±3.63	93.63 ±2.96	-	99.89 ±3.47	96.55 ±3.04	95.35 ±3.17	94.58 ±3.72
12	99.42 ±3.19	99.42 ±3.56	96.95 ±3.44	98.27 ±3.59	-	-	99.36 ±3.12	99.67 ±3.34	99.35 ±3.77



CONCLUSION

From the study, it was evident that selected superdisintegrants for study played vital role in dissolution behavior. The results of the current study clearly indicate, a promising potential of the Doxofylline bilayer matrix tablet system as an alternative to the available marketed conventional as well as sustained release dosage form,

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Conflict of Interest

The authors declare that they have no conflict of interest