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Original Article

Development and Characterization of Bilayer Tablets Containing Metformin Hydrochloride in Sustained Release Layer and Atorvastatin Calcium in Immediate Release Layer

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Abstract

Diabetes, being one of the most prevalent disease in India, accounts for several other complications like development of atherosclerosis, hypertension and many other physiological complications which cannot be treated using single drug therapy. The low compliance and high cost are the major hindrance blocks for multiple drug therapy. The main aim of present work is to develop an optimized bilayer tablets of metformin hydrochloride and atorvastatin calcium for overcoming the problem associated with multiple drug therapy. The prepared tablets were evaluated for uniformity of weight, friability and drug release characteristics. The stability studies revealed that developed tablet can be stored at room temperature.

Keywords: Bilayer tablet, diabetes, optimization, multiple drug therapy .

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1. Introduction

Diabetes is a disease noted as one of the leading causes of death and disability worldwide. India has highest number of diabetic patients in the world. Type II Diabetes constitutes more than 95% of diabetic patients in our country [1]. Diabetes mellitus is mainly caused by autoimmune beta cell destruction, genetic susceptibility, environmental factors, obesity etc. Chronic complications for Type II Diabetes mellitus include micro vascular (retinopathy, nephropathy and neuropathy) and macro vascular complications (hyperlipidaemia, hypertension, cardiomyopathy, stroke, ischemic cerebrovascular disease) [2].

The most common strategy used for diabetes mellitus management is the control of blood sugar level using single drug therapy. But Diabetes mellitus is strongly associated with coronary artery disease (CAD), especially with the progression of atherosclerosis. Recent studies have shown

that statin treatment is also beneficial in managing patients with diabetes mellitus, not only through their hypolipidemic effects, but also through a number of pleiotropic effects, which are able to control the multifactorial atherosclerosis observed in diabetes [3, 4]. Also it has been reported that higher blood glucose level impairs endothelial functions and promotes atherogenesis in diabetic patients.So, the combination of statin with antidiabetic drug is more beneficial in reducing the morbidity and mortality associated with diabetes [5, 6, 7]. But the low patient compliance and high cost are the main barriers for multiple drug therapy.

Tablets are most common, economic and reliable pharmaceutical dosage form so it is very much useful to formulate the tablet having extended release of the drug. Nowadays this extended release in tablets is achievable by formulating tablets containing two layers, one containing the immediate release layer and one containing the sustained release layer. Bilayer tablet can achieve the initial plasma concentration which is achievable with conventional tablets and maintain for long time as sustained release tablets. Such tablets increase patient compliance. They also allow for controlling and modulating the dissolution and release characteristics of drug [8, 9].

For lowering hyperlipidaemia first line drug is atorvastatin and that for hyperglycaemia is metformin. So keeping in view the hyperlipidaemia complication with diabetes, the present work was undertaken to develop a bilayer tablet containing atorvastatin as immediate layer and metformin as sustained layer of bilayer tablet.

2. Experimental Work

Design and development of bilayer tablet:

Bilayer tablet was prepared by wet granulation technique. Immediate and sustained layer granules were prepared by keeping in view GMP-way. The ingredients of both layers were mixed separately and the wet mass obtained after the addition of binder was passed through the sieve to obtain granules. These granules were further dried using tray dryer. The glidant was added to dried granules and then compressed in bilayer compression machine (27 Station CADMACH, Ahmedabad India) using punch 18.5 X8 mm and thickness 6.0±0.2mm to form caplet shaped tablets.

Optimization:

Optimization is a phenomenon of finding the best possible composition or operating conditions. It is the implementation of systematic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions.

The granules of Metformin Hydrochloride having different composition (table 1) were prepared and evaluated. Similarly, the granules of Atorvastatin having different composition (table 2) were prepared and evaluated for finding out the best ratio of drug and excipients.

Evaluation of tablets:

Description:

Bilayer tablets were examined under magnifying lens for their surface characteristics like shape colour etc. [10, 11]

Metformin Hydrochloride Sustained Release Layer (Layer-1)								
Sr. No.	Ingredients	F-1	F- 2	F- 3	F- 4	F-5	F-6	F-7
1	Metformin HCl	502.76	502.76	502.76	502.76	502.76	502.76	502.76
2	Acrypol 974-P	-	45	55	59	62	64	64
3	Stearic acid	-	-	-	50	50	50	50
4	IPA	-	75	100	112	118	120	125
5	Magnesium Stearate	16	16	16	16	16	16	16
6	Average weight of layer-I	757.76	757.76	757.76	757.76	757.76	757.76	757.76

Table 1: Composition of different granules of metformin hydrochloride

S. No	Ingredients	F-1	F- 2	F- 3	F- 4	F-5	F-6	F-7
1	Atorvastatin calcium	10.34	10.34	10.34	10.34	10.34	10.34	10.34
2	Calcium carbonate	37.84	37.84	37.84	37.84	37.84	37.84	37.84
3	Lactose monohydrate	45.00	44.56	43.60	43.00	42.75	42.60	42.53
4	Croscarmellose sodium	5.2	5.2	5.2	5.2	5.2	5.2	5.2
5	Sodium ascorbate	0.043	0.043	0.043	0.043	0.043	0.043	0.043
6	HPC-L	3.00	3.00	3.00	3.00	3.00	3.00	3.00
7	Tween-80	-	-	0.5	0.6	0.68	0.70	0.70
8	Croscarmellose sodium	5.2	5.2	5.2	5.2	5.2	5.2	5.2
9	MCC PH-102	53.95	53.95	53.95	53.95	53.95	53.95	53.95
10	Magnesium stearate	1.35	1.35	1.35	1.35	1.35	1.35	1.35
11	Sunset yellow lake	0.2	0.2	0.2	0.2	0.2	0.2	0.2
12	Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
13	Average weight of layer-II	160.353	160.353	160.353	160.353	160.353	160.353	160.353

Table 2: Composition of different granules of atorvastatin calcium

Tablet dimensions:

The thickness and diameter of five randomly selected tablets was measured using calibrated Vernier callipers [10, 11]

Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked and hardness of the tablets was determined.

Weight variation:

The weight of twenty randomly selected tablets was measured and their deviation from average weight was calculated [10, 11].

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Weight variation:

The weight of twenty randomly selected tablets was measured and their deviation from average weight was calculated [10, 11].

Friability test:

Roche friabilator was used to measure the friability of the tablets. 10 tablets were weighed collectively and placed in the chamber of the friabilator. The friabilator was then rotated for 4 min. at 25 rpm. Tablets were removed and the intact tablets were again weighed collectively. The percent friability was determined using the equation 1.

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} X100$$

Where, W_1=weight of the tablet before test

W_2=weight of the tablets after test

***In vitro* dissolution study:**

The different parameters of dissolution studies were given below:

Atorvastatin calcium

Apparatus (Paddle)	:	Dissolution apparatus I IP
Medium	:	6.8 pH phosphate buffer
Volume	:	900ml
Speed	:	75 rpm
Time	:	30 minutes
Temperature	:	37^0 C ± 0.5^0C
λmax	:	246 nm

Metformin hydrochloride

Apparatus (Basket)	:	Dissolution Apparatus II IP
Medium	:	6.8 pH phosphate buffer
Volume	:	1000 ml
Speed	:	100 rpm
Time	:	1 hour, 3 hours & 10hours.
Temperature	:	37^0C± 0.5^0C
λmax	:	233 nm

To analyse the mechanism of the drug release from the dosage form, the data obtained was fitted into zero, first and Higuchi release model [12, 13].

Stability studies:

For determining the storage condition and shelf life, the stability studies were carried out according to ICH guidelines. The optimized tablets were stored at 40°C ± 2°C/75% ± 5%RH and the samples were withdrawn after 0, 1, 3 months.

Results and discussions

Design and development of bilayer tablet:

The prepared granules were evaluated for different physicochemical properties like flowability, bulk density, compressibility etc. The obtained results were shown in table 4 and 5. The results were well within the limits for all formulation granules but the best results were obtained with F-7 granules. The granules were compressed to form caplet shaped tablets. The parameters like hardness, thickness, weight variation and friability of tablets were determined (table 5).

***In vitro* dissolution studies:**

The dissolution studies were carried out for determining the drug release characteristics of tablet. The plot of % drug release with time for all formulations was shown in figure 2. The atorvastatin showed burst release whereas metformin had sustained released. After 20 minutes, the atorvastatin was completely released from formulation F-7 whereas for others drug release was less than 80 %. The steady state concentration of metformin for all formulation was reached within 2-3h. The *in vitro* release studies data was quantified to determine the release mechanism, to fit various mathematical models and to determine which the best-fit model was. The model studied was zero order, first order and Higuchi model. Values of regression coefficient (R^2) and release rate constant (k) for Metformin were shown in table 6. The correlation coefficient was found to be equal to one for first order model. So, the

developed tablets showed first order release behaviour.

Formulation	Loss on drying (%)	Bulk density (kg/m^3)	Tapped density (kg/m^3)	Angle of repose	Compressibility Index	Hausner's Ratio
F-1	0.85	0.334	0.437	$32^0 55''$	23.56	1.31
F-2	1.91	0.449	0.579	$29^0 35''$	22.4	1.29
F-3	2.08	0.412	0.515	$34^0 29''$	20.0	1.25
F-4	1.76	0.402	0.482	$37^0 46''$	16.5	1.20
F-5	2.73	0.337	0.525	$32^0 31''$	35.8	1.15
F-6	1.98	0.332	0.570	$29^0 45''$	29.3	1.41
F-7	1.54	0.434	0.5	$27^0 30''$	13.2	1.15

Table 3: Evaluation results of metformin hydrochloride granules

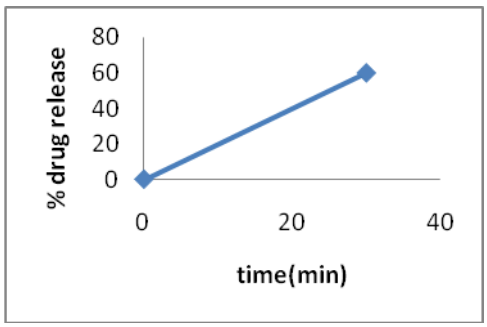
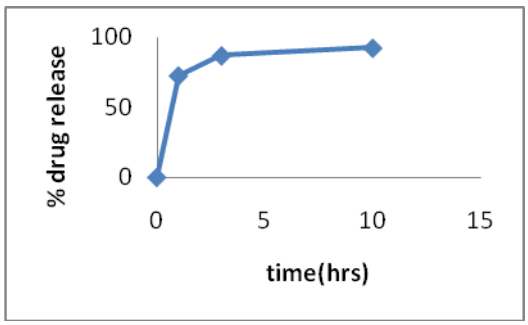
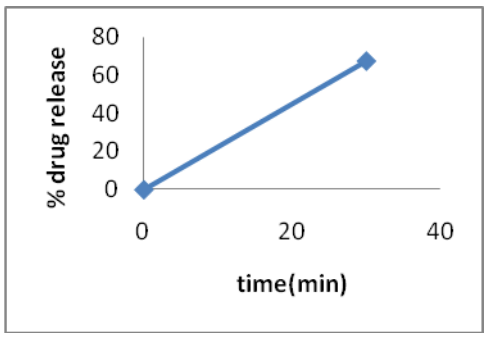
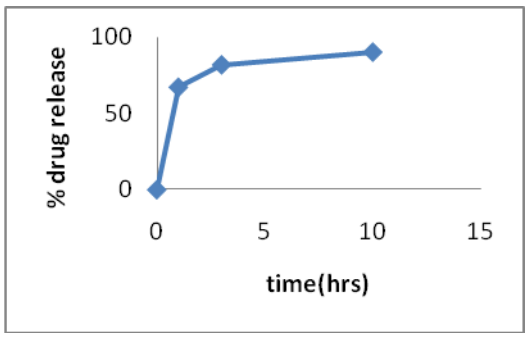
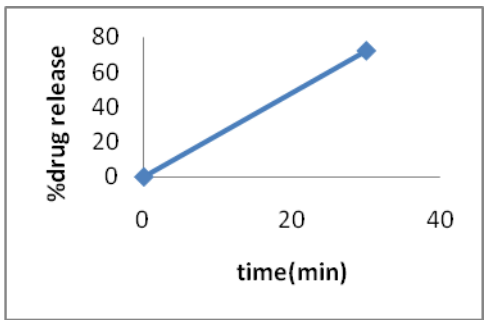
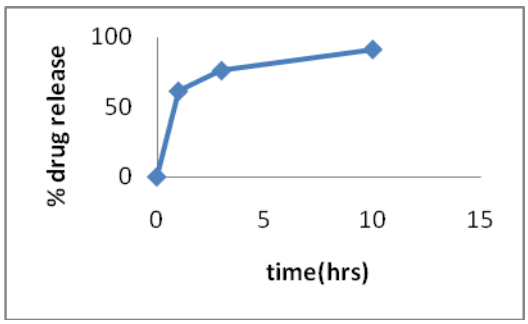
Formulation	Loss on drying (%)	Bulk density (kg/m^3)	Tapped density (kg/m^3)	Angle of repose	Compressibility Index	Hausner's Ratio
F-1	2.62	0.410	0.575	$35^0 53''$	28.6	1.40
F-2	2.82	0.482	0.684	$31^0 19''$	29.5	1.42
F-3	4.31	0.376	0.579	$35^0 18''$	35.0	1.54
F-4	2.52	0.472	0.604	$33^0 3''$	21.8	1.28
F-5	2.31	0.537	0.703	$30^0 23''$	23.6	1.31
F-6	3.73	0.5	0.789	$26^0 25''$	36.6	1.57
F-7	1.28	0.561	0.637	$27^0 50''$	11.9	1.13

Table 4: Evaluation results of atorvastatin calcium

S. no	Tests	Specifications	F-1	F-2	F-3	F-4	F-5	F-6	F-7
1	Description	White/yellow colour, Caplet shape	Complies	Complies	Complies	Complies	Complies	Complies	Complies
2	Average weight (mg)	872.1-963.9	852	875	899	890	950	913	929
3	Weight variation	±5%	2.1%	1.23%	2.6%	2.1%	2.4%	3.2%	1.8%

4	Thickness (mm)	5.8-6.2 mm	6.17	5.88	5.92	6.24	5.84	6.23	6.19
5	Hardness (kg/cm^2)	8.0-12.0 kg/cm^2	9.3	11.5	10.9	10.2	9.5	11	9.7
6	Friability (%w/w)	Not more than 0.8%	0.24	0.56	0.55	0.15	0.09	0.1	0.08

Table 5: Tablets evaluation

Formulation	Atorvastatin Calcium	Metformin hydrochloride
F-1		
F-2		
F-3		

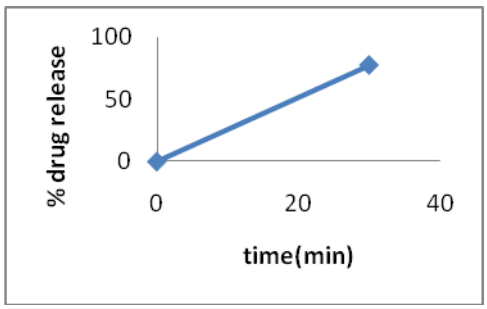
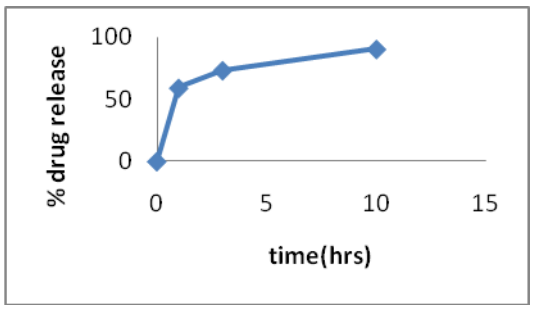
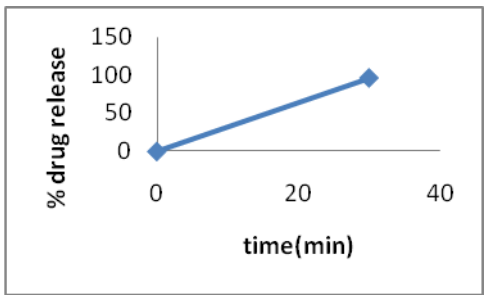
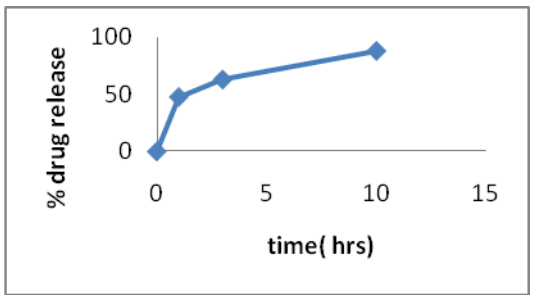
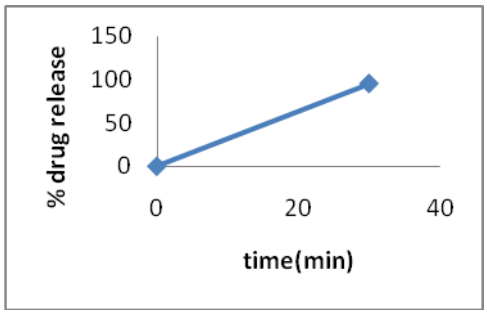
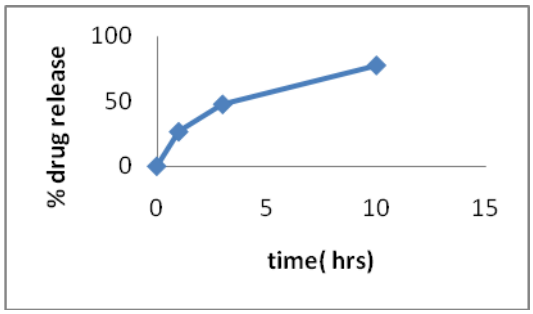
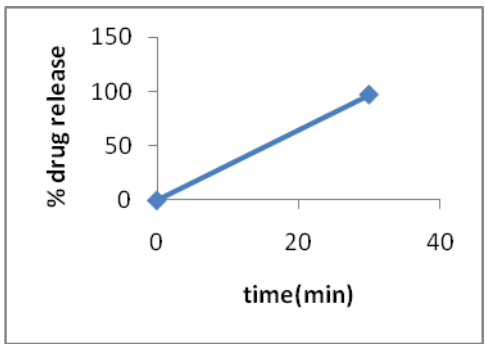
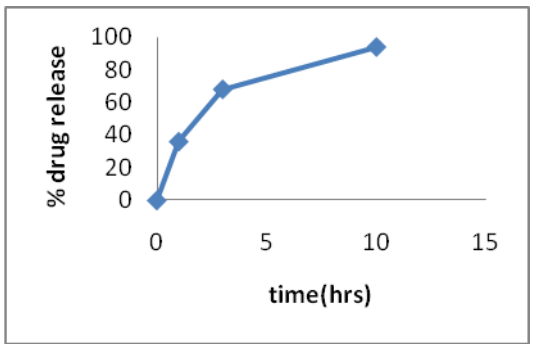
F-4		
F-5		
F-6		
F-7		

Figure 1: Plots of percent drug release with time

Sr. No.	Zero order		First order		Higuchi	
	R^2	K	R^2	K	R^2	K
F-1	0.784	7.981	0.987	1.311	0.605	0.651
F-2	0.569	7.023	0.976	1.415	0.685	0.604
F-3	0.789	6.236	0.919	1.256	0.712	0.984
F-4	0.802	7.025	0.948	1.480	0.601	0.658
F-5	0.768	6.952	0.926	1.259	0.611	0.679
F-6	0.856	6.325	0.956	1.306	0.625	0.612
F-7	0.791	7.001	0.997	1.562	0.712	0.603

Table 6: Model fitting

Tests	Limits	Initial Result	1 Month Result	2 Month Result	3 Month Result
Appearance	Yellow/white, caplet shaped bilayer tablets	No change	No change	No change	No change
Average weight (mg)	872.1-963.9 mg	910	910	908	907
Hardness (kg/cm^2)	8.0-12.0	9.3	9.3	9.5	10.0
Thickness (mm)	5.8-6.2	6.0	6.02	6.09	6.12
Dissolution: Atorvastatin	NLT 80% of the labelled amount dissolved in 30min	98.7 %	97.25 %	96.23 %	95.4 %
Metformin					
1 h	Between 25.0- 50.0%	31.5 %	33.4 %	37.2 %	38.1%
3 h	Between 45.0- 75.0%	71.9 %	72.5 %	72.9 %	73.2%
10 h	NLT 80%	94.6 %	94.9 %	95.2 %	96.4%

Table 7: Stability studies

Of all the developed batches, the results of F-7 were found to be within desired specifications and hence selected for stability studies.

Stability studies:

The purpose of stability testing was to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-

lives. The results of stability studies were shown in table 7. All the evaluated parameters of selected formulation F-7 were found to be satisfactory and within specifications. So, the optimized formulation can be safely stored at room temperature.

Conclusion

The optimized bilayer tablets of metformin and atorvastatin were successfully developed. The developed tablets can be stored at room temperature with no compromise in potency and efficacy.

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