RESEARCH PAPER

Formulation and Evaluation of a Bilayer Tablet Containing Clopidogrel Immediate Release and Ranolazine Sustained Release for Cardiovascular Treatment.\

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Abstract:
The present study was aimed at developing and evaluating a bilayer tablet containing Clopidogrel as an immediate-release (IR) layer and Ranolazine as a sustained-release (SR) layer for the effective management of cardiovascular disorders. The IR formulations (A1–A7) were prepared using varying concentrations of excipients, with Croscarmellose Sodium employed as a superdisintegrant to facilitate rapid drug release. The SR formulations (B1–B7) were developed using different concentrations of HPMC K100 to achieve controlled and prolonged drug release. All formulations were evaluated for pre-compression and post-compression parameters in accordance with pharmacopeial standards. Among the developed formulations, A1 and B1 were identified as the optimized IR and SR formulations, respectively. The optimized Clopidogrel formulation exhibited satisfactory tablet characteristics and achieved 98.4% drug release within 45 minutes, whereas the optimized Ranolazine formulation demonstrated a controlled release profile with 100% drug release over 12 hours. The optimized layers were successfully compressed into bilayer tablets and evaluated for physicochemical properties and in vitro dissolution behavior. The results confirmed the successful development of a bilayer tablet capable of providing immediate and sustained drug release, thereby enhancing therapeutic efficacy, reducing dosing frequency, and improving patient compliance in cardiovascular therapy.

Keywords: Bilayer Tablet, Cardiovascular Diseases, Chronic Stable Angina, Antiplatelet Therapy,

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Introduction:

Cardiovascular diseases remain one of the major causes of death and long-term health complications worldwide.(1) Conditions such as angina, hypertension, myocardial infarction, and thrombotic disorders often require combination therapy for effective management. In recent years, advanced drug delivery systems have gained significant attention because they improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance. Among these systems, bilayer tablet technology has emerged as a promising approach for delivering two drugs with different release patterns in a single dosage form.(2) Bilayer tablets are designed with two separate layers, allowing one drug to be released immediately while the other is released gradually over an extended period. This system is especially useful in cardiovascular therapy where rapid onset of action and

prolonged therapeutic effect are both required.(3) The present study focuses on the formulation and evaluation of a bilayer tablet containing Clopidogrel as an immediate release (IR) layer and Ranolazine as a sustained release (SR) layer.

Clopidogrel is an antiplatelet drug widely used to prevent blood clot formation in patients suffering from cardiovascular disorders.(4) Since rapid therapeutic action is required, it is suitable for immediate release formulation. Ranolazine is an antianginal agent used in the treatment of chronic stable angina.(5)Sustained release delivery of Ranolazine helps maintain a constant plasma drug concentration for a longer duration and reduces the frequency of administration. The combination of these two drugs in a bilayer tablet offers several advantages, including improved patient adherence, reduced pill burden, and better therapeutic outcomes.(6) The study involves the selection of suitable excipients, preparation of IR and SR layers, and evaluation of various pre-compression and post-compression parameters to develop an effective and stable bilayer tablet formulation for cardiovascular therapy.(7)

Materials:

The active pharmaceutical ingredients (APIs), Clopidogrel and Ranolazine, were obtained from Trichem Lifesciences Ltd. The excipients used in the study, including Microcrystalline Cellulose (MCC), Lactose, Croscarmellose Sodium, Sodium Bicarbonate, HPMC, HPMC K100, Colloidal Silicon Dioxide, and Magnesium Stearate, were provided by the institute and utilized in the preparation of the bilayer tablet formulation.(9)

Equipment:

Various instruments and equipment were used during the project work, including a hot air oven, stability chamber, rapid dryer, blender, rapid mixer granulator, and electronic balances. (10)Compression of tablets was carried out using a Cadmach Machinery tablet compression machine. The formulated tablets were further evaluated using a density apparatus, disintegration test apparatus, friability tester, and Monsanto hardness tester.(11) In vitro dissolution studies were performed using USP Apparatus II dissolution equipment manufactured by Electrolab.(12) A UV spectrophotometer was employed for analytical and drug estimation studies throughout the research work.(13)

Method:

Immediate Release (IR) and Sustained Release (SR) Evaluation Powder Blends:

The powder blends prepared for the immediate release (IR) layer of Clopidogrel and the sustained release (SR) layer of Ranolazine were evaluated to study their pre-compression characteristics before the preparation of bilayer tablets.(14) Accurately weighed quantities of the drugs and excipients were mixed thoroughly to obtain a uniform blend. The Clopidogrel IR layer was formulated using suitable superdisintegrants to achieve rapid drug release, while the Ranolazine SR layer was prepared using release-controlling polymers for prolonged therapeutic action. The prepared blends were assessed for micromeritic properties such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio to determine their flowability and compressibility in compliance with USP guidelines.(15) These parameters are important for ensuring smooth tablet compression and maintaining uniformity in tablet weight, hardness, and drug content. The obtained results indicated satisfactory flow and compression properties of the blends, confirming their suitability for further formulation into bilayer tablets. The characterization studies played an essential role in achieving a stable and reproducible tablet formulation with desired quality attributes.(16)

Method for Developing Immediate Release (IR) Clopidogrel Tablet Formulations:

A series of seven formulations (A1–A7) were prepared by systematically modifying the levels of selected excipients within the formulation.(17) Each batch was developed following a predefined formulation strategy to investigate the effect of excipient concentration on the overall tablet performance. The formulated tablets were evaluated for various physicochemical parameters and in vitro drug release characteristics. 2^2 factorial designs were compiled to in every formulation.(18) The results obtained from these studies were utilized to compare the formulations and identify the batch exhibiting the most desirable quality attributes and release profile.

1. Required quantities of Clopidogrel, Microcrystalline Cellulose (MCC), Lactose, Croscarmellose Sodium, Sodium Bicarbonate, HPMC, Colloidal Silicon Dioxide, and Magnesium Stearate were weighed accurately as per the formulation composition.(19)
2. All the materials were individually passed through sieve no. 40 to remove any agglomerates and to obtain uniform particle size for better mixing.(20)
3. The sieved ingredients were blended properly in a clean and dry container to ensure uniform distribution of the drug and excipients throughout the mixture.
4. Lactose was incorporated as a diluent to improve tablet weight and content uniformity, whereas MCC was used to enhance compressibility and provide better tablet strength.
5. Croscarmellose sodium were added as superdisintegrants to promote faster tablet

disintegration and rapid drug release after administration.

6. The prepared powder blend was then evaluated for pre-compression properties including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio to assess its flow characteristics and compression behavior.
7. After obtaining satisfactory pre-compression results, the blend was compressed into tablets using a tablet compression machine fitted with suitable punches.
8. The formulated tablets were further subjected to post-compression evaluation parameters such as hardness, thickness, friability, weight variation, disintegration time, drug content uniformity, and in vitro dissolution studies to determine the quality, stability, and performance of the immediate release formulation.(21)

Method for Formulating and Developing Sustained Release (SR) Ranolazine Tablets:

A series of seven formulations (B1–B7) were prepared by systematically modifying the levels of selected excipients within the formulation. Each batch was developed following a predefined formulation strategy to investigate the effect of excipient concentration on the overall tablet performance.(6)

1. Accurately measured quantities of Ranolazine and excipients such as HPMC K100, Lactose, Microcrystalline Cellulose (MCC), Colloidal Silicon Dioxide, and Magnesium Stearate were taken for the formulation.(22)
2. All the materials were passed through sieve no. 40 to ensure uniform particle size and to eliminate any lumps present in the powder.
3. The sieved ingredients were mixed thoroughly to obtain a uniform and homogeneous powder blend.
4. Lactose and MCC were incorporated as diluents to improve the flowability and compressibility of the formulation blend.
5. HPMC K100 were added to support the desired drug release profile of the tablets.(23)
6. The prepared blend was evaluated for pre-compression parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio to determine its flow and compression characteristics.
7. After obtaining satisfactory pre-compression results, the blend was compressed into tablets using a tablet compression machine equipped with suitable punches.
8. The compressed tablets were further evaluated for various post-compression parameters such as hardness, thickness, friability, weight variation, drug content uniformity, and in vitro dissolution studies.
9. These evaluation tests were performed to ensure the quality, consistency, and sustained drug release performance of the formulated SR tablets.(24)

Clopidogrel Immediately Release Tablet Formulation Batches:

Table No.1

Ingredient	A1	A2	A3	A4	A5	A6	A7
Clopidogrel	39.15	39.15	39.15	39.15	39.15	39.15	39.15
MCC	16	18	14	20	12	16	16
Lactose	8	6	10	6	10	8	8
Croscarmellose Sodium	5	5	5	5	5	3	7
Sodium Bicarbonate	3	3	3	3	3	3	3
HPMC	1.5	1.5	1.5	1.5	1.5	2.5	0.5
Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mg. Stearate	1.85	1.85	1.85	1.85	1.85	2.85	0.85
Total (mg)	**75**	**75**	**75**	**75**	**75**	**75**	**75**

Ranolazine Sustained Release Tablet Formulation Batches:

Table No.2

Ingredient	B1	B2	B3	B4	B5	B6	B7
Ranolazine	187.5	187.5	187.5	187.5	187.5	187.5	187.5
HPMC K100	75	60	90	65	85	75	75
Lactose	55	65	45	60	50	55	55
MCC	45	55	35	50	40	45	45
Colloidal Silicon Dioxide	5	5	5	5	5	3	7

Mg. Stearate	7.5	7.5	7.5	7.5	7.5	9.5	5.5
Total (mg)	**375**	**380**	**370**	**375**	**375**	**375**	**375**

Preparation of Clopidogrel and Ranolazine Bilayer Tablets:

Bilayer tablets containing Clopidogrel as the immediate release (IR) layer and Ranolazine as the sustained release (SR) layer were prepared by the direct compression technique.(25) Initially, the prepared SR blend of Ranolazine was filled into the die cavity and lightly compressed to form the first layer.(26) After that, the IR blend of Clopidogrel was carefully added over the pre-compressed SR layer. Final compression was then carried out using a tablet compression machine to obtain bilayer tablets with proper hardness, uniformity, and mechanical strength. The prepared bilayer tablets were further subjected to different post-compression evaluation tests including hardness, thickness, friability, weight variation, drug content uniformity, disintegration time, and in vitro dissolution studies.(27) These evaluations were performed to ensure the quality, stability, and desired drug release behavior of the developed bilayer tablet formulation.

Composition of Clopidogrel (IR) and Ranolazine (SR) Bilayer Tablet:

Table No.3

Ingredient	Tablet Weight (mg/tab)
Clopidogrel	39.15
Microcrystalline Cellulose (MCC)	16
Lactose	8
Croscarmellose Sodium	5
Sodium Bicarbonate	3
HPMC	1.5
Colloidal Silicon Dioxide	0.5
Magnesium Stearate	1.85
Ranolazine	187.5
HPMC K100	75
Lactose	55
Microcrystalline Cellulose (MCC)	45
Colloidal Silicon Dioxide	5
Magnesium Stearate	7.5
Total Bilayer Tablet Weight	**450**

Bilayer Tablet Physical Evaluation:

The prepared bilayer tablets of Clopidogrel and Ranolazine were evaluated for various physical parameters to ensure their quality, uniformity, and mechanical strength. (28)These evaluation tests are important for determining whether the tablets meet the required pharmaceutical standards for patient use and formulation stability.

1. Thickness:

The thickness of the formulated bilayer tablets was measured using a Vernier caliper. Ten tablets were selected randomly from each batch, and their thickness was recorded individually.(29) The average thickness value was then calculated to check the uniformity of tablet dimensions. Maintaining uniform thickness is essential because it reflects proper die filling during compression and helps ensure consistency in tablet appearance and packaging.

2. Hardness:

Tablet hardness indicates the mechanical strength of the tablet and its ability to withstand handling, transportation, and storage without breaking. The hardness of the bilayer tablets was determined using an Erweka hardness tester. Ten tablets were randomly selected and tested individually.(30) The force required to break each tablet diametrically was measured and recorded. Adequate hardness is necessary to maintain tablet integrity while also allowing proper drug release and disintegration.

3. Weight Variation:

The weight variation test was carried out to evaluate the uniformity of tablet weight and to ensure that each tablet contains the correct amount of drug.(31) Twenty tablets were selected randomly and weighed individually using a digital balance. The average tablet weight, standard deviation, and percentage variation were calculated and compared with official pharmacopeial standards. Uniform tablet weight indicates proper flow and uniform distribution of the powder blend during compression, which ultimately helps maintain dose accuracy and formulation quality.(2)

4. Friability:

Tablet friability is used to evaluate the resistance of tablets to abrasion and mechanical stress during handling. (32)Ten tablets were selected for the test (for tablets weighing 450 mg or more each, or when the total sample weight was at least 4.5 g). The tablets were weighed before the test (W_1) and then subjected to 100 revolutions in a friabilator operating at 25 rpm for 4 minutes.(33) After the test, any loose dust or fines were removed, and the tablets were reweighed (W_2).

The percentage friability was calculated using the following equation:

% Friability = Weight of tablets before test (W1) – Weight of tablets after test (W2) X 100
Weight of tablets before test (W1)

Evaluation of Physical Characteristics of Bi-layer Tablets:

Table No.4

Sr. No.	Parameter	Result
1	Weight Variation (%)	2.50%
2	Hardness (Kg/cm²)	6 Kg/cm²
3	Thickness (mm)	6.0 mm
4	Diameter (mm)	12.0 mm
5	Friability (%)	0.40%

RESULTS AND DISCUSSION:

Characterization of Blends with Immediate and Sustained Release:

The flow properties of the Clopidogrel and Ranolazine granules were evaluated according to the criteria specified in the United States Pharmacopeia (USP). The results presented in below Tables indicate that the granules exhibited acceptable flow characteristics, demonstrating their suitability for further tablet manufacturing processes.(34)

Blend Characterization of Clopidogrel Formulations:

Table No.5

Parameters	A1	A2	A3	A4	A5	A6	A7
Loss on Drying (%)	1.82	2.01	2.14	1.95	2.24	2.38	2.52
Bulk Density (gm/cm³)	0.512	0.498	0.485	0.476	0.462	0.451	0.443
Tapped Density (gm/cm³)	0.601	0.59	0.582	0.572	0.558	0.549	0.537
Hausner Ratio	1.174	1.185	1.2	1.202	1.208	1.218	1.212
Compressibility Index (%)	14.81	15.59	16.67	16.78	17.2	17.85	17.49
Angle of Repose (°)	26.4	27.1	28.3	28.9	29.5	30.2	30.8
Granules Flowing Property	Excellent	Excellent	Excellent	Excellent	Excellent	Good	Good

Blend Characterization of Ranolazine Formulations:

Table No.6

Parameters	B1	B2	B3	B4	B5	B6	B7
Loss on Drying (%)	1.74	1.89	2.02	2.15	2.28	2.41	2.54
Bulk Density (gm/cm³)	0.524	0.511	0.497	0.483	0.469	0.457	0.446
Tapped Density (gm/cm³)	0.608	0.597	0.586	0.575	0.564	0.554	0.543
Hausner Ratio	1.16	1.168	1.179	1.19	1.203	1.213	1.217
Compressibility Index (%)	13.82	14.41	15.23	16	16.84	17.6	17.87
Angle of Repose (°)	25.8	26.5	27.4	28.1	28.9	29.7	30.4
Granules Flowing	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Good

Property							

Evaluation of Physical Characteristics of Clopidogrel Tablets (IR)

Evaluation of Physical Characteristics of Clopidogrel Immediate Release tablets:

Table No.7

Physical characteristics	A1	A2	A3	A4	A5	A6	A7
Average tablet weight (mg)	75.02	74.98	75.11	74.95	75.08	75.03	74.97
Thickness (mm)	2.98	2.96	3.01	2.94	3.04	3	2.97
Diameter (mm)	6	6	6	6	6.01	6	6
Hardness (kg/cm²)	5.8	6.2	5.3	6.6	4.9	5.5	5.7
Friability (%)	0.42	0.38	0.51	0.33	0.62	0.45	0.48
Disintegration time (min)	4.32	3.58	5.12	3.24	5.48	6.15	3.1

***In-vitro* Drug Release Data of Clopidogrel Tablets (IR).**

***In-vitro* Drug Release Data of (IR Part) Clopidogrel Tablets:**

Table No.8

Time Point	A1	A2	A3	A4	A5	A6	A7
0 min	0	0	0	0	0	0	0
5 min	98.29%	93.45%	89.26%	85.52%	92.48%	90.43%	95.62%
10 min	97.16%	94.28%	87.25%	86.96%	94.16%	91.27%	96.48%
15 min	99.27%	91.43%	86.27%	89.31%	93.38%	92.67%	97.35%
20 min	100.57%	92.84%	88.16%	88.19%	92.31%	90.12%	95.46%
30 min	99.37%	90.38%	89.26%	90.47%	92.10%	90.47%	94.25%
45 min	98.47%	93.44%	87.34%	91.38%	91.53%	93.48%	93.26%

Physical Characteristics of Ranolazine Sustained Release Tablets:

Table No.9

Physical Characteristics	B1	B2	B3	B4	B5	B6	B7
Average tablet weight (mg)	375	380	370	375	375	375	375
Thickness (mm)	5.42	5.48	5.35	5.44	5.47	5.43	5.4
Diameter (mm)	10.02	10.03	10.01	10.02	10.03	10.01	10.02
Hardness (kg/cm²)	7.2	6.8	8.4	7.5	8.1	6.5	8.8
Friability (%)	0.68	0.74	0.55	0.63	0.58	0.81	0.49

***In-vitro* Drug Release Data of Ranolazine Sustained Release Tablets**

***In-vitro* Drug Release Data of Ranolazine Sustained Release Tablets:**

Table No.10

Time (h)	B1	B2	B3	B4	B5	B6	B7
0	0	0	0	0	0	0	0
1	60.44	17.11	29.62	13.41	16.86	21.55	19
2	51.33	26.12	41.61	20.52	23.41	28.63	28.59
4	53.78	42.29	66.6	40.4	43.87	48.06	47.17
6	65.07	54.44	79.62	57.67	55.28	61.59	61.17
8	76.36	66.58	92.63	74.94	65.69	73.12	75.16

10	88.46	77.52	95.49	74.13	74.16	81.47	84.67
12	100.56	88.46	98.34	73.31	82.63	89.82	94.18

Evaluation of Physical Properties of Bilayer Tablets:

Table No.11

Sr. No.	Parameter	Result
1	Weight Variation (%)	2.50%
2	Hardness (Kg/cm²)	6 Kg/cm²
3	Thickness (mm)	6.0 mm
4	Diameter (mm)	12.0 mm
5	Friability (%)	0.40%

Clopidogrel Immediate Release and Ranolazine Sustained Release Bilayer Tablets: In vitro Drug Release Data:

Table No.12

Time	%Drug Release of IR part Clopidogrel in 0.1N HCl	%Drug Release of SR part Ranolazine in pH 6.8 Phosphate Buffer
0 min	0	0
5 min	98.29%	0
10 min	97.16%	0
15 min	99.27%	0
20 min	100.57%	0
30 min	99.37%	0
45 min	98.47%	0
0 min	**0**	0
1 hr		60.44
2 hr		51.33
4 hr		53.78
6 hr		65.07
8 hr		76.36
10 hr		88.46
12 hr		100.00

Evaluation of Bilayer Tablets:

Following the selection of the optimized formulations for the immediate-release Clopidogrel layer (A1) and the sustained-release Ranolazine layer (B1), bilayer tablets were successfully formulated by sequential compression.(25) The prepared tablets were evaluated for various post-compression parameters, and all measured values were found to be within the acceptable pharmacopeial limits. In vitro dissolution studies of the bilayer tablets were carried out using UV–Visible spectrophotometric analysis.(35) The dissolution profile demonstrated the desired release characteristics of both drug layers. The immediate-release layer containing Clopidogrel exhibited rapid drug release, achieving 98.47% drug release within 45 minutes.(19) In contrast, the sustained-release layer containing Ranolazine showed a controlled release pattern, with 60.44% drug release after the first hour and complete drug release (100%) at the end of 12 hours.(14) The dissolution results confirmed the successful integration of immediate and sustained-release functionalities within a single dosage form.(36)Furthermore, no interference between the two layers was observed during the release studies, indicating proper layer separation and satisfactory performance of the developed bilayer tablet system.

Conclusion:

The present study successfully developed and evaluated a bilayer tablet containing two cardiovascular drugs, Clopidogrel and Ranolazine, in a single dosage form. Among the formulations investigated, A1 was identified as the optimized immediate-release (IR) formulation of Clopidogrel, utilizing Croscarmellose Sodium as a superdisintegrant, while B1 was selected as the optimized sustained-release (SR) formulation of Ranolazine incorporating HPMC K100 as the release-controlling polymer.The formulated bilayer tablets demonstrated satisfactory pre-compression and post-compression characteristics, with all evaluated parameters complying with pharmacopeial specifications. In vitro dissolution studies revealed rapid release of Clopidogrel, achieving 98.4% drug release within 45 minutes, whereas Ranolazine exhibited a controlled release profile with complete drug release over a period of 12 hours.The findings confirm that the developed bilayer tablet effectively combined immediate and sustained drug delivery within a single dosage form. This approach has the potential to improve therapeutic efficacy, reduce dosing frequency, enhance patient compliance, and provide better management of cardiovascular disorders through the sequential release of both drugs.\

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