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FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF BILAYER TABLETS OF RAMIPRIL AND METFORMIN USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

Bilayer tablets were prepared by using combination of fast dissolving Ramipril along with sustained release Metformin. The FTIR study conducted using a combination of drugs along with excipients and polymers revealed that combination can be safely prepared. The precompression parameters for powder blends of individual layers suggested good to fair flowability and compressibility. Ramipril was formulated as immediate release layer using Sodium starch glycolate, Croscarmellose sodium, Crospovidone as superdisintegrants and evaluated for physical parameter and disintegration time. The optimized Ramipril fast dissolving layer with highest in vitro release of 98 % was selected. Metformin was formulated as sustained release layer using different polymers like Hydroxypropylmethylcellulose, guar gum, Xanthan gum and Eudragit and evaluated for physical parameter along with in vitro release studies. The optimized sustained release layers which extend the Metformin release more than 8h was selected. Finally bilayer tablets were prepared by double compression of optimized metformin sustained release layer and Ramipril fast dissolving layer. Bilayer tablets were evaluated for various post compression parameters and Dissolution studies. All the physical parameters were in acceptable limit of pharmacopoeial specification. Hence bilayer tablets of Ramipril and Metformin as fast and sustained release combination could be used to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

KEY WORDS

Bilayer tablets, Ramipril, Metformin, Immediate release layer, Sustained release layer.

INTRODUCTION

In the recent years, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. Combination of drugs used for treatment of multiple diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy have various advantages over mono therapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may potentiate effects of other agent [1]. Using low dosage of two different agents minimizes the clinical and metabolic side effects that occur with maximal dosage of individual component of the combined tablet and thus dose of the single components can be reduced. Bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level [2].

Metformin is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by

decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake [3].

Ramipril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is metabolized to Ramiprilat in the liver and, to a lesser extent, kidneys. Ramiprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). Ramipril may be used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events [4].

In this study attempt has made to develop an advanced drug delivery of oral hypoglycaemic agents and Antihypertensives, particularly the development of Bilayer tablets containing sustained release layer of Metformin and immediate release Ramipril combination, both of which have great promise in treatment of Type 2 diabetes mellitus and hypertension.

MATERIALS AND METHODS

Materials

Metformin and Ramipril were obtained as gift samples from Madras Pharmaceuticals Ltd, Chennai, Hydroxy propyl methyl cellulose, Eudragit, Xanthan gum and Guar gum were received as gift samples from Drugs India, Hyderabad. Croscarmellose sodium, Crospovidone, and Sodium starch glycolate were received from Dr.Reddy's laboratories, Hyderabad. All others reagents and chemicals used were of analytical reagent grade.

METHODS

PRE FORMULATION STUDIES

Drug-Excipient Compatibility Studies

FTIR was used for the detection of any possible chemical reaction between the drug and the excipients. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Preparation of Immediate Release layer of Ramipril:

Ramipril and microcrystalline cellulose were mixed with disintegrant for 15 min in porcelain mortar, passed through 60# sieve. This blend was mixed with magnesium stearate for 5min and processed for direct compression [4, 5]. Compression force was maintained at constant level and magnesium stearate as lubricant for all formulations. Disintegrants are used at 3, 5, and 7.5 % in tablets. Compositions of all batches are represented in Table 1.

Table 1: Formulation of Ramipril Tablets (F1-F9)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	10	10	10	10	10	10	10	10	10
Croscarmellose sodium	3.6	6	9	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	3.6	6	9	-	-	-
Crospovidone	-	-	-	-	-	-	3.6	6	9
Microcrystalline cellulose	104	101.6	98.6	104	101.6	98.6	104	101.6	98.6
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Total weight	120	120	120	120	120	120	120	120	120

Preparation of Metformin HCl Sustained Release Tablets

Different formulations containing Metformin HCl were prepared by wet granulation technique using 20, 25 and 30 % concentrations of polymer and lactose as filler. All the powders were passed though #60 sieve. To this a liquid binder is added, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules[6,7]. Dried granules were passed through #20 and lubricated it with magnesium stearate and Aerosil was added to the granules. Then the lubricated granules were compressed into tablets using tablet punching machine. The compressed tablets were de dusted and evaluated for various tablet properties shown in Table 2.

Table 2: Formulation of Metformin HCl Tablets (F1-F12)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metformin	500	500	500	500	500	500	500	500	500	500	500	500
HPMC	160	200	240	--	--	--	--	--	--	--	--	--
Guar gum	--	--	--	160	200	240	--	--	--	--	--	--
Xanthan gum	--	--	--	--	--	--	160	200	240	--	--	--
Eudragit	--	--	--	--	--	--	--	--	--	160	200	240
Lactose monohydrate	128	88	48	128	88	48	128	88	48	128	88	48
Magnesium stearate	8	8	8	8	8	8	8	8	8	8	8	8
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	800	800	800	800	800	800	800	800	800	800	800	800

EVALUATION

Pre Compression Studies

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [8].

Tan θ = h/r

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index [9].

Carr's index (%) = [TBD-LBD] / TBD X 100

Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following Formula

Hausner's ratio= D_t/D_b

Where, D_t is the tapped density, D_b is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters

Weight variation:

All prepared matrix tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.

Friability:

Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020).

The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

Hardness:

Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester).

Thickness:

Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

Drug content:

An accurately weighed amount of Ramipril and Metformin drug (100mg) were dissolved in 250ml methanol separately. Further dilutions were made. Then the drug content was estimated at suitable wavelength of Ramipril and Metformin against blank reference using UV-Visible Spectrophotometer [9].

Disintegration time:

The disintegration test was performed using disintegrating apparatus. Placed one tablet in each of the six tubes of the basket and operate the apparatus using 0.1N HCl maintained at 37±0.5ºC as the immersion fluid. Than noted down the time to complete disintegration of tablets [10].

***In vitro* drug release studies:**

Ramipril Immediate release layer

Dissolution rate was studied by using USP type-II apparatus at 75 rpm using 900ml of 0.1N HCl solution as dissolution medium. at 37±0.5°C, aliquot of 5 ml of dissolution medium was withdrawn at every 10 min interval. The absorbance of solution was measured by UV Spectrophotometric method at 210 nm and concentration of the drug was determined from standard calibration curve [11].

Metformin Sustained Release layer

The *in vitro* release of drug from Metformin layer was carried out for 8 hours using paddle type tablet dissolution apparatus containing 900 ml of dissolution medium maintained at 37±0.5ºC and speed of agitation at 100 rpm. For the first 2 hours, 0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 6.8 phosphate buffer for further 6 hours. At prefixed time interval, 5 ml of solution was withdrawn and analyzed spectrophotometrically at 233 nm after suitable dilution [12].

RESULTS

The compatibility of Ramipril and Metformin with different super disintegrating agent and polymer was studied by FTIR spectroscopy. The IR spectra of pure drugs of Ramipril & Metformin are depicted in Figure 1&3. The IR spectra of combination of drugs along with superdisintegrants and polymer are shown in Figure 2&4. The overall observation of IR study suggested that formulation development of drugs in combination with excipients, the functionalities of drugs were unreacted and hence combination of drugs along with excipients can be formulated safely.

The Precompression parameters for Ramipril fast dissolving layer are shown in Table 3. The bulk density was found in range of 0.25 to 0.28 gm/cm^3 indicating good packing characteristic. The tapped density was found between 0.28 to 0.31 gm/cm^3.The Carr's compressibility index was in the range of 6.89 to 14.81 suggested good compressibility of blend. The values of Hausner's ratio were found in the range of 1.07 to 1.16 suggested good flowability of powder blend. The angle of repose of all the blend was within range of 21.66 to 26.26^o indicated excellent flow property of powder blend.

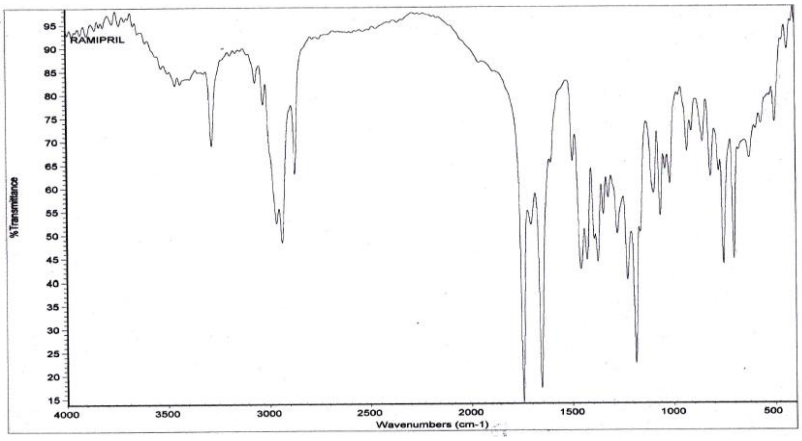

Fig: 1 FTIR of Ramipril

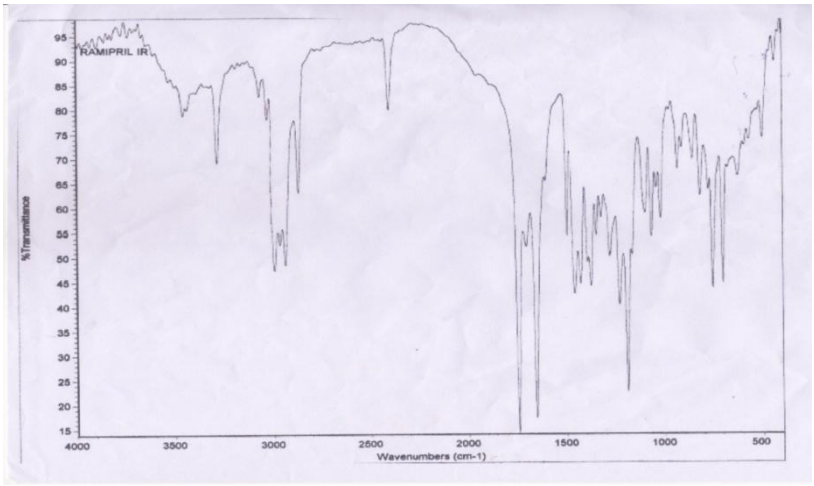

Fig: 2 FTIR of Ramipril with Excipients

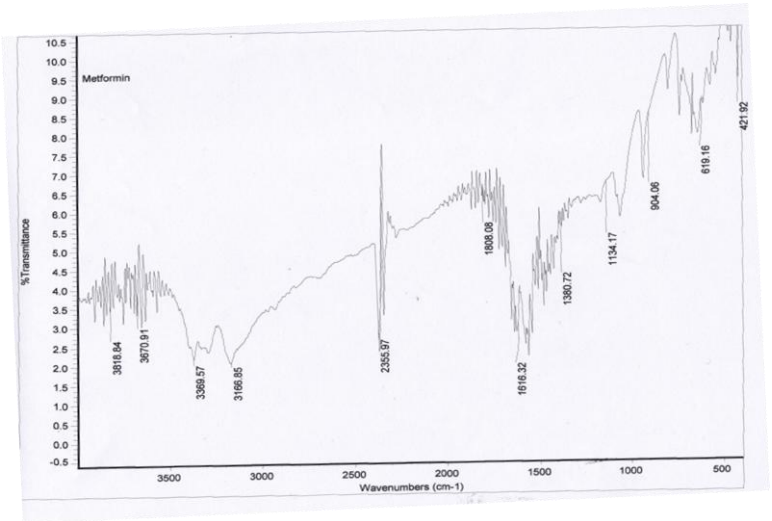

Fig: 3 FTIR of Metformin

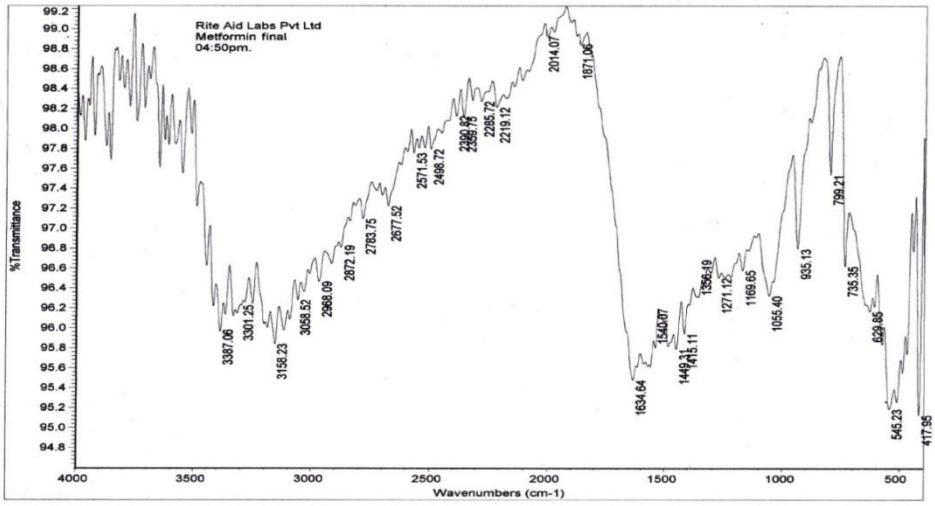

Fig: 4 FTIR of Metformin with Excipients

Table 3: Precompression Parameters of Ramipril Immediate Release layer

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose(°)
F1	0.27 ±0.05	0.31 ± 0.01	14.81±0.10	1.15 ± 0.02	24.61±0.05
F2	0.26 ± 0.05	0.28 ± 0.05	7.14 ± 0.10	1.08 ± 0.04	22.05±0.05
F3	0.28 ± 0.05	0.31 ± 0.01	9.67 ± 0.05	1.10 ± 0.07	26.00±0.05
F4	0.26 ± 0.07	0.31 ± 0.01	13.33±0.05	1.15 ± 0.05	25.49±0.05
F5	0.25 ± 0.01	0.29 ± 0.01	13.79±0.01	1.16 ± 0.01	21.66±0.01
F6	0.25 ± 0.01	0.28 ± 0.07	10.71±0.10	1.12 ± 0.01	26.26±0.01
F7	0.27 ± 0.07	0.30 ± 0.05	10.00±0.10	1.11 ± 0.07	22.12±0.05
F8	0.27 ± 0.07	0.29 ± 0.01	6.89 ± 0.05	1.07 ± 0.07	23.11±0.01
F9	0.27 ± 0.01	0.31 ± 0.01	12.90±0.05	1.14 ± 0.02	21.96±0.05

Each value represents as mean±SD of three determinants

The precompression parameters of powder blend for metformin sustained release layer are shown in Table 4. The bulk density was within range of 0.612 to 0.680 gm/cm^3 with tapped density in range of 0.754 to 0.847 gm/cm^3 indicated good to fair packaging capacity of blend. The Carr's compressibility index was within 18.27 to 20.67 value suggested fair compressibility of powder blend. The angle of repose was 25.48 to 29.51º suggested good flowability with Hausner's ratio of 1.22 to 1.26 suggested fair flowability of powder blend. Hence all the

precompression parameter obtained for the powder blends to be compressed as Ramipril fast dissolving layer and Metformin sustained release layer were within the acceptable limits of pharmacopoeial specification.

The Ramipril fast dissolving tablets was evaluated for hardness, thickness, friability, weight variation, drug content uniformity and *in vitro* disintegration time as represented in Table 5. The hardness was in the range of 4.40 to 4.83 kg/cm^2 which was in accordance with the fast dissolving tablet. The thickness was from 2.17 to 2.30 cm^2 suggested uniformity in thickness for fast dissolving layer. The friability was less than 1% indicated good handling of the layer. The weight variation results suggested uniformity in weight of layers. The content uniformity was in range of 98.13 to 99.51% indicated uniform dispersion of Ramipril in the layer. The *in vitro* disintegration time for the layer containing Sodium Starch Glycolate was 31.66 to 38.66 sec for the layer containing Crospovidone 35.66 to 41.00 sec, and the layer containing Croscarmellose Sodium showed 40.66 to 52.33 sec. The disintegration time for all the prepared layer was less than 1 minute indicated that the prepared layer was fast dissolving. The dissolution study of Ramipril fast dissolving layer was conducted using 0.1N HCl as dissolution media. The *in vitro* release data of Ramipril is tabulated in Table 7. The *in vitro* release of Ramipril was plotted as percent drug release versus time as depicted in figure 5. The *in vitro* release of Ramipril was rapid from all the layers. The layer prepared by using Croscarmellose Sodium showed 98 to 89% within 45 mins which was due to enormous swelling followed by rapid disintegration. The rapid *in vitro* release of Ramipril was 96 to 90% within 20 min from fast dissolving layer containing Sodium Starch Glycolate as super disintegrating agent which was attributed to high capillary activity with pronounced hydration capacity of the superdisintegrants. The in vitro release of Ramipril in the range 99 to 93 in 45 mins from the layer containing Crospovidone which was attributed to strong swelling of this disintegrants. The disintegration time and in vitro release study IF5 layer was selected as fast dissolving layer of Ramipril for further preparation of bilayer tablet (Figure 5).

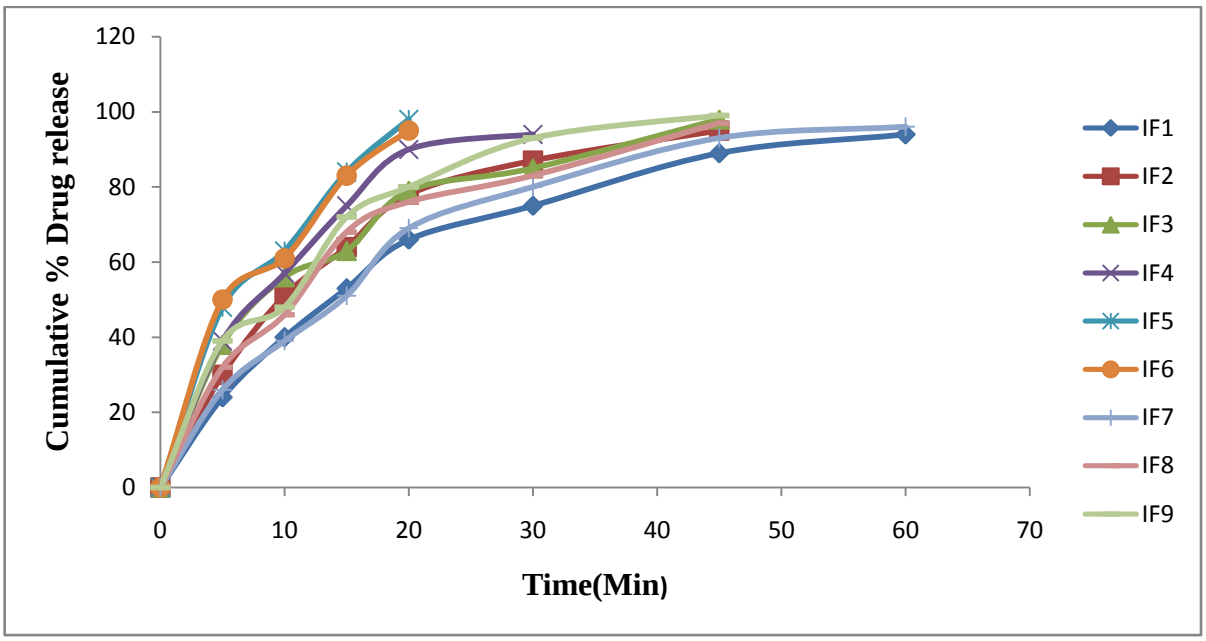

Figure 5: Comparison of Dissolution Profile of all formulations containing Ramipril as immediate release layer (IF1-IF9)

Table 4: Precompression parameters of Metformin Sustained Release layer

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose(°)
F1	0.614±0.01	0.754±0.04	18.56±0.05	1.22±0.03	28.38±0.06
F2	0.661±0.01	0.812±0.03	18.59±0.06	1.22±0.02	27.36±0.04
F3	0.648±0.02	0.793±0.02	18.27±0.03	1.23±0.03	25.55±0.03
F4	0.612±0.01	0.766±0.03	20.12±0.03	1.25±0.02	29.11±0.06
F5	0.668±0.01	0.828±0.02	19.34±0.03	1.23±0.02	27.72±0.07
F6	0.663±0.03	0.820±0.03	19.19±0.05	1.23±0.02	28.14±0.07
F7	0.676±0.02	0.847±0.03	20.19±0.02	1.25±0.04	28.39±0.06
F8	0.659±0.02	0.831±0.02	20.67±0.01	1.26±0.04	26.31±0.02
F9	0.634±0.02	0.787±0.02	19.53±0.01	1.24±0.03	25.48±0.06
F10	0.668±0.01	0.833±0.02	19.64±0.02	1.24±0.05	28.47±0.04
F11	0.680±0.02	0.835±0.04	18.57±0.03	1.22±0.04	27.23±0.05
F12	0.660±0.03	0.812±0.01	18.73±0.03	1.23±0.05	29.51±0.04

Each value represents as mean±SD of three determinants

Table 5: Evaluation Parameters of Ramipril Immediate release layer Tablets

Formulation	Hardness (Kg/cm^3)	Thickness (cm)	Friability (%)	Weight Variation (mg)	Drug content (%)	*In- vitro* disintegration time(sec)
F1	4.76 ± 0.05	2.27 ± 0.04	0.16 ± 0.05	120 ± 0.02	98.46	52.33 ± 2.51
F2	4.70 ± 0.00	2.24 ± 0.05	0.20 ± 0.00	120 ± 0.05	98.79	46.66 ± 1.52
F3	4.83 ± 0.05	2.23 ± 0.04	0.20 ± 0.00	121 ± 0.01	98.96	40.66 ± 1.15
F4	4.46 ± 0.05	2.24 ± 0.05	0.43 ± 0.05	121 ± 0.01	98.13	38.66 ± 1.15
F5	4.40 ± 0.00	2.30 ± 0.00	0.33 ± 0.05	120 ± 0.02	99.51	35.33 ± 1.15
F6	4.43 ± 0.05	2.23 ± 0.04	0.40 ± 0.01	120 ± 0.01	99.26	31.66 ± 1.00
F7	4.50 ± 0.00	2.17 ± 0.04	0.53 ± 0.05	120 ± 0.57	98.32	41.00 ± 2.88
F8	4.56 ± 0.05	2.24 ± 0.05	0.56 ± 0.05	120 ± 0.57	99.16	37.63 ± 2.51

F9	4.56 ± 0.05	2.19 ± 0.03	0.50 ± 0.05	120 ± 0.02	98.34	35.66 ± 2.51

Each value represents as mean±SD of three determinants

Table 6: Evaluation parameters of Metformin sustained release layer

Formulations	Hardness Kg/cm3	Thickness (cm)	Friability (%)	Weight Variation (mg)	Drug content (%)
F1	7.25±0.02	6.10±0.03	0.58±0.05	800±0.01	98.70
F2	7.53±0.02	6.12±0.03	0.50±0.05	800±0.03	99.25
F3	7.46±0.01	6.10±002	0.52±0.05	802±0.03	98.42
F4	7.31±0.03	6.40±0.01	0.33±0.05	801±0.02	97.52
F5	7.59±0.03	6.41±0.01	0.31±0.03	800±0.03	99.24
F6	7.87±0.02	6.41±0.01	0.32±0.05	801±0.03	98.63
F7	7.94±0.05	6.11±0.02	0.45±0.04	800±0.05	98.15
F8	7.81±0.06	6.11±0.03	0.49±0.01	803±0.04	99.42
F9	7.48±0.05	6.12±0.02	0.51±0.01	800±0.05	99.14
F10	7.66±0.06	6.18±0.03	0.37±0.01	800±0.05	99.25
F11	7.87±0.04	6.19±0.03	0.34±0.02	800±0.04	99.30
F12	7.75±0.06	6.18±0.02	0.41±0.01	800±0.05	99.17

Each value represents as mean±SD of three determinants

Table 7: In vitro Drug release data of Ramipril from immediate layer

Time (min)	% Drug release								
	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9
5	24	30	38	39	48	50	26	32	39
10	40	51	56	57	63	61	39	46	48
15	53	64	63	75	84	83	51	68	72
20	66	78	79	90	98	95	69	76	80
30	75	87	85	94	--	--	80	83	93
45	89	95	98	--	--	--	93	97	99
60	94	--	--	--	--	--	96	--	--

Table 8: In vitro Drug release data of Metformin Sustained Release layer

Time(hr)	% Drug release											
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
1	42	38	35	37	28	23	56	40	37	50	39	30
2	57	49	47	46	36	32	69	54	52	63	51	45
3	76	62	58	58	50	41	82	70	64	78	64	56
4	88	76	72	72	62	58	93	83	78	89	78	69
6	101	88	84	85	68	64	-	98	89	103	89	80
8	-	97	93	93	75	68	-	-	101	-	103	93
10	-	-	-	-	89	76	-	-	-	-	-	-
12	-	-	-	-	97	84	-	-	-	-	-	-

Table 9: Optimized Formula of Bilayer Tablet

INGREDIENTS(mg)	F5
Metformin	500
Guar gum	200
Lactose monohydrate	88
Magnesium stearate	8
Aerosil	4
Ramipril	10
SSG	6
MCC	101.6
Mg.stearate	2.4
TOTAL(mg)	920

Table 10: Evaluation parameters of Bilayered tablets

Formulation	Hardness Kg/cm^3	Thickness (cm)	Friability (%)	Weight Variation (mg)
F5	8.3	4.5	0.68±0.05	920±0.05

Table 11: In vitro drug release of Bilayer tablets

Time(min)	% Cumulative Drug release
IMMEDIATE RELEASE LAYER	
5	46
10	59
15	86
20	99
SUSTAINED RELEASE LAYER	
0.1 N HCl	
Time in hours	**% Cumulative Drug Release**
1	25
2	35
6.8 pH Phosphate Buffer	
3	50
4	61
6	69
8	76
10	87
12	98

The sustained release layer of Metformin was formulated by Wet granulation method using different drug to polymer ratios and finally optimized in the ratio of 1:2.5 for the drug to polymer. In the entire formulated sustained release layer, the ratio of Metformin was fixed. All the batches of formulated layers were produced under similar condition to avoid processing variables. The prepared sustained release layer of Metformin was evaluated for post compression parameters and dug content and results were tabulated in Table 6. The hardness of prepared Metformin layer was in the range of 7.25-7.94 kg/cm^2 which was in acceptable range of sustained release formulation. The hardness was high for the layers containing Xanthan gum and low hardness was observed in layer containing HPMC. The thickness of the entire formulated sustained release layer was in range of 6.10 to 6.41 due to the constant tablet press setting across all the batches irrespective of weight variation. The average weight of formulated layer was found to be uniform in the range of 800-803mg and the percent deviation in weight variation for all the formulated layer was within the acceptable range of pharmacopoeial specification. The percent friability value for all formulated layer was in range

0.31 to 0.58% indicated good handling properties of formulated layers. The drug content was in the range of 95.08 to 98.94% for the entire formulated layer suggested uniform dispersion of Metformin in formulated sustained release layer.

The *in vitro* release study of Metformin from sustained release layer was conducted for first two hour in 0.1N HCl and then the dissolution study was continued in pH 6.8 phosphate buffer for next 10 hours. The *in vitro* release data of Metformin from sustained layer is tabulated in Table 8 and illustrated in figure 6. The *in vitro* release of Metformin was slow in 0.1N HCl due to the slow swelling of polymer matrix used in the preparation of sustained release layer. After two hours 57 % from HPMC, 46% from Guar gum, 69 % from Xanthum gum and only 63 % from Eudragit polymer matrix of sustained release layer was released. The *in vitro* release was rapid in pH 6.8 phosphate buffer due to the more swelling of polymer matrix in alkaline medium. A maximum of 97% from Guar gum polymer matrix of sustained release layer was released within 12h. The *in vitro* release is depending upon nature of drug, nature of polymer, drug to polymer ratio and the medium used. The overall results of *in vitro* release study suggested that the addition of a Guar gum more pronouncedly retard the drug release (Figure 6).

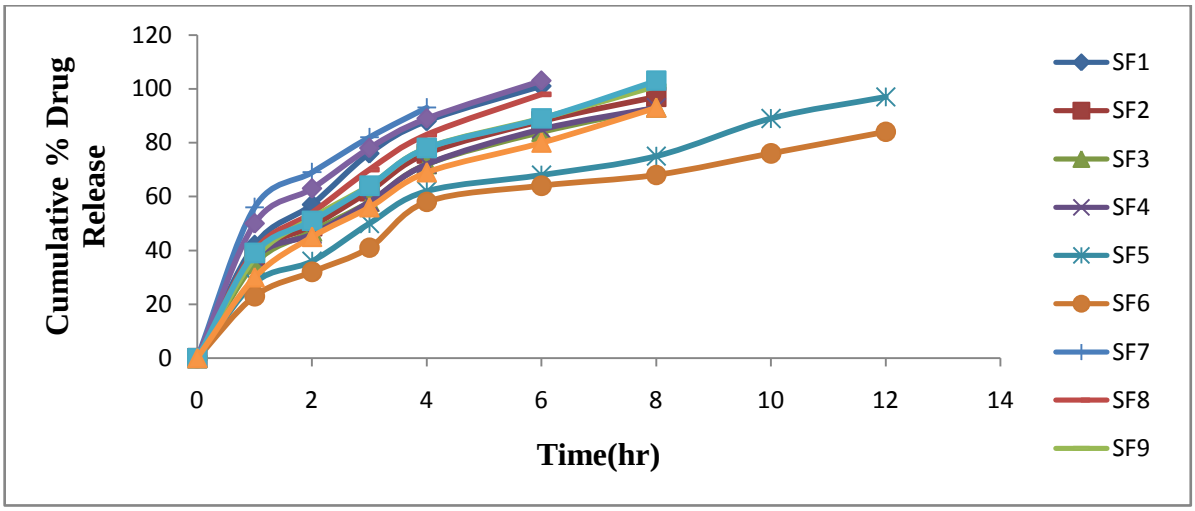

Figure 6: Comparison of Dissolution Profile of all formulations containing Metformin as sustained release layer (SF1-SF12).

The bilayer tablet were prepared by double compression of optimized Metformin sustained release layer (SF5) and Ramipril fast dissolving layer (IF5) as shown in Table 9 using 19x9 mm punches on tablet punching machine. The bilayer tablets were evaluated for different physical parameter like hardness, thickness, friability and weight variation. The results of parameter are tabulated in Table 10. The hardness of bilayer tablet was found in the range of 8.3 kg/cm^2 which was more as compare to individual layer because of double compression. The thickness of the bilayer tablet was in the range of 4-5 cm^2 which was increased as compare to individual layer because of increase in amount of excipients. The friability was 0.68 % for bilayer tablet which was less than 1 indicating good handling of tablet. The weight variation study showed low standard deviation uniformity in weight of the tablets.

The *in vitro* disintegration time was 31.66-38.66 sec for all the tablets suggested rapid disintegration of only Ramipril layer whereas the Metformin layer was not disintegrated but swells. Hence the physical parameter evaluated for all the bilayer tablet were within acceptable range of pharmacopoeial norm with good physical properties. The *in vitro* drug release study for bilayer tablets was conducted and Ramipril immediate release layer showed 99% drug

release in 20min. Metformin sustained release layer provided 98% drug release in 12 hours (Table 11).

CONCLUSION

In the present study Bilayer tablets were prepared with Ramipril as immediate release layer using SSG as superdisintegrant and Metformin as sustained release layer using Guar gum as polymer. The tablets showed good results with drug release of 99% in 20min (immediate release layer) and 98% in 12hours (sustained release layer). Hence bilayer tablets of Ramipril and Metformin as fast and sustained release combination is a better approach to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

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Conflict of interest statement

We declare that we have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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