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Original Article

Development and Charecterisation of Ramipril as Immediate Release and Metformin Hydrochloride as Sustained Release Bilayered Tablets

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ABSTRACT

The purpose of this research work was to formulate an anti diabetic and anti hypertensive in a single dosage form i.e. Metformin HCl in sustained release layer and Ramipril in immediate release layer of the bilayer tablet. The tablets were prepared using Hydroxypropylmethylcellulose (HPMC K4M & HPMC K100M, METHOCEL 40-101,METHOCEL K15MPCG) and hydroxyl ethyl cellulose(HEC) an as release retarding polymers in various combination and concentrations. The effect of different super disintegrants on immediate release in various concentrations was also studied. Nine formulations of immediate release layer were prepared using SSG, CCS, Crosspovidine superdisintegrants with different proportions and were evaluated for different parameters. Among the nine formulations R6 containing CCS as disintegrant showed a better release of 99.73% for 45 mins was selected. Using this R6 formulation Nine formulations of sustained release layer of Metformin.HCL was prepared with different Hydroxypropylmethylcellulose (HPMC K4M & HPMC K100M, METHOCEL 40-101,METHOCEL K15MPCG) and hydroxyl ethyl cellulose(HEC) polymers and evaluated. Among nine formulations of bilayered tablets RM9 was showed 99.32% at the end of 12hrs was selected as optimized formulation. This optimized formulation was evaluated for parameters like , thickness, hardness, friability, weight variation, drug content, *in vitro* drug release and stability and results were found to be within limits

Keywords: Bilayer Tablets, Croscarmellose sodium, HPLC, Hydroxypropylmethylcellulose, Metformin HCl, Ramipril, Sustained release

1. INTRODUCTION

Patients with diabetes mellitus have an increased prevalence of hypertension and associated

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cardiovascular disease (CVD). The risk of an individual of developing CVD is much greater when both diseases coexist. [1] Hypertension (HTN) and Diabetes Mellitus (DM) frequently coexist which increases with age. The frequency of hypertension in diabetic population is almost twice as compared to non-diabetic general population. In India about 50% of diabetics have hypertension. [2] A recent study on the prescribing pattern of diabetic-hypertensive patients revealed that 84 (28%) out of 300 patients in year 2008 were having associated Diabetes mellitus. 70% of the patients were on monotherapy and the most commonly prescribed drug group was Angiotensin Converting Enzyme Inhibitors (ACEI) (Enalapril & Ramipril). In year 2009,105 of 450 patients were having DM. 72% of the patients were on mono-therapy. Most prescribed drugs were ACEIs (47%). [3] A fixed dose combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form and available in certain fixed doses. FDC pharmaceutical products can be used to treat the same disease state, multiple disease states or counteract the negative side-effects. The merits of drug combinations are increased compliance, convenience and cost savings. In contrast, demerits include reduced flexibility in dosing, exposure of some patients to therapies they do not require and possible increased risks of adverse effects without added benefits. [4] Considering the prevalence of diabetic hypertension as well as the prescribing pattern of drugs in patients suffering from such complications, it is apparent that anti diabetic and antihypertensive drugs seem to be potential candidates for incorporating in a combination product. Survey of prescribing pattern and physician's opinion, rationalized the suitability to formulate a combination product containing an oral hypoglycemic agent and an ACE inhibitor.

The recent study on the prescribing pattern of diabetic-hypertensive patients revealed that out of the 534 prescriptions, 225 contained both oral antidiabetic and antihypertensive drugs. The physicians prescribe ACE inhibitors at a greater frequency in diabetic-hypertensive patients and the trend is observed in most of the countries. [5]

In this context, an attempt was made to formulate bilayer tablet of Anti Diabetic and Anti Hypertensive in a single dosage form. Metformin Hydrochloride (Metformin HCl) was chosen as an Anti Diabetic drug and Ramipril as an Anti Hypertensive drug on the basis of the prescription survey. Metformin has a short and variable biological half life of 1.5-4.5 hr, it is therefore administered (500mg thrice a day) to maintain effective plasma concentration. In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with Metformin HCl suffers from certain problems of which the most prominent is the high dose (1.5-2.0 g/day), low bio-availability (60%) and high incidence of gastrointestinal tract side effects(30% case).Therefore, continuous efforts are made to improve the pharmaceutical formulation of Metformin HCl in order to achieve an optimal therapy. These efforts mainly focus on extended release of the drug. Administration of an extended release, once-a-day Metformin HCl could reduce the dosing frequency and improve patient compliance [6]. Ramipril is a prodrug and is converted to the active metabolite Ramiprilat by liver esterase enzyme. The main criterion for immediate release dosage form is poor solubility of the drug and need for immediate action ofdrug. The long biological half life (3-16hours), dose (2.5-10 mg / day) and long elimination phase (9-18 hours) suggest its immediate action for treating hypertension. [7]

Therefore, bilayer tablets were formulated containing Metformin HCl, an anti diabetic as sustained release layer and Ramipril, an anti hypertensive as immediate release layer. The main objective of the present study

was to develop polytherapy for the treatment of Diabetes mellitus and Hypertension. Though there are numerous drugs for treating Type-II diabetes and hypertension, Biguanides and Angiotensin Converting Enzyme Inhibitors (ACEI) are used commonly by a wide section of patients. Pharmacokinetically these two drugs appear to be compatible, as Metformin hydrochloride (Metformin HCl) is not plasma protein bound and does not get metabolized in the liver, so interaction with Ramipril (having 73%plasma protein binding metabolized via liver) does not appear to be possible. Hence the combination would help in the treatment of Non Insulin Dependent Diabetes Mellitus (NIDDM) and hypertension and probably prevention of its associated macrovascular and microvascular complications. In the present study, prototype formulations containing these two drugs in a bilayer tablet were prepared and evaluated using standard recommended tests.

2. MATERIALS AND METHODS

Metformin HCl USP and Ramipril USP were gifts from Lupin Research Park, Pune, India Ltd; All other reagents and chemicals used were of pharmaceutical grade.

Preformulation studies

Physical and chemical properties of drugs alone and when combined with each other and excipients were investigated. FTIR and DSC were used for the analysis of drug-excipient compatibility. **Analytical methods for estimation of drug**s

U.V Spectroscopic Method was used to analyze Metformin HCl at wavelength of 233 nm and Ramipril analysed using HPLC method. Mobile Phase was mixture of Buffer (pH-3.0): Acetonitrile in the ratio of 50:50.

FORMULATION AND DEVELOPMENT

Preparation of Sustained Release Layer of Metformin HCl

The dose of Metformin HCl for sustained release was fixed as 800mg. The Metformin HCl (M-01 to M-07) sustained release layer was prepared by direct compression with various excipients. Metformin HCl, polymer and spray-dried lactose were mixed in various proportions as shown in Table-1

Preparation of Immediate Release Layer of Ramipril

The dose of Ramipril for immediate release was fixed as 200mg. Immediate release layer of Ramipril (R-01 to R-07) was prepared by direct compression. All the ingredients were taken as shown in Table-2 and mixed in geometric proportion.

Preparation of Bilayer Formulation

The quantity of Metformin HCl granules for the sustained release layer was compressed lightly using a single punch tableting machine (Cadmach machinery Co. Pvt. Ltd) equipped with 15mm round flat and plain punches. Over this compressed layer, the required quantity of Ramipril, the fast release layer was placed and compressed to obtain hardness in the range of 5 – 6 kg/cm2 to form a bilayer matrix tablet.

Characterization of Granules

Prior to compression, granules were evaluated for their characteristic parameters, such compressibility index and Hausner's ratio. [9]

Evaluation of tablets

The tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, friability, weight variation and drug content. [10, 11]

***In vitro* release studies for bilayered tablets**

Release of Metformin HCl was determined using a Dissolution Apparatus USP-II (Paddle) at 100 rpm. The dissolution medium was 1000 ml of Phosphate Buffer pH-6.8. The samples were withdrawn at different time intervals and analyzed for Metformin HCl content using U.V Spectrophotometer. The percentage of Metformin HCl released was calculated.

Release of Ramipril was determined using a Dissolution Apparatus USP-II (Paddle) at 75 rpm. The dissolution medium was 500 ml of 0.1 M HCl. The samples were withdrawn at different time intervals and analyzed for Ramipril content using chromatogram. The percentage of Ramipril release was calculated. [11]

Stability studies

The optimized formulation of bilayer tablets, were packed in a butter paper and wrapped with aluminum foil. The initial drug content was evaluated. Then the formulations were charged for the accelerated stability studies in accordance with the ICH guidelines.

3. RESULTS AND DISCUSSION:

Uniformity of Weight

All the prepared Bilayer tablets of Ramipril and Metformin HCl were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ± 5%.

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 6.3 to 7.2 kg/cm^2. The friability values were found to be in the range of 0.65to 0.72 %.

Uniformity of drug content

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 97.16 to 102.6 percent (which was within the acceptable limits of ±5%.).

All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

FTIR Studies

The IR spectrum of Metformin, Ramipril HCl and Drug Excipients mixture was shown in **figure number 6sss**. In the present study, it has been observed that there is no chemical interaction between Metformin.HCL, Ramipril and the polymers used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Drug release studies

Among all formulations, RM9 shows better drug release of (99.32%) at the end of 12 hrs, when compared with all other formulations. So formulation RM9 selected as optimized formula.In the dissolution studies the combination of HPMC and hydroxyl ethyl cellulose polymers were showing better drug release up to 12 hrs.

Drug release kinetics

To know the drug release kinetics from these formulations, the dissolution data were subjected to different kinetic model such as Zero order and Higuchi kinetics model. The line of equations and regression coefficient of kinetic study for all the formulations are shown in table no.28 the regression coefficient was considered as main parameter to interpret release kinetics. from the above results obtained the drug release mechanism was found to be diffusion control.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation RM9 after 3 Months, for parameters like % drug release and assay values at various conditions(at 40^{0}C/ 75% RH) was observed as per ICH guidelines.

Formulation of bilayer tablets

Table 1: Formulation of sustained release layer with optimized formulation

S.NO.	INGREDIENTS	RM 1	RM 2	RM 3	RM 4	RM 5	RM 6	RM 7	RM 8	RM 9
1	Ramipril (mg)	10	10	10	10	10	10	10	10	10
2	Croscarmellose sodium (mg)	8	8	8	8	8	8	8	8	8
3	Microcrystalline Cellulose (mg)	79	79	79	79	79	79	79	79	79
4	yellow iron oxide(mg)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
5	Aerosil-200 (mg)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
6	Megnesium stearate(mg)	2	2	2	2	2	2	2	2	2
Total wt (mg)		100	100	100	100	100	100	100	100	100
7	Metformin.HCL (mg)	500	500	500	500	500	500	500	500	500
8	Methocel 40-101(mg)	50	100	-	-	-	-	50	50	-
9	Methocel k15m pcg	-	-	50	100	-	-	50	-	50
10	Methocel k4m	-	-	-	-	50	100	-	50	50
11	HEC natrosol 250L (mg)	50	50	50	50	50	50	50	50	50
12	Microcrystalline Cellulose (mg)	95	45	95	45	95	45	45	45	45
13	Iso Propyl Alcohol (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
14	Sodium Steryl fumarate(mg)	3	3	3	3	3	3	3	3	3
15	Talc (mg)	2	2	2	2	2	2	2	2	2
Total Wt (mg)		800	800	800	800	800	800	800	800	800

***R=optimised Ramipril formulation**

Evaluation of prepared bilayered tablets for post compression parameters

Table 2: Evaluation of post compression parameters for Bilayered tablets

Parameter	RM 1	RM 2	RM 3	RM 4	RM 5	RM 6	RM7	RM 8	RM 9
Weight variation	800±0.4	799±0.3	798±0.7	800±0.1	799±0.3	800±0.2	799±0.9	800±0.8	800±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	6.1±1.4	6±1.2	6±1.2	7±0.9	6.2±1.9	6.5±1.7	6.3±1.5	6.4±1.6	6.9±1.4
Friability (%)	0.15±0.2	0.19±0.23	0.14±0.19	0.17±0.26	0.12±0.22	0.19±0.1	0.14±0.4	0.17±0.5	0.11±0.7
Assay of Metformin	97.56	98.22	99.34	97.48	98.24	97.88	97.56	99.35	99.73
Assay of Ramipril	99.12	97.44	99.42	98.57	98.37	99.55	99.12	99.44	99.64

In-vitro dissolution studies:

Table No: 3 In-vitro dissolution data of bilayer tablets

Time (Hrs)	RM1	RM 2	RM 3	RM 4	RM 5	RM 6	RM 7	RM 8	RM 9
0	0	0	0	0	0	0	0	0	0
1	18.78	18.65	17.98	15.56	21.24	19.66	18.57	23.49	21.89
2	37.94	34.92	26.91	23.68	35.78	39.73	34.67	45.78	34.78
4	64.68	47.93	51.24	56.98	46.48	49.48	47.89	49.48	53.48
6	87.98	89.72	73.97	79.97	73.18	67.18	77.89	83.18	82.18
10	94.59	95.92	98.92	96.15	97.94	86.94	97.96	95.94	92.94
12	99.85	98.83	99.13	98.99	98.56	99.16	99.34	99.36	99.32

Drug release kinetics for optimized formulation:

Table 4: Drug Release Kinetics data of optimized formulation

S.NO	TIME (Hrs.)	LOG T	SQUARE ROOT OF TIME	%CR	%DRUG REMAINING	LOG %CR	LOG%DRUG RETAINED	CUBE ROOT OF %DRUG REMAINING
1	0	0	0	0	100	0	2	4.641589
2	1	0	1	21.89	78.11	1.340246	1.892707	4.274666
3	2	0.30103	1.414214	34.78	65.22	1.54133	1.814381	4.025257
4	4	0.60206	2	53.48	46.52	1.728191	1.66764	3.596499
5	6	0.778151	2.44949	82.18	17.82	1.914766	1.250908	2.611976
6	10	1	3.162278	92.94	7.06	1.968203	0.848805	1.918381
7	12	1.079181	3.464102	97.29	2.71	1.988068	0.432969	1.394194

stability studies

Table 5: Stability Studies data of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug content ± SD					
			METFORMIN			RAMIPRIL		
			25^{0}C/60 %	30^{0}C/75 %	40^{0}C/75 %	25^{0}C/60 %	30^{0}C/75 %	40^{0}C/75 %
1.	01	No Change	99.73±0.49	99.68±0.49	99.68±0.49	99.64±0.12	99.64±0.12	99.64±0.12

		e					
	30	No	99.52±	99.47±	99.46±	99.31	99.58	99.39
3.		Change	0.39	0.42	0.83	±0.37	±0.41	±0.34
		e						
	60	No	99.45±	99.32	99.55	99.24	99.46	99.73
5.		Change	0.81	±0.80	±0.45	±0.37	±0.32	±0.31
		e						
	90	No	99.22	98.94	99.71	99.10	99.21	99.81
7.		Change	±0.43	±0.73	±0.19	±0.91	±0.43	±0.99
		e						

Table 6: Comparison between in-vitro release data of optimized formulation before and after stability testing for 90 days stored at accelerated temp and humidity conditions

Time in hrs	% Cumulative drug release at **40^0C/75%**			
	day 1	**30 days**	**60 days**	**90 days**
1	21.89	21.85	21.84	21.84
2	34.78	34.72	34.72	34.71
4	53.48	53.45	53.45	53.44
6	82.18	82.17	82.15	82.15
10	92.94	92.90	92.88	92.88
12	99.32	99.31	99.30	99.29

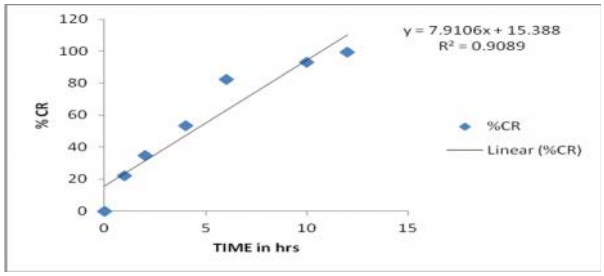

Fig 1: zero order plot of optimised formulation

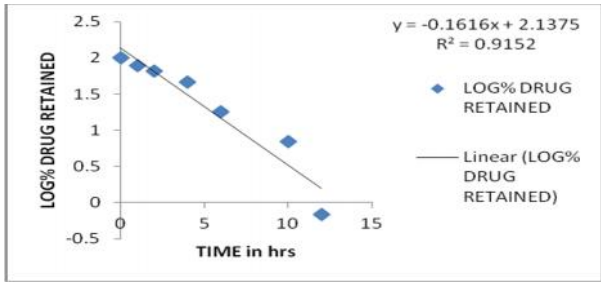

Fig 2: first order plot of optimised formulation

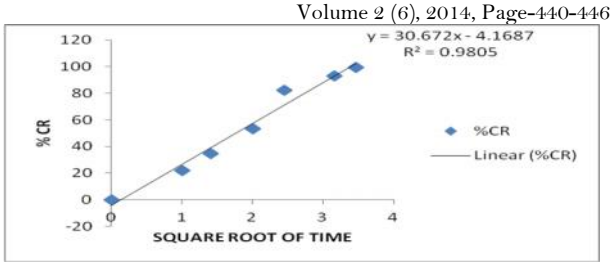

Fig 3: Higuchi plot of optimised formulation

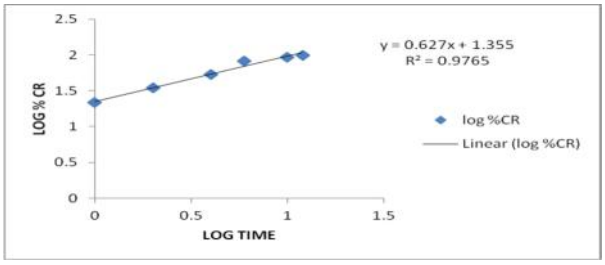

Fig 4: Kores Mayer Peppas plot of optimized formulation

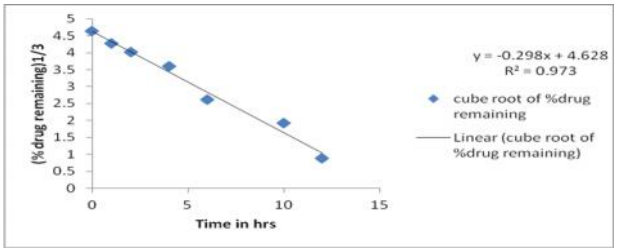

Fig 5: Hixson crowell plot of optimized formulation

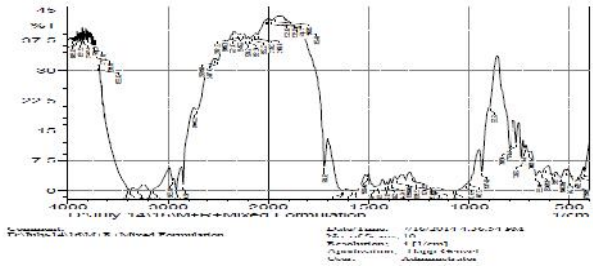

Fig 6 : FT-IR graph for Bilayer optimised formulation

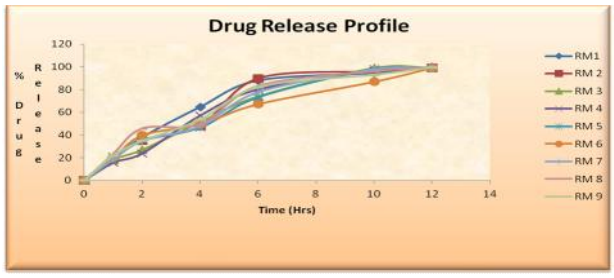

Fig 7: An overview of In-vitro dissolution Profiles for Bilayer tablet of all formulations

4. CONCLUSION

Considering the prevalence of diabetic hypertension as well as the prescribing pattern of drugs in patients

suffering from such complications, it is apparent that anti diabetic and anti hypertensive drugs seem to be potential candidates for incorporating in a combination product. The Physical drugs-excipients compatibility studies, FTIR revealed that there was no interaction between Metformin HCl, Ramipril and excipients used in the preparation of tablets. The bilayer tablets were prepared by direct compression technique in which Metformin HCl was compressed as sustained release layer with the help of different controlled release polymers Ramipril was present as the immediate release layer with different concentrations of super disintegrants. The bilayer tablets prepared were found to be within the official limits with respect to hardness, thickness, weight variation, drug content and friability. The *in vitro* studies of formulations were studied. The cumulative percentage drug release of Metformin HCl from the formulation containing combination of HPMC K4M Methocel 40- 101, Methocel K 15 M PCG and Methocel K 4 M was found to be identical when compared to the marketed tablet. The *in vitro* studies of formulations showed the identical cumulative percentage drug release of Ramipril containing 5% Cross Carmellose Sodium (Ac-disol) when compared to the marketed tablet.

The optimized tablets showed no changes after exposing to accelerated conditions for a period of one month with respect to physical characteristics. The drug content of Metformin HCl in the formulation was well within the limits for a period of one month and showed no degradation, but the drug content of Ramipril was not found within the limits. The drug content of marketed tablet of Ramipril was also found to be less. The degradation of Ramipril was found to the same extent as marketed tablet.

In conclusion, the present study demonstrated the successful formulation and evaluation of an anti diabetic and anti hypertensive in a single dosage form.

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