RESEARCH ARTICLE

Formulation and Evaluation of Bilayer Tablets of Ramipril as Immediate Layer and Propranolol Hydrochloride as Sustained Layer

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Abstract

Aim: The purpose of this research work was to develop a bilayer tablet of antihypertensive drugs having sustained release (SR) layer of propranolol hydrochloride and immediate release (IR) layer of ramipril. **Objectives:** In the present investigation, an attempt was made to reduce the frequency, units of dose administration, and to improve the patient compliance**. Materials and Methods:** The tablets were prepared using ethyl cellulose and hydroxypropyl methylcellulose K-15M for sustained layer of propranolol hydrochloride and superdisintegrants crospovidone and sodium starch glycolate for IR layer of ramipril. Preformulation studies of propranolol hydrochloride and ramipril like compatibility studies with polymers using Fourier-transform IR were carried out. The drugs and excipients were found to be compatible with each other. Compressed tablets were evaluated for hardness, thickness, weight variation, friability, drug content, *in vitro* drug release studies, and stability studies **Results and Discussion:** Nine batches of bilayer tablets of propranolol hydrochloride and ramipril were developed using wet granulation and direct compression techniques, respectively. Among the nine formulations, F9 batch showed best drug release over 12 h and subjected to stability studies for 2 months. **Conclusion:** The optimized F9 formulation for IR showed a release of 99.27% and propranolol hydrochloride has an *in vitro* release of 99.39%. Therefore, bilayer ramipril IR and SR tablets of propranolol hydrochloride can be used to improve the management of hypertension.

Key words: Bilayer tablet, crospovidone, ethyl cellulose, hydroxypropyl methyl cellulose K-15M, propranolol hydrochloride, ramipril, sodium starch glycolate

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery.[1] Recently, combined therapy with drugs of same therapeutic effects or different therapeutic effects shows an effective way in the treatment of diseases. To optimize their effects, different drugs should be used at their optimal dose and different periods in the treatment. One of the main challenges of combined therapy is to control the release behavior of each drug independently. On the basis of these considerations, we have proposed a new oral delivery device, in the form of antihypertensive bilayer tablets, that is IR layer of ramipril as the first layer and the second layer is SR layer of propranolol hydrochloride.[2] Ramipril is an ACE inhibitor and propranolol hydrochloride is a beta-blocker they are used to the treatment of hypertension. Hypertension is the most common cardiovascular disease; its prevalence increases with increasing age. A combination of ACE inhibitors and beta-blockers helps for the improvement in cardiac function after myocardial infarction. This combination does not have any pharmacokinetic interactions. Bilayer tablets formulated as IR layer of ramipril to obtain a prompt release of drug with the aim of reaching a high serum concentration in a short period of time. The second layer is SR layer of propranolol hydrochloride is a prolonged release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period time, to avoid repeated administrations.[3,4] Bilayer tablets are formulated for decreasing the dosing frequency, separate two

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incompatible substances, and gradual release of two drugs in a single dosage form.[5,6]

MATERIALS AND METHODS

Ramipril and propranolol hydrochloride gifted from Hetero. Ethyl cellulose, hydroxypropyl methylcellulose (HPMC) K-15M, crospovidone, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, talc, hydrochloric acid, sodium hydroxide, and methanol purchased from Finar Chemicals. Lactose monohydrate and lactose spray dried gifted by Merck.

Experimental work

Preformulation studies

FTIR absorption spectra of pure drug and all polymers used like and the combination of drugs and polymers were shown no significant interaction between drug and polymers. The graphs obtained were shown in Figure 1-3.

Distinguishable difference was observed in the release of Ramipril and Propranolol hydrochloride layers in all formulations and the comparative graphs were shown in Figure 4-6.

Preparation of bilayer tablets

Bilayer tablets prepared by two steps, IR layer of ramipril was prepared by direct compression method using crospovidone and sodium starch glycolate as superdisintegrants in various concentrations and the SR layer of propranolol hydrochloride was prepared by wet granulation method using ethyl cellulose and HPMC K-15M in different concentrations as the drug release-retarding polymers.

Manufacturing process of the immediate release (IR) layer of ramipril

The procedure for the preparation was direct compression. All ingredients were mixed, except magnesium stearate, and talc. Finally, dye was added together with magnesium stearate and talc, later, the powder mixture was punched with 12 mm size punch.

Manufacturing process of the sustained release (SR) granules of propranolol hydrochloride

Wet granulation method was followed, all the ingredients were mixed, except magnesium stearate and talc with water and a wet mass was formed. The formed mass was passed through mesh 10# and the formed granules were dried and then passed through mesh 24# and punched with 12 mm size punch [Table 1].

Evaluations

Characterization of granules

Bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose.[7]

Evaluation of bilayer tablets

Thickness, hardness, friability, disintegration time, weight variation test, drug content, *in vitro* release study, and stability study as per ICH guidelines [Table 2].[8,9]

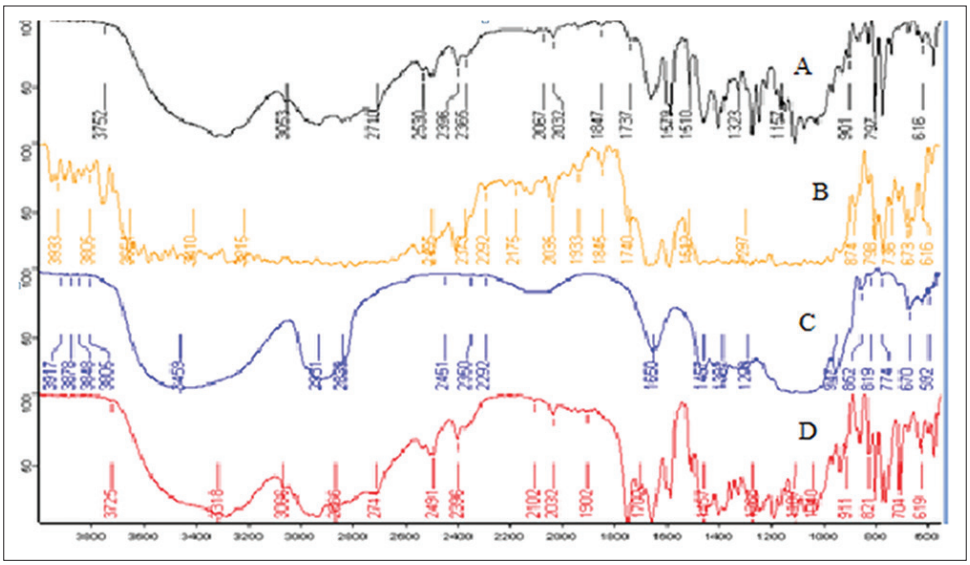

Figure 1: Fourier-transform infrared overays of drugs and excipients. (A) Propranolol hydrochloride, (B) propranolol hydrochloride + ethyl cellulose, (C) propranolol hydrochloride + hydroxypropyl methyl cellulose K-15M, (D) propranolol hydrochloride + polyvinylpyrrolidone K-30

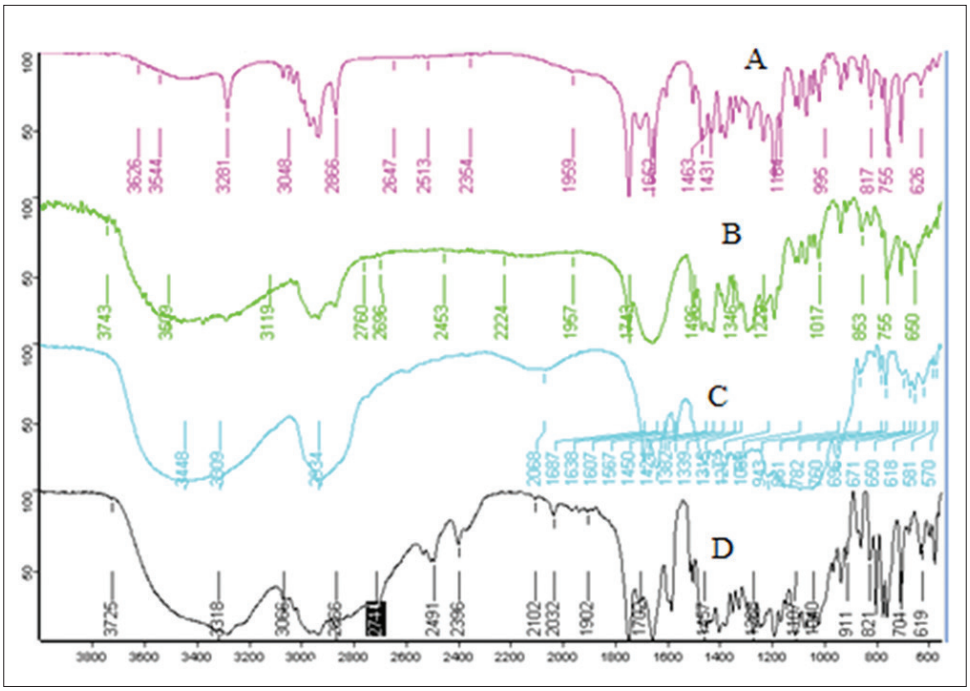

Figure 2: Fourier-transform infrared overays of drugs and excipients. (A) Ramipril, (B) ramipril + crospovidone, (C) ramipril + sodium starch glycolate, (D) ramipril + polyvinylpyrrolidone K-30

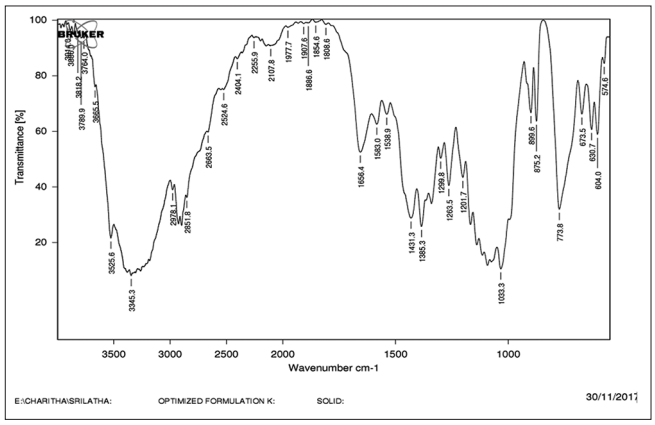

Figure 3: Fourier-transform infrared of optimized formulation

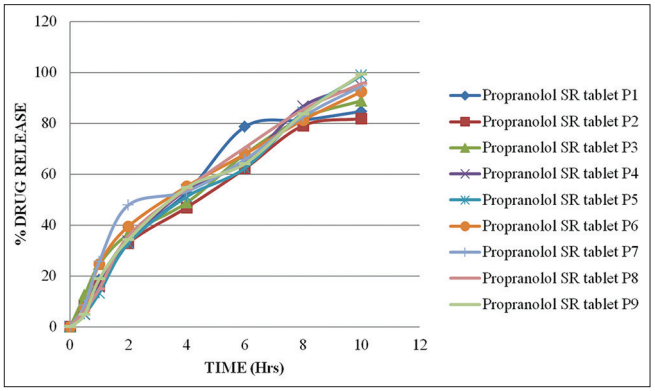

Figure 5: % Drug release propranolol hydrochloride sustained release tablets

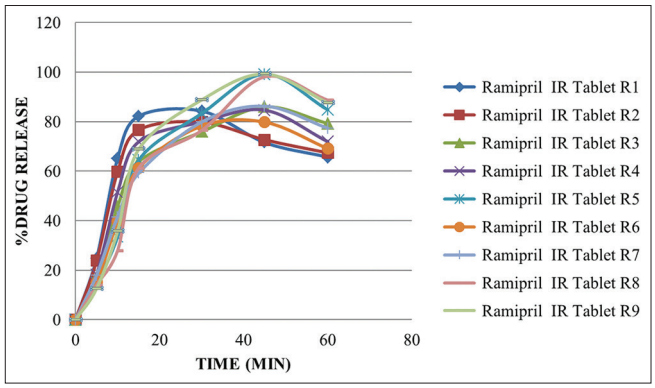

Figure 4: % Drug release of ramipril immediate release tablets

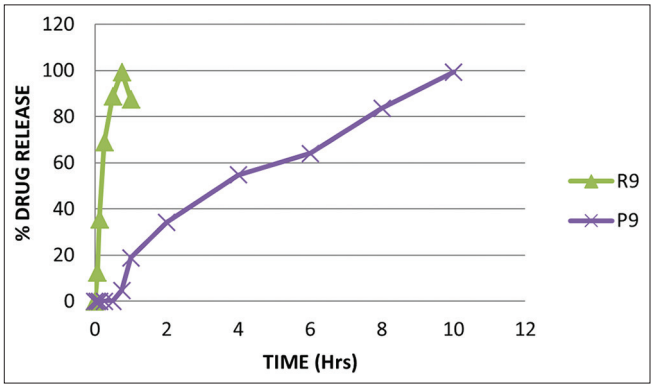

Figure 6: % Drug release of optimized formulation

Table 1: Formulation trials of bilayer tablets

Ingredients (mg/Tab)	Bilayer tablets formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
IR layer formulation									
Ramipril	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Crospovidone	2.5	5	7.5	10	12	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	2.5	5	7.5	10
PVPK-30	3	3	3	3	3	3	3	3	3
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Lactose monohydrate	91	88.5	86	83.5	81	91	88.5	86	83.5
Color	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total IR layer weight	100	100	100	100	100	100	100	100	100
SR layer formulation									
Propranolol	80	80	80	80	80	80	80	80	80
Ethyl cellulose	40	80	120	160	200	-	-	-	-
HPMC K-15M	-	-	-	-	-	20	40	60	80
PVP K-30	10	10	10	10	10	10	10	10	10
Mg stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Lactose spray dride	265	225	185	145	105	285	265	245	225
Total SR layer weight	400	400	400	400	400	400	400	400	400
Total bilayer tablet weight	500	500	500	500	500	500	500	500	500

Table 2: Precompression parameters for ramipril blend and propranolol hydrochloride granules

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Carr's index (%)	Angle of repose
R1	0.672±0.004	0.632±0.002	1.18±0.02	20.60±0.65	25.3±0.98
R2	0.565±0.013	0.844±0.004	1.23±0.03	18.98±0.87	28.8±0.17
R3	0.873±0.215	0.675±0.002	1.12±0.02	19.24±1.11	26.3±0.76
R4	0.672±0.153	0.814±0.003	1.10±0.02	21.29±0.87	29.4±0.88
R5	0.436±0.023	0.515±0.001	1.9±0.01	20.52±0.76	28.6±0.12
R6	0.734±0.012	0.623±0.004	1.23±0.03	17.85±0.65	25.8±0.23
R7	0.54±0.006	0.67±0.003	1.2±0.017	19.40±0.45	19.91±0.92
R8	0.56±0.032	0.66±0.004	1.12±0.02	15.21±0.96	19.42±0.47
R9	0.49±0.041	0.57±0.002	1.1±0.019	14.26±0.12	18.23±0.80
P1	0.546±0.002	0.842±0.006	1.12±0.01	18.60±0.45	21.3±0.98
P2	0.446±0.003	0.812±0.003	1.28±0.02	14.98±0.89	26.3±0.17
P3	0.623±0.241	0.683±0.001	1.23±0.02	19.24±0.21	21.9±0.76
P4	0.612±0.231	0.723±0.002	1.9±0.03	20.29±0.34	23.8±0.88
P5	0.321±0.021	0.620±0.001	1.8±0.01	21.52±0.65	28.1±0.12
P6	0.781±0.014	0.738±0.002	1.16±0.02	18.85±0.43	25.3±0.23
P7	0.692±0.003	0.83±0.004	1.23±0.01	16.92±0.29	15.42±0.92
P8	0.663±0.051	0.821±0.002	1.24±0.03	19.53±0.72	15.83±0.47
P9	0.712±0.041	0.853±0.002	1.19±0.02	17.25±0.14	16.25±0.80

All values expressed as mean±SD (*n*=3)

Assay method was performed for the tablets and was shown in Table 3.

RESULTS AND DISCUSSION

In vitro dissolution studies

The *in vitro* drug release test was carried out using the USP type-II apparatus (paddle). The dissolution medium is 900 mL of 0.1 N HCl for the first 2 h and lateral 10 h with 6.8 pH phosphate buffer. The paddle was rotated at 75 rpm at the temperature (37°C ± 0.5°C). The sampling was carried out at regular intervals and was replaced by means after each sampling interval. The sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analyzed spectrophotometrically at λ_{max} of the drug.[10,11] The *in vitro* dissolution studies were tabulated in Tables 4-6.

Table 3: Postcompression parameters for bilayer tablets

Batch	Thickness (mm)	Hardness (kg)	Friability (%)	Disintegration time	Weight variation (mg)	Assay%	
						Ramipril	Propranolol hydrochloride
F1	5.29±0.015	15.21±1.2	0.15	12m 53s	498±1.95	83.18	71.16
F2	5.12±0.013	14.23±0.89	0.32	11m 47s	495±1.23	88.72	85.61
F3	5.83±0.025	15.23±1.02	0.27	9m 18s	500±1.35	94.17	88.49
F4	5.86±0.014	16.35±0.8	0.25	9m 41s	512±1.29	97.96	94.13
F5	5.12±0.032	14.23±1.3	0.4	8m 30s	500±1.56	96.87	95.11
F6	5.89±0.153	15.6±6.2	0.31	8m 32s	506±1.8	97.17	97.62
F7	6.1±0.038	17.2±1.3	0.9	9m 12s	503±1.2	95.51	96.92
F8	6±0.056	17.9±1.2	0.82	10m 24s	499±1.25	98.36	97.96
F9	6±0.051	18.63±1.73	0.76	08m 86s	500±3.7	99.58	99.87

All values expressed as mean±SD (*n*=3)

Table 4: Percentage drug release of ramipril IR tablets

Time (min)	Percentage drug release of ramipril IR tablets								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
5	24.8±0.3	23.8±0.5	17.19±0.4	18.24±0.3	13.92±0.5	15.27±0.7	17.96±0.6	14.81±0.4	12.57±0.5
10	65.2±0.5	59.8±0.4	45.71±0.6	51.47±0.5	27.91±0.4	39.81±0.6	41.51±0.7	33.47±0.5	35.69±0.4
15	82.2±0.6	76.6±0.5	63.82±0.5	71.86±0.6	61.23±0.3	61.27±0.4	59.16±0.5	64.37±0.6	68.81±0.3
30	84.3±0.4	79.8±0.3	75.91±0.4	79.91±0.4	76.47±0.5	78.24±0.5	79.87±0.3	83.27±0.7	88.79±0.7
45	71.6±0.7	72.7±0.6	85.97±0.3	84.67±0.7	98.14±0.7	79.81±0.3	86.27±0.4	99.17±0.6	99.27±0.6
60	65.7±0.4	67.4±0.7	79.26±0.7	71.92±0.4	88.67±0.6	69.13±0.5	77.39±0.6	84.78±0.5	87.58±0.4

All values expressed as mean±SD (*n*=3)

Table 5: Percentage drug release of propranolol hydrochloride SR tablets

Time (Hr)	Percentage drug release of propranolol Hcl SR tablets								
	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0
0.5	8.91±0.5	8.59±0.6	12.47±0.4	4.92±0.3	6.49±0.5	7.21±0.6	8.54±0.7	5.13±0.5	4.87±0.4
1	18.47±0.3	16.25±0.4	24.61±0.6	15.72±0.5	14.92±0.7	24.68±0.6	25.67±0.4	13.28±0.4	18.83±0.6
2	34.69±0.4	32.91±0.5	36.47±0.4	33.67±0.4	35.76±0.6	39.55±0.4	47.91±0.6	32.87±0.3	34.37±0.4
4	52.67±0.6	46.97±0.5	48.87±0.3	53.89±0.4	54.41±0.5	55.23±0.5	53.29±0.4	51.18±0.6	54.75±0.5
6	78.71±0.7	62.28±0.6	67.92±0.5	64.71±0.5	70.49±0.3	67.94±0.6	65.81±0.3	62.46±0.7	64.19±0.7
8	81.28±0.6	79.17±0.4	82.17±0.3	86.78±0.6	85.48±0.4	81.37±0.4	82.72±0.4	84.37±0.4	83.82±0.3
10	84.79±0.4	81.93±0.3	88.96±0.3	94.67±0.7	95.71±0.5	92.47±0.5	94.73±0.3	98.99±0.7	99.39±0.5

All values expressed as mean±SD (*n*=3)

Table 6: Stability study of optimized formulation (at 30° C temperature and 65% relative humidity)

Assay		
Test	**1st Month**	**2nd Month**
F9	99.97±1.39	99.51±1.13

All values expressed as mean±SD (*n*=3)

CONCLUSION

Nine formulations of the ramipril and propranolol hydrochloride bilayer tablets were prepared using direct compression and wet granulation technique. The physical drug and excipients compatibility studies using FT-IR were conducted the studies revealed that there was no interaction between ramipril, propranolol hydrochloride, and excipients used in the preparation of bilayer tablet. The IR layer of ramipril was prepared using with different superdisintegrants such as crospovidone and sodium starch glycolate with different ratios. The sustained layer of propranolol hydrochloride was prepared by wet granulation technique using ethyl cellulose and HPMCS K-15M as polymers with different ratios. The prepared nine batches of bilayer tablets were evaluated for hardness, thickness, weight variation, friability, drug content, *in vitro* drug release studies, and stability studies. The formulation F9 was showed best drug release among all nine formulations. Finally, it concludes that F9 formulation shows the best drug release in both the layers (ramipril and propranolol hydrochloride). The drug release of propranolol hydrochloride is 99.39% and 99.27% for ramipril. Stability studies were performed for optimized formulation. The tablets were observed for accelerated stability studies for 2 months; the obtained results were within specifications.

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