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Formulation and evaluation of a bilayer matrix tablet encompass ramipril as immediate release and metformin as sustained release

L.Satyanarayana[1*], Srikanth Choudary Pallothu[2]

[1]*Professor, Department of Pharmacy, Omega College of Pharmacy, Edulabad, Hyderabad, Ghatkesar, Telangana 501301.*

[2]*Associate Professor, Department of Pharmacy, Omega College of Pharmacy, Edulabad, Hyderabad, Ghatkesar, Telangana 501301.*

Corresponding author: L.Satyanarayana

Email id: satyadna_l@yahoo.co.in

ABSTRACT

In current scenario oral drug delivery has been notorious for decades as the most widely utilized route of administration among all the routes that have been explode for systematic delivery of drug via various pharmaceutical products of different dosage form. And hence only, aim of the present study was to formulate and evaluate a bilayer matrix tablet containing Ramipril as immediate release and Metformin as sustained release. Ramipril was formulated as fast dissolving layer using sodium starch glycolate, crospovidone, croscarmellose sodium as superdisintegrants in different concentration and Metformin as sustained release layer using matrix forming material like HPMC, Guargum, xanthum, Eudragit. Ramipril fast dissolving layer and metformin sustained release layer was prepared by direct compression method and wet granulation method and prepared layer were evaluated for hardness, thickness, weight variation, friability, drug content, in vitro disintegration time(not for metformin layer) and *in vitro* drug release study as described in chapter-4. The in vitro release of Ramipril from formulated fast dissolving layer was rapid. Consequently 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 nephropathic diseases.

Keywords: Bilayer tablets, Ramipril, metformin, Iimmediate and Sustain release

INTRODUCTION

In recent times, various developed and developing countries move towards combination therapy for treatment of multiple diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy have various advantages over monotherapy 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. 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 [1,10]. 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. Bilayer tablet are very common dosage form for drugs such as captopril, metoprolol, amoxicillin and potassium clavuanate, propranolol hydrochloride, bambuterol hydrochloride. Joint National Committee VI recognized the value of combination therapy and suggested that combining drug with different modes of action will often allow smaller doses of drugs to be used to achieve control and minimize the potential dose dependent side effects. JNC VI recommended sthat the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment of any chronic disease. Hence management of multiple diseases can be effectively and better done by bilayer tablet or layering in tablet [11, 15].

MATERIALS AND METHODS

Estimation of Ramipril

Determination of λmax of Ramipril in 0.1N HCl solution

Stock solution: Ramipril in 0.1 HCl solutions (100 mg in 100 ml). Scanning: from the stock solution 20 □g/ml solution of Ramipril was prepared in 0.1 HCl solution and scanned between 200-400nm. The absorption maxima of 210 nm was selected and used for further studies[16-19].

ESTIMATION OF METFORMIN

Determination of λmax of Metformin in 0.1N HCl solution

Stock solution: Metformin in 0.1 HCl solutions (100 mg in 100 ml). Scanning: From the stock solution 10 □g/ml solution of Metformin prepared in 0.1 HCl solution and scanned between 200-400nm. The absorption maxima of 233 nm was selected and used for further studies.

Drug-polymer interaction study by Fourier-transformation infrared

Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 150 cm^{-1} in a shimadzu FT-IR spectrophotometer. 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.

Preformulation Studies

Preformulation may be described as a phase of the research & development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms[20].

Preparation of Immediate Release layer of Ramipril

Tablets containing Ramipril were prepared by wet granulation technique using 3,5,7.5 % concentrations of disintegrants and MCC as filler. Different tablets formulations were prepared by wet granulation method. All the powders were passed though #60 sieve. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, 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. Ramipril tablets were prepared with super disintegrants and other additives. Ramipril and, mcc were mixed together, and granulate it solution until a wet mass was obtained. Then the coherent mass was passed through #16 and the granules were dried at 40 ±2°C for 2 hours. Dried granules were passed through #20 and lubricated it with magnesium stearate. Then the lubricated granules were compressed into tablets using tablet punching machine. The compressed tablets were dedusted and evaluated for various tablet properties [21,26].

Preparation of Metformin HCL Sustained Release Tablets

Tablets containing Metformin HCl were prepared by wet granulation technique using 20, 25 and 30 % concentrations of polymer and lactose as filler. Different tablets formulations were prepared by wet granulation method. All the powders were passed

though #60 sieve. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through ascreen 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[27-29]. Metformin HCl and, lactose were mixed together, and granulate it with polymer solution until a wet mass was obtained. Then the coherent mass was passed through #16 and the granules were dried at 40 +2°C for 2 hours. 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 dedusted and evaluated for various tablet properties[30].

RESULTS AND DISCUSSION

Table No.1. Calibration curve of Ramipril

S.No	Concentration	Absorbance
1.	0	0
2.	10	0.171
3.	20	0.305
4.	30	0.460
5.	40	0.620
6.	50	0.712

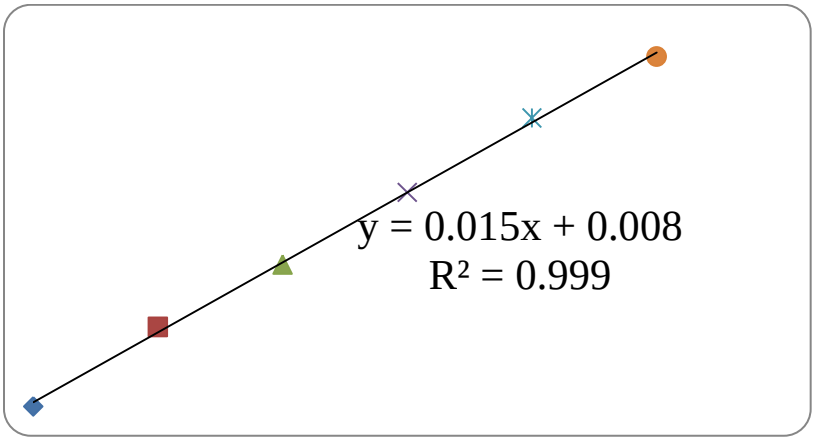

Figure No. 1. Calibration curve of Ramipril in 0.1 N HCl solution

Table No. 2. Calibration curve of Metformin

Sr.No	Concentration (µg/ml)	Absorbance in 0.1 N HCl	Absorbance in phosphate buffer(pH6.8)
1.	0	0	0
2.	2	0.0422	0.1563
3.	4	0.0813	0.2901
4.	6	0.1238	0.4199
5.	8	0.1561	0.5801
6.	10	0.1971	0.7184

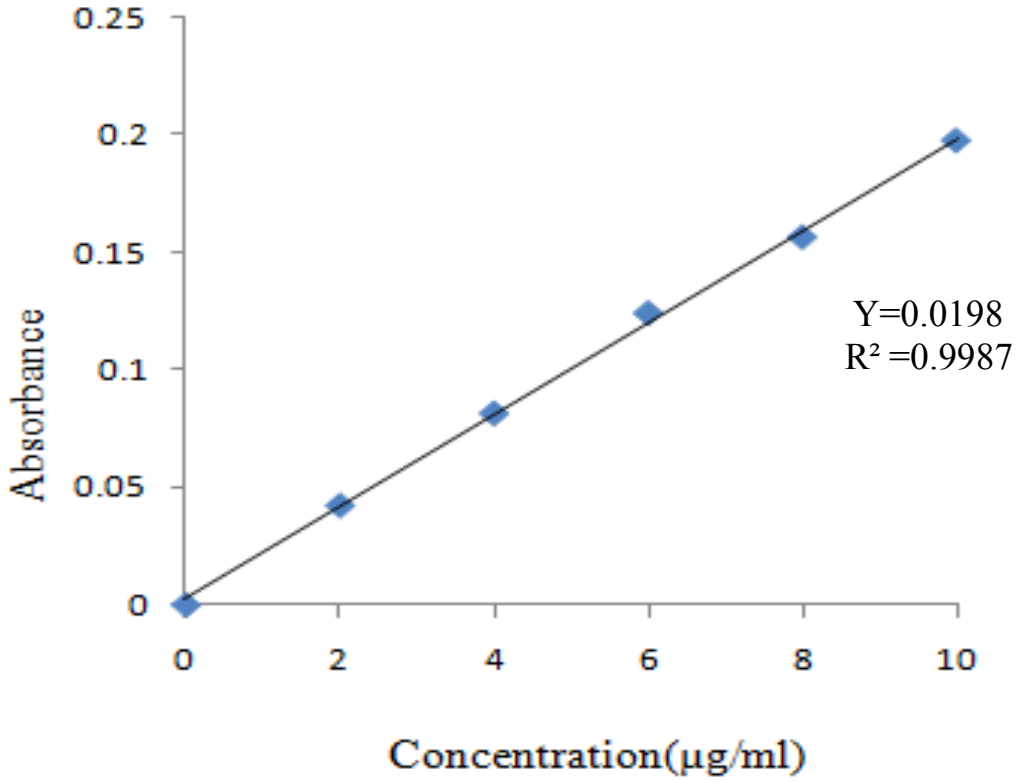

Figure No. 2. Calibration curve of Metformin HCl in 0.1N HCL

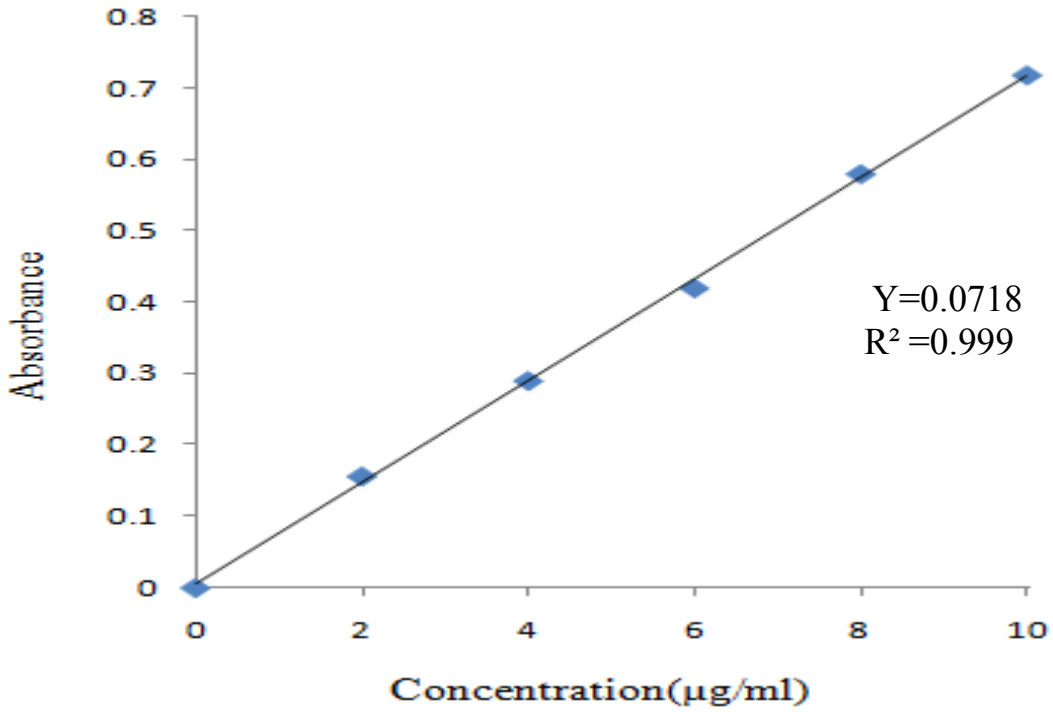

Figure No. 3. Standard curve of Metformin HCl in phosphate buffer pH 6.8

Table No. 3. Evaluation parameters of Ramipril immediate release layer.

Formulations	Hardness Kg/cm3	Thickness (cm)	%Friability	Weight Variation (mg)	*In- vitro* disintegration time(sec)
F1	4.76 ± 0.05	2.27 ± 0.04	0.16 ± 0.05	120 ± 0.02	52.33 ± 2.51
F2	4.70 ± 0.00	2.24 ± 0.05	0.20 ± 0.00	120 ± 0.05	46.66 ± 1.52
F3	4.83 ± 0.05	2.23 ± 0.04	0.20 ± 0.00	121 ± 0.01	40.66 ± 1.15
F4	4.46 ± 0.05	2.24 ± 0.05	0.43 ± 0.05	121 ± 0.01	38.66 ± 1.15
F5	4.40 ± 0.00	2.30 ± 0.00	0.33 ± 0.05	120 ± 0.02	35.33 ± 1.15
F6	4.43 ± 0.05	2.23 ± 0.04	0.40 ± 0.01	120 ± 0.01	31.66 ± 1.00
F7	4.50 ± 0.00	2.17 ± 0.04	0.53 ± 0.05	120 ± 0.57	41.00 ± 2.88
F8	4.56 ± 0.05	2.24 ± 0.05	0.56 ± 0.05	120 ± 0.57	37.63 ± 2.51
F9	4.56 ± 0.05	2.19 ± 0.03	0.50 ± 0.05	120 ± 0.02	35.66 ± 2.51

Table No. 4. Evaluation parameters of merformin sustained release layer.

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

Table No. 5. *In vitro* release data of ramipril from immediate layer.

Time in mins	% Drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
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	96	95	69	76	80
30	75	87	85	94	-	-	80	83	93
45	89	95	98	-	-	-	93	97	99
60	94	-	-	-	-	-	96	-	-

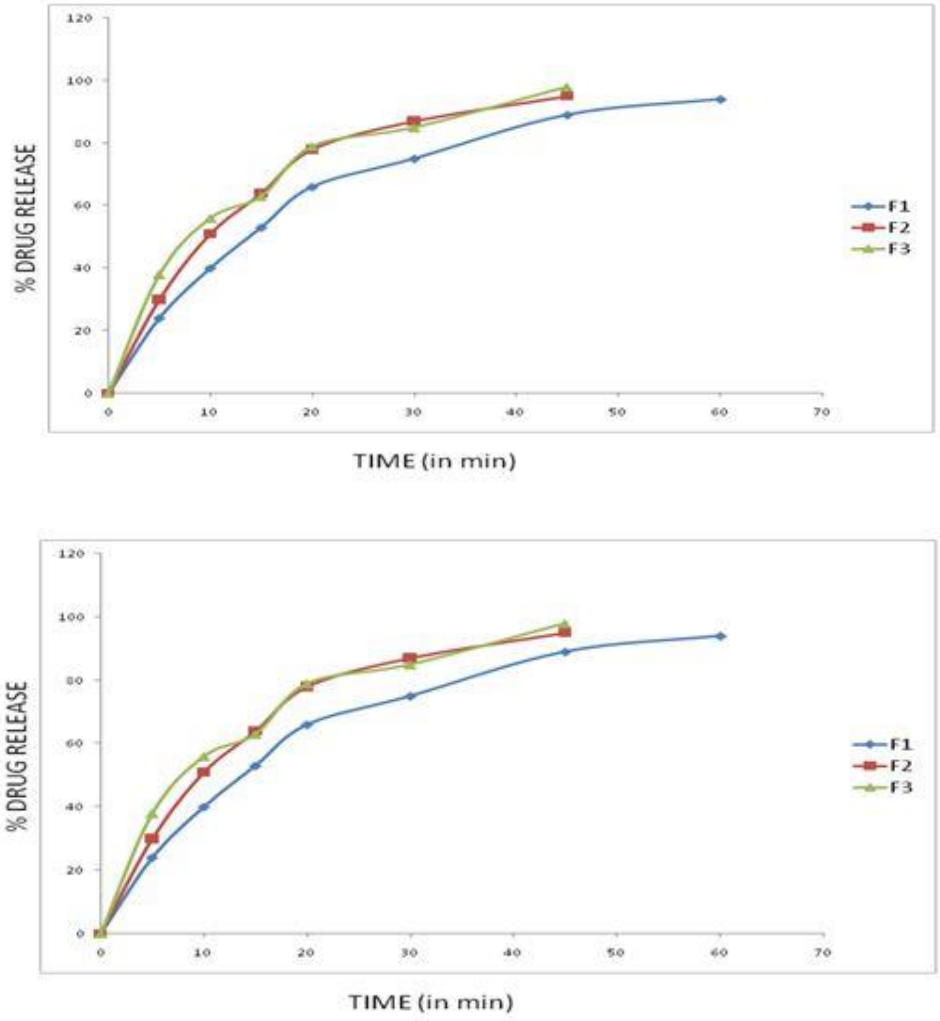

Figure No. 4. *In vitro* release of ramipril from immediate layer containing croscarmellose sodium.

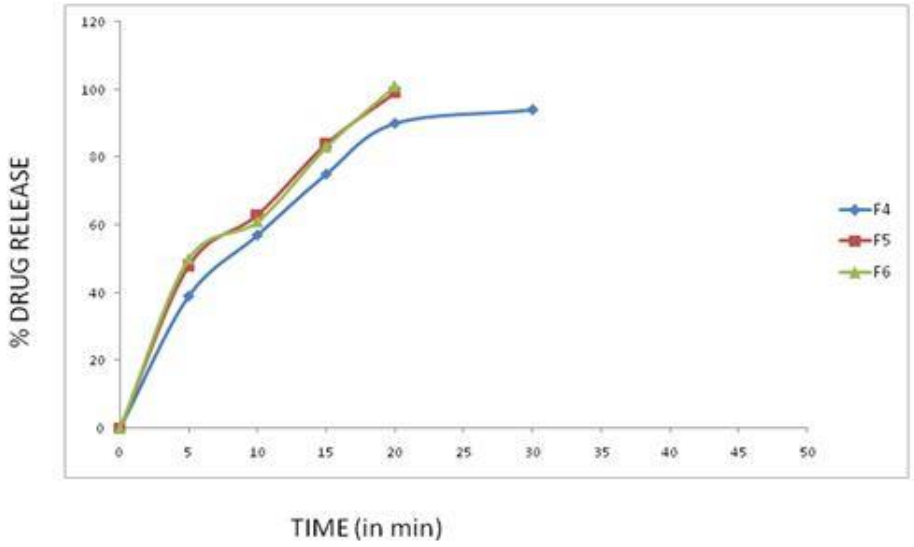

Figure No. 5. *In vitro* release of Ramipril from immediate layer containing sodium starch glycolate.

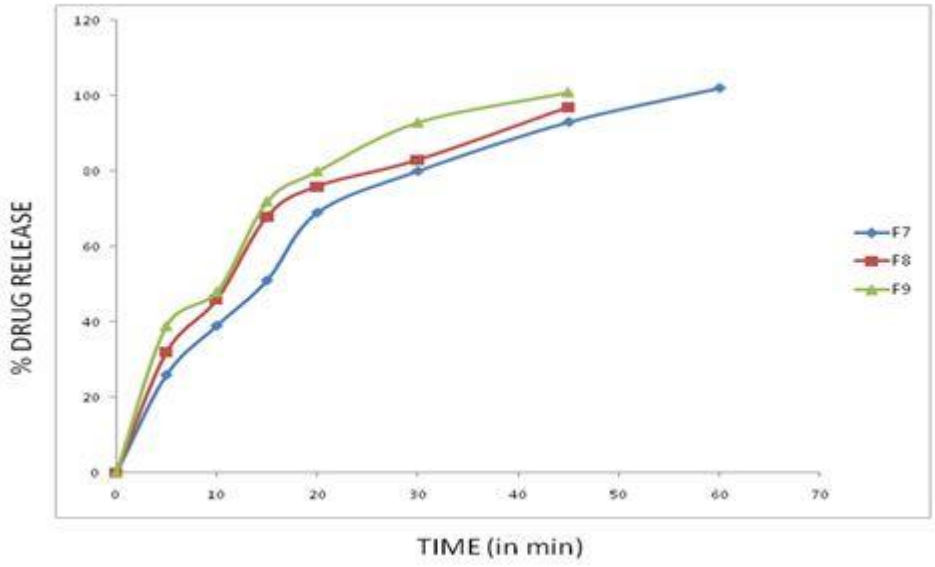

Figure No. 6. *In vitro* release of Ramipril from immediate layer containing crospovidone

Table No. 6. *In vitro* release data of Metformin from sustained layer.

Time In hours	% Drug release											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
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	-	-	-	-	-	-

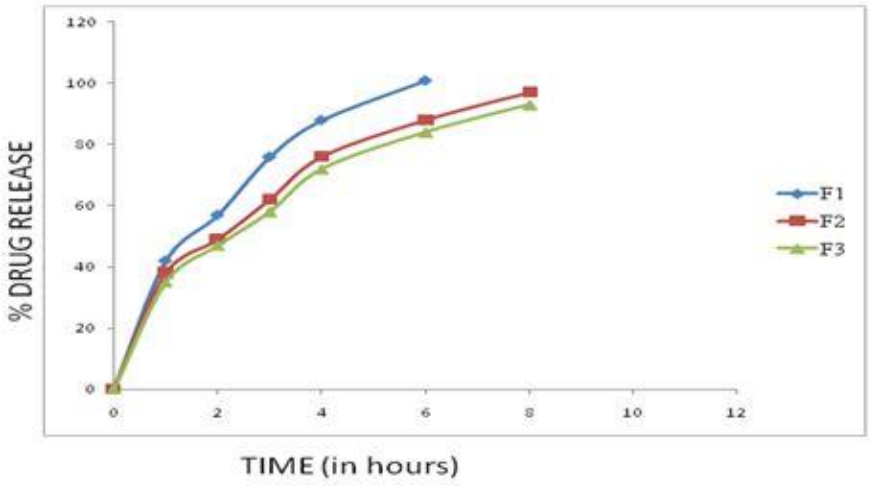

Figure No. 7. *In vitro* release of Metformin from sustained layer containing HPMC

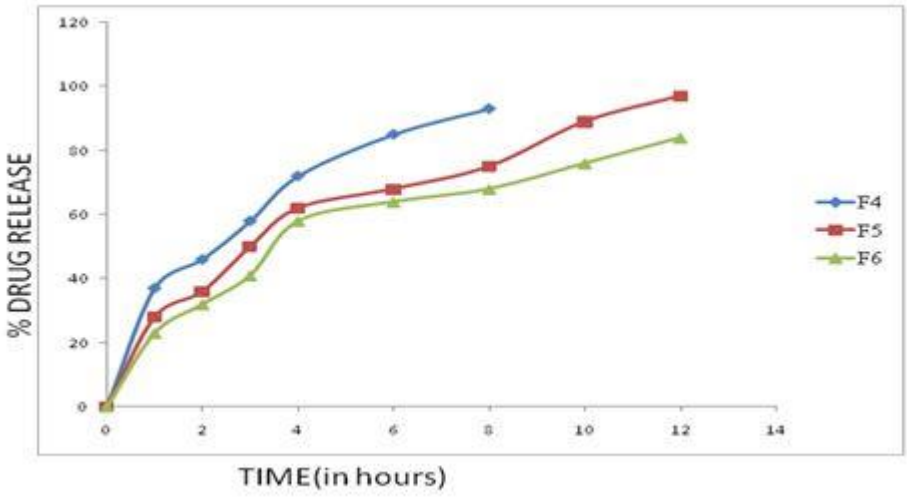

Figure No. 8. *In vitro* release of Metformin from sustained layer containing Guar gum

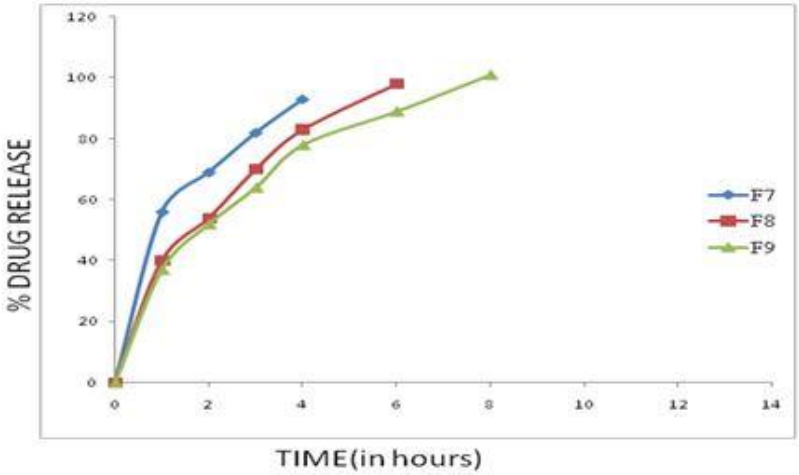

Figure No. 9. *In vitro* release of Metformin from sustained layer containing Xanthum

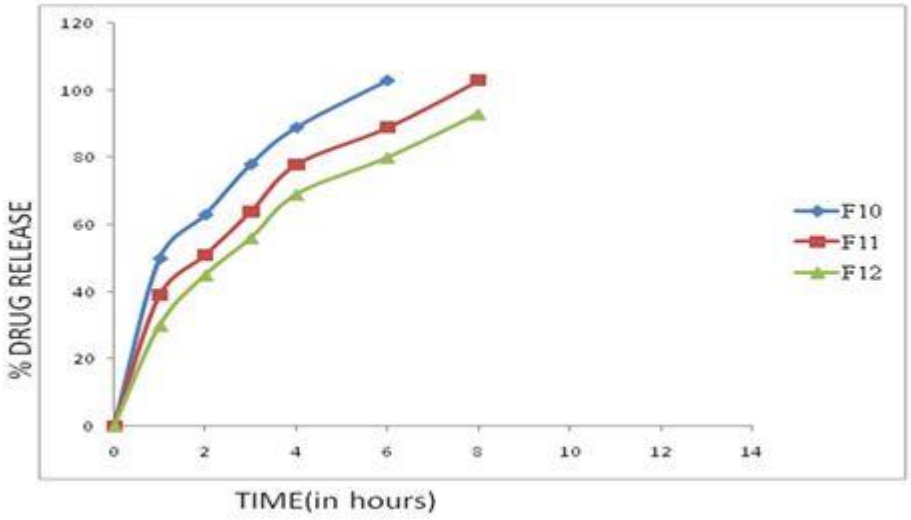

Figure No. 10. *In vitro* release of Metformin from sustained layer containing Eudragit

Table No. 7. Evaluation parameters of bilayered tablets

Formulations	Hardness Kg/cm3	Thickness (cm)	%Friability	Weight Variation (mg)
Bilayer formulation	8.3	4.5	0.68±0.05	920±0.05

Time in minutes	% Cumulative Drug Release
5	46
10	59
15	86
20	101
Sustained Release Layer	
Acidic buffer	
Time in hours	**% Cumulative Drug Release**
1	25
2	35
Basic buffer	
3	50
4	61
6	69
8	76
10	87
12	98

The bilayer tablet were prepared by double compression of optimized Metformin sustained release layer (F-5) and Ramipril fast dissolving layer (F5) as shown in Table-4 using 19x9 mm punches on a cadmech tablet press. The bilayer tablets were evaluated for different physical parameter like hardness, thickness, friability, weight variation and *in vitro* disintegration time. The results of parameter are tabulated in Table-15. The hardness of bilayer tablet was found in the range of 7-9 kg/cm2 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 which was increased as compare to individual layer because of increase in amount of excipients. The friability was 0.68 % bilayer tablet which was less than 1 indicating good handeling 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 pharmacopeial norm with good physical properties.

CONCLUSION

In this research, successfully the formulation and evaluation of bilayer tablet of Ramipril and Metformin for the effective management of diabetes along with diabetic hypertension has been developed. All of the pre and post compressional paramerets and drug release profile of the formulation has been found satisfactory indeed. Consequently bilayer tablets of Ramipril and Metformin as fast sustained release combination could be used to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

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