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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE COMBINATION TABLET FOR CARDIOVASCULAR DISEASES

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ABSTRACT: Obesity is known to have significant impact on physical and psychological health related issues in many countries. Although researcher has shown good results achieved by combine dietary, exercise and behavioral therapy interventions, but it needs multi-drug at different levels of treatment lead to patient non-compliance. Therefore, combination therapy of Atorvastatin Calcium, a lipid lowering agent and Bisoprolol Fumarate, an antihypertensive agent was preferred for obesity treatment. The present research work was envisaged to develop immediate release tablet of Atorvastatin Calcium and Bisoprolol Fumarate by direct compression method to minimize dose-dependent side effect and improve patient compliance for obese people. The physical parameters were carried out as per standard USP procedures. *In vitro* dissolution studies were carried out in USP dissolution apparatus type II, using pH 1.2 HCl buffer. The formulation that showed more than 90% release was considered to be optimized formulation of combination tablet. Study reveals that combination of beta-blocker and statins were good candidate for blood pressure and lowering lipoproteins in obese patient and may increases patient compliance by reducing the multi dosage form therapy and prescription costs.

KEYWORDS: Combination tablet, Atorvastatin Calcium, Bisoprolol Fumarate, hypertensive, dyslipidemia.

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INTRODUCTION

There is a constant risk of obesity in various countries, which leads to many other risk factors related to heart and other major organs, due to fat deposit. Various problems related to Obesity are Hyperlipoproteinemia, Hypercholesterolemia, Atherosclerosis, Hypertension, Diabetes, Cardiovascular diseases etc. These disorders or diseases require multidrug treatments at various time periods, which can lead to patient non-compliance[1]. To improve patient compliance and improve bioavailability of drugs, combination of two or more drugs in the form of tablets or capsules were formulated. The combination of a beta-blocker and cholesterol lowering agent drugs with acceptable adjuvants is a better method of treatment of obesity[1][2]. Atorvastatin Calcium, a lipid lowering

agent, is a HMGCoA inhibitor which is a rate limiting step in cholesterol synthesis and it belongs to Class II compound of BCS Classification. Bisoprolol Fumarate is known to have a positive effect on various cardiovascular diseases, especially hypertension. Bisoprolol Fumarate is also said to suppress atrial fibrillation. Bisoprolol Fumarate belongs to Class I of the BCS Classification. According to literatures, extensive works have been done on individual drugs, but not as a combination of these two drugs using different superdisintegrants, as immediate release formulations[3][4]. Hence, Atorvastatin Calcium and Bisoprolol Fumarate, were considered for formulation of immediate release tablet, in order to reduce total dose of drug needed in a day and also dosing frequency. In this study, various formulations for the combination therapy of Bisoprolol Fumarate and Atorvastatin Calcium were carried out with varying superdisintegrant concentrations and all the formulations were subjected to drug release studies and further fitted to various kinetic models[5]. Finally formulation was optimized based on drug release studies.

TABLE I - PHYSICOCHEMICAL PARAMETERS OF ATORVASTATIN CALCIUM AND BISOPROLOL FUMARATE

Physicochemical Parameters	Atorvastatin Calcium	Bisoprolol Fumarate
Pharmacodynamics	Selective, competitive HMG-CoA reductase inhibitor.	Competitive, cardioselective β1-adrenergic antagonist. Lower the heart rate and blood pressure.
Mechanism of action	HMG-CoA reductase is in control of converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, Atorvastatin Calcium, inhibits the hepatic enzyme, which reduces hepatic cholesterol levels.	Selectively blocks stimulation of β1-adrenergic receptors in heart and vascular muscle, which reduces heart rate, cardiac output, blood pressure and reflex hypotension.
Absorption	Rapid absorption after oral administration with maximum plasma concentrations achieved in 1 to 2 hours.	Well absorbed, bioavailability more than 80%. absorption not affected by food.
Half life	14 hours	9-12 hours
Volume of Distribution	381 Litres	3.51 Litres/Kg
Protein Binding	>98% bound to plasma proteins	Approximately 30% bound to serum proteins.
Metabolism	CYP3A4 engages in the metabolism of Atorvastatin calcium	50% primarily metabolized by CYP3A4 to inactive metabolites.
Route of Elimination	After hepatic metabolism eliminated in bile.	50% dose administered, eliminated unchanged in urine, with remainder appearing as inactive metabolites.

MATERIALS AND METHODS

Atorvastatin Calcium and Bisoprolol Fumarate were received as a gift sample from Amoli Organics Pvt. Ltd., Vadodara and Mangalam Drugs, Mumbai respectively. Other chemicals used were of analytical grade.

Precompression studies:

Precompression studies were performed, to check drug-drug and drug-excipient interactions. Drugs proposed to be used, both alone and in combination along with excipients to be used, was filled into amber colored vials and sealed with rubber stoppers and placed in stability chamber (Remi Lab, Mumbai, India) for accelerated condition at 40 ± 2^{o}C and 75 ± 5 % RH for 30 days. IR spectra of the samples were obtained with FT-IR spectrophotometer (FTIR-8001, Shimadzu, Japan) and compared with the initial spectra of drugs.

Development of Atorvastatin Calcium and Bisoprolol Fumarate of Immediate Release Combination tablet:

Various composition of formulation trials are given in Table II. The corresponding amount of drugs were weighed and screened through 40 mesh sieve (425µ) belonging to ASTM (American Standard Test Sieves)[6][7]. Similarly, Microcrystalline Cellulose, Lactose and other ingredients were also weighed and passed through 40 mesh sieve. The sifted powders were transferred into a polybag and sealed properly. The contents of the polybag were mixed thoroughly for 5 minutes. After each round of mixing the contents of the bag were passed through screen no.40. The blend was again mixed thoroughly in the polybag[8]. The blend was subjected to physical evaluation. The blend was compressed into tablets using 8-station rotary tablet compression machine (Kambert, 8 station, Ahmadabad) equipped with punches of beveled flat-face, 8mm diameter, a tablet weight of 230mg. The tablets were collected after compression for in-process testing (weight, hardness, and friability).[9]

TABLE II - FORMULATION TRIALS OF ATORVASTATIN CALCIUM AND BISOPROLOL FUMARATE COMBINATION TABLET

Ingredients	**Quantity per tablet (mg)**				
	F1	**F2**	**F3**	**F4**	**F5**
Atorvastatin Calcium	10	10	10	10	10
Bisoprolol Fumarate	2.5	2.5	2.5	2.5	2.5
Microcrystalline cellulose	100.5	100	100	100	100
Lactose	111	110.5	110.5	109.5	107.5
Magnesium stearate	2	2	2	2	2
SLS	2	2	3	3	4
Sodium starch glycolate	2	3	2	3	4
Tablet fill weight **230mg**					

Figure I - Atorvastatin Calcium and Bisoprolol Fumarate IR Tablets

Evaluation of Blend:

Lubricated blend of Atorvastatin Calcium and Bisoprolol Fumarate IR tablets, prior to compression, was characterized for physical parameters like angle of repose, bulk density and tapped density and percentage compressibility.[10]

Evaluation of Tablets:

Compressed tablets properties, like, Thickness (Digital Vernier Caliper, Mitutoyo Corp., New Delhi), Hardness (Pfizer hardness tester, Pfizer, Haryana), Friability (Inlab equipments Pvt. ltd., Madras), Disintegration time (Inlab equipments Pvt. ltd., Madras) and Weight Variation was evaluated. The content of Atorvastatin Calcium and Bisoprolol Fumarate in IR tablets was determined as per the procedure in USP.[11]

Calibration Curve for Atorvastatin Calcium:

Preparation of Stock Solution :- 50mg of Atorvastatin Calcium was weighed and dissolved in 50ml of Methanol in a 50ml volumetric flask. (Concentration 1mg/ml)

10ml of stock solution was diluted to 100ml with Methanol to get a concentration of 10µg/ml, and scanned in the range of 200 - 400nm and the λ_{max} was found to be 241nm.[12]

From standard stock solution,2.5ml was withdrawn and diluted to 25ml with methanol in a 25ml volumetric flask. From the above solution, 0.5ml, 1ml, 1.5ml, 2ml, and 2.5ml was withdrawn and added to 10ml volumetric flask and volume made up with Methanol to obtain concentration in the range of 5-25µg/ml. The absorbance was recorded at 241nm.

Calibration Curve for Bisoprolol Fumarate:

Preparation of Stock Solution :- 5mg of Bisoprolol Fumarate was weighed and transferred to a 100ml volumetric flask, and dissolved using about 50ml of distilled water and the volume made up to 100ml with distilled water. (Concentration 50µg/ml)

The above stock solution itself was used to estimate the λ_{max} of Bisoprolol fumarate scanning from a range of 200 to 400nm and it was found to be 222nm.[13]

From Standard stock solution, 1,2,3,4 and 5ml solution was pipetted out into 10ml volumetric flasks and the volume made up with distilled water, to obtain final concentration of 5,10,15,20 and 25µg/ml. The absorbance was recorded at 222nm.

***In vitro* drug release:**

In vitro dissolution studies was carried out as per USP specifications. The USP dissolution test apparatus type II (Electrolab, TDT 08L, USP) at 75 rpm was used for studies[14]. 900ml of 0.1N HCl was used as the dissolution medium at 75rpm maintained at a temperature of 37.5°c ± 0.5°c. Aliquots of sample were withdrawn at specific time intervals, filtered and replaced with buffer to maintain sink condition[15]. The absorbance of the filtered solution were measured at 222nm and 241nm for Bisoprolol fumarate and Atorvastatin calcium respectively for drug content determination.

Assay of Bulk drug:

20mg of Atorvastatin Calcium and 5mg of Bisoprolol Fumarate were accurately weighed and transferred into a 100ml volumetric flask, and dissolved in 50ml of methanol and the volume was made up with the same. Appropriate dilutions were made using methanol to obtain concentrations of 20µg/ml of Atorvastatin Calcium and 10µg/ml of Bisoprolol Fumarate[16][17]. The resulting solutions were analyzed at wavelengths 241nm and 222nm respectively.

Assay of Formulated Tablet (Simultaneous Equation Method):

Twenty tablets having label claim of 10mg of Atorvastatin Calcium and 2.5mg of Bisoprolol Fumarate were weighed, their average taken and crushed into fine powder. The powder equivalent to 10mg of Atorvastatin Calcium and 2.5mg of Bisoprolol Fumarate was weighed accurately and transferred into 100ml volumetric flask and about 50ml of methanol was added and the flask was sonicated for 15-20 minutes. The solution was filtered through whatman grade filter paper and the volume was made up to 100ml with methanol. From this solution, appropriate dilution was made to obtain concentration of 20µg/ml of Atorvastatin Calcium and 10µg/ml of Bisoprolol Fumarate[18]. The resulting solution was analyzed at the wavelengths 241nm and 222nm.

Drug Release Kinetics Model:

Mathematical models of release kinetics studies plays a important role as it provides mechanism of drug release and more general guidelines for the development of various systems. Such models can be used for optimization of release kinetics, to deduct mass transport mechanisms, to design new drug delivery systems based on general release expressions[19].

The mathematical models was used to evaluate the mechanism of drug release from the tablets and kinetics. Based on the correlation coefficient (r) value in various models, the model that best fits the release data was selected. The model giving the high 'r' value was considered as the best fit of the release data. Goodness of fit test is the criterion for selecting the best fit model

The mathematical models used were:[20]

i. Zero Order Kinetics Model
ii. First Order Kinetics Model
iii. Higuchi Model
iv. Korsmeyer-Peppas Model

RESULTS AND DISCUSSIONS

Precompression Studies:

The FT-IR spectra were compared of physical mixture of drugs after 30 days of accelerated stability (Figures II, III and IV). The physical appearance of the samples was not changed and the spectras showed no additional peaks when compared to their individual IR spectrum. The physical mixture of drug with the excipients used also showed no interactions between them in the spectras.

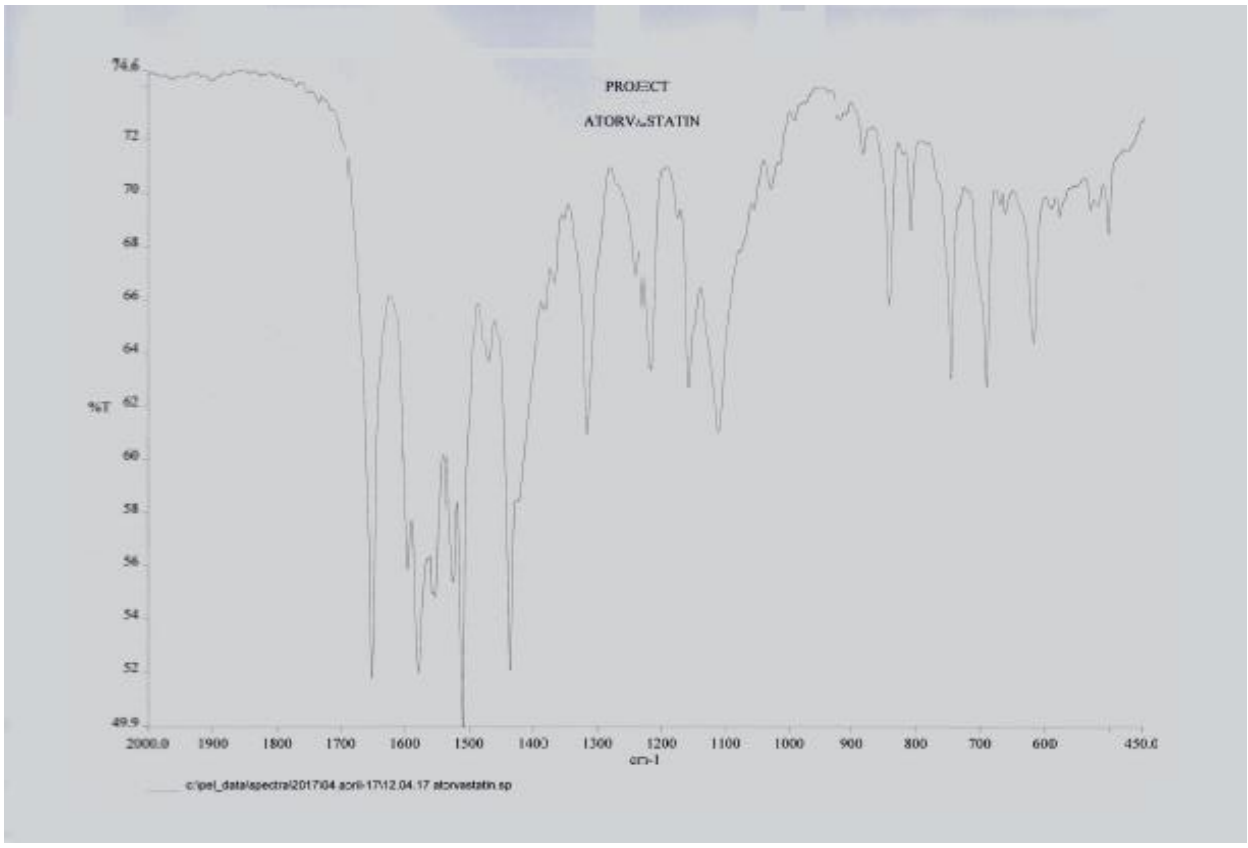

Figure II - FTIR spectra of Atorvastatin Calcium pure drug

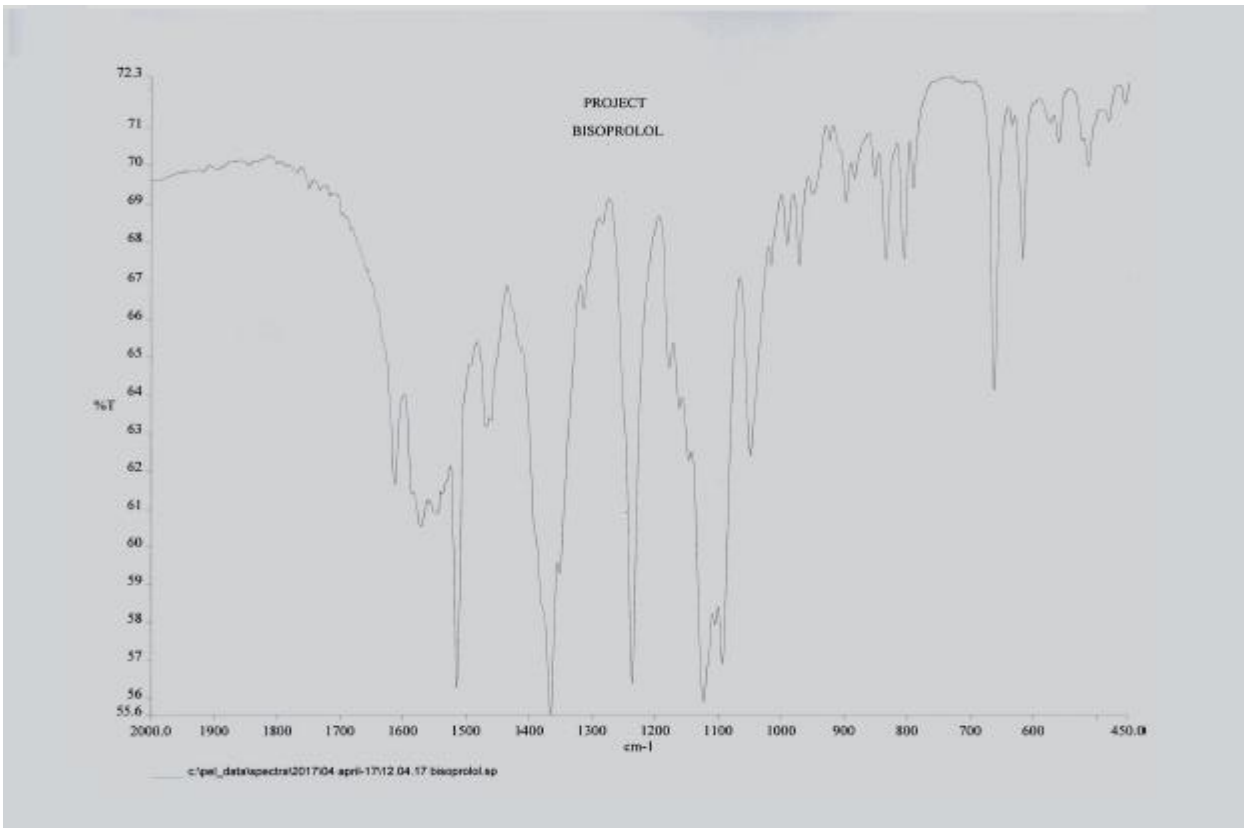

Figure III - FTIR Spectra of Bisoprolol Fumarate Pure drug

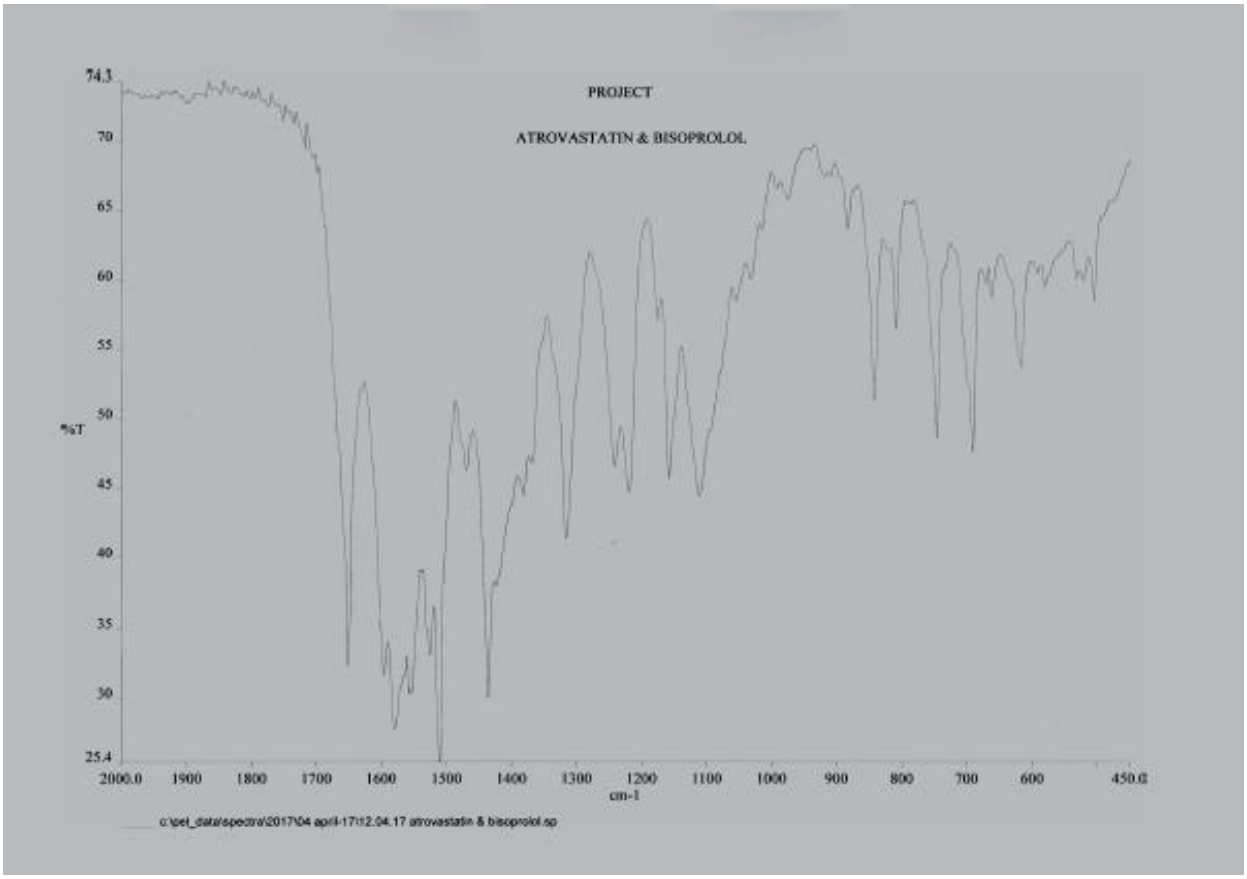

Figure IV - FTIR Spectra of Combination of Atorvastatin Calcium and Bisoprolol Fumarate

Blend Evaluation:

The powder blend thus prepared was evaluated and the results thus obtained were given in Table III.

TABLE III - BLEND CHARACTERIZATION OF ATORVASTATIN CALCIUM AND BISOPROLOL FUMARATE IR BLEND

FORMULATIONS	Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	31.25	0.40	0.45	12.5	1.12
F2	29.50	0.40	0.45	12.5	1.12
F3	28.95	0.43	0.50	15.9	1.16
F4	28.30	0.38	0.42	10.52	1.10
F5	30.45	0.41	0.47	14.63	1.14

Angle of repose for the powder blends of all the formulations were within the limits, to indicate good flow property. The bulk density of the powder blend of all formulations along with drugs and the excipients was found to be in the range of 0.38gm/ml to 0.43gm/ml, whereas tapped density was found to be in the range of 0.42gm/ml to 0.50gm/ml. From bulk density and tapped density values of Carr's index and Hausner's ratio was calculated. The value of Carr's index was found to be between 10.52 to 15.9. The value of Hausner's ratio was found to be between 1.10 to 1.16. All the above obtained values were within the specified limits which indicates good flow property and compressibility of the blend. Overall the blend showed good flow property which indicated better hopper flow and die fill and better compressibility.

Physical Evaluation of Tablets:

Table IV shows the results for the Physical evaluation parameters of the formulated tablets.

TABLE IV - EVALUATION OF ATORVASTATIN CALCIUM AND BISOPROLOL FUMARATE COMBINATION TABLETS

PARAMETERS	FORMULATIONS				
	F1	F2	F3	F4	F5
Weight(mg)	228.55	230.85	230.5	228.65	229.8
Diameter(mm)	8	8	8	8	8
Thickness(mm)	4	4	4	4	4
Hardness(N)	6	7	6	6	8
Friability(%)	0.25	0.27	0.24	0.26	0.24
Disintegration Time(min)	7	6.5	6	5	5

The weight variation of all the tablets were within the limits as specified in I.P (the limit should not exceed ±7.5), that implies that there is uniformity in powder flow. The thickness of all the formulations

was found to be uniform indicating good flow to the die during compression. Hardness for all the formulations was proper, which proves good tensile strength. Test for friability lies within the range of I.P. specifications, i.e. less than 1% indicating the formulations to have good physical strength. Disintegration time was found to be in the range of 5 to 7 minutes depending upon the concentration of the disintegrant added, and also was within the range of I.P. specifications for any conventional release tablets. Disintegration time of formulation F4 was found to be 5 minutes, which is more suitable for immediate release tablets as per specifications.

Calibration:

The absorbance for the calibration of Atorvastatin Calcium and Bisoprolol Fumarate are given in tables V and VI respectively. Their respective calibration curves are given in figures V and VI. The linearity range of Atorvastatin Calcium is 5-25µg/ml and the linearity range of Bisoprolol Fumarate is 5-25µg/ml.

Calibration Curve of Atorvastatin Calcium:

TABLE V: CALIBRATION CURVE OF PURE DRUG ATORVASTATIN CALCIUM

S.No	Concentration (µg/ml)	Absorbance
1	5	0.2389
2	10	0.4857
3	15	0.7108
4	20	0.9553
5	25	1.2204

Calibration Curve of Bisoprolol Fumarate:

TABLE VI: CALIBRATION CURVE OF PURE DRUG BISOPROLOL FUMARATE

S.No	Concentration (µg/ml)	Absorbance
1	5	0.2471
2	10	0.4561
3	15	0.7011
4	20	0.9751
5	25	1.2234

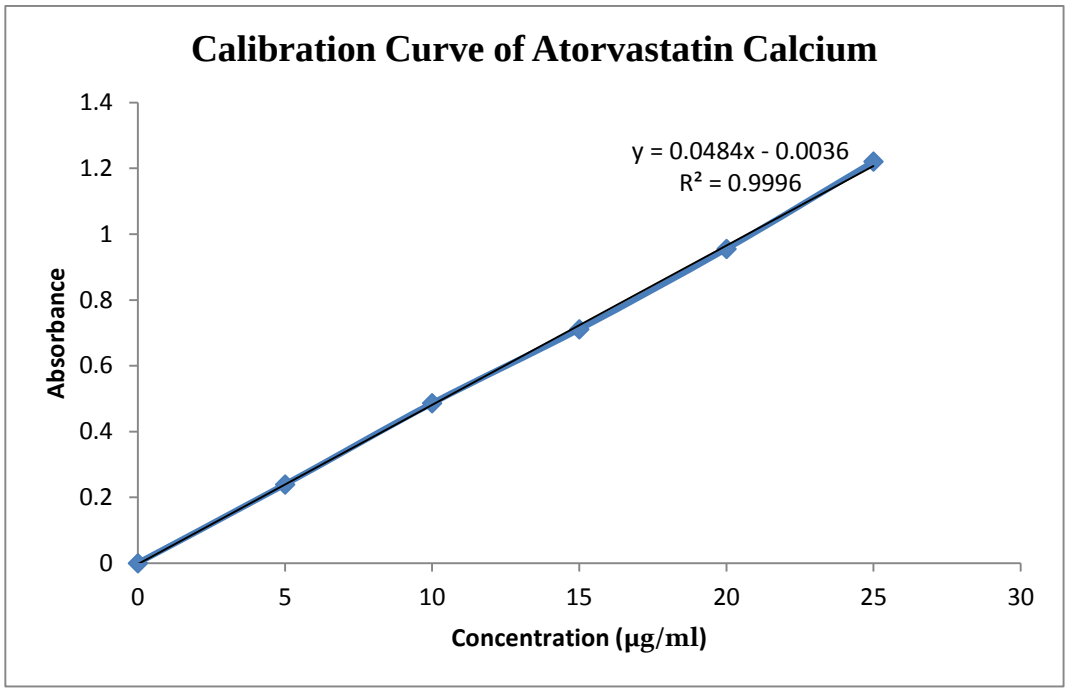

Figure V: Calibration Curve of Atorvastatin Calcium

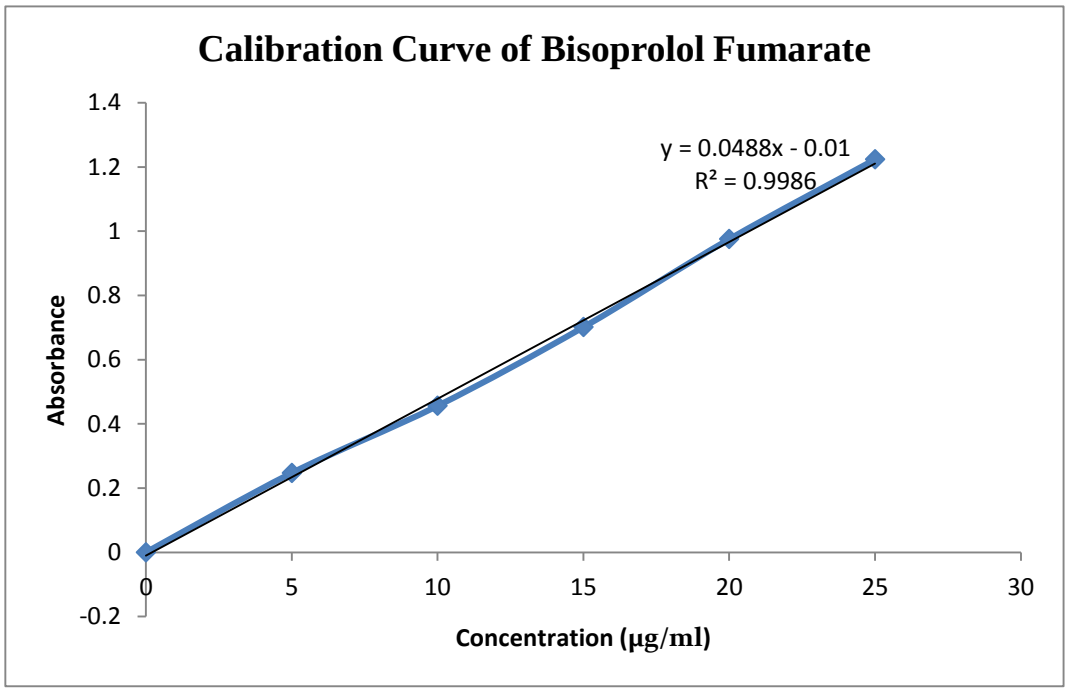

Figure VI: Calibration Curve of Bisoprolol Fumarate

***In Vitro* Drug Release:**

In vitro drug release study was conducted over a period of 60 minutes., all the formulations showed gradual increase in drug release. Table VII and VIII shows the Percent Drug release for Atorvastatin Calcium and Bisoprolol Fumarate respectively. Formulations F3 and F4 showed better drug release for both Atorvastatin Calcium and Bisoprolol Fumarate. Hence Formulations F3 and F4 showed quick

and better release as it contains highest percentage of disintegrant concentration. Figures VII and VIII show the graphical representation of percent drug released. Formulations F3 and F4 showed a drug release of 93.2% and 96.29% for Atorvastatin Calcium respectively and 91.25% and 92.01% for Bisoprolol Fumarate respectively and hence optimized as immediate release tablets.

TABLE VII - DISSOLUTION PROFILE OF ATORVASTATIN CALCIUM

TIME (min)	PERCENT DRUG RELEASED (%) (Atorvastatin Calcium)				
	F1	F2	F3	F4	F5
10	39.25	35.47	32.09	30.27	34.29
20	46.47	49.28	48.91	49.21	48.79
30	69.95	70.51	65.14	67.29	67.28
45	85.97	84.01	82.53	85.20	80.21
60	89.32	88.79	93.20	96.29	89.81

TABLE VIII- DISSOLUTION PROFILE OF BISOPROLOL FUMARATE

TIME (min)	PERCENT DRUG RELEASED (%) (Bisoprolol Fumarate)				
	F1	F2	F3	F4	F5
10	41.05	37.09	40.57	41.34	39.81
20	67.39	63.27	61.97	60.20	62.61
30	75.81	73.20	75.29	72.61	75.28
45	80.63	81.94	83.67	84.57	83.63
60	85.17	87.84	91.25	92.01	88.83

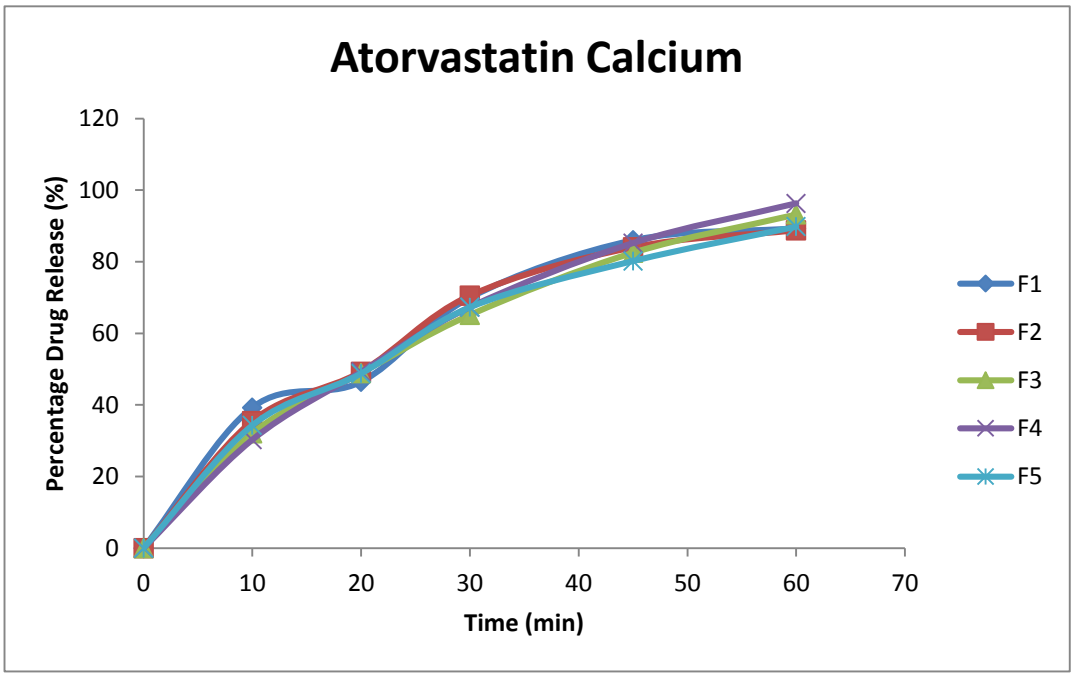

Figure VII - Percentage Drug Release of Atorvastatin Calcium in F1-F5

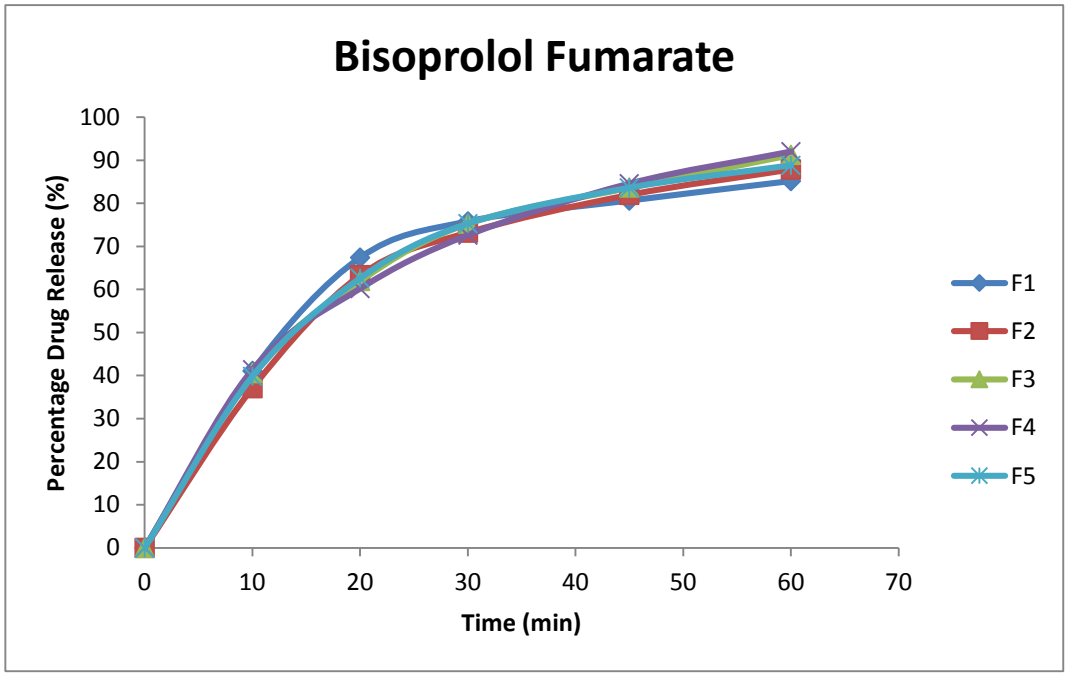

Figure VIII - Percentage Drug Release of Bisoprolol Fumarate in F1-F5

Assay of Bulk Drug and Formulated Tablet:

The assay of the formulated tablets was performed by Simultaneous equation method. The assay of Bulk Drug (20mg Atorvastatin Calcium and 5mg of Bisoprolol Fumarate) and that of Formulated tablets (10mg Atorvastatin Calcium and 2.5mg of Bisoprolol Fumarate) was analyzed using UV Spectroscopic method at the respective wavelengths.

The percent drug content in the Bulk drug was found to be 100.84% and 101.03% for Atorvastatin Calcium and Bisoprolol Fumarate respectively. The drug content of Formulated tablet was found to be 98.1% and 99.7% for Atorvastatin Calcium and Bisoprolol Fumarate respectively.

Drug Release Kinetics:

The drug profiles from the combination tablets were fitted into various mathematical kinetic models.. The values of correlation coefficient (r^2) and release rate constants (K) from different models for the prepared tablets are given in Tables IX and X for Atorvastatin Calcium and Bisoprolol Fumarate respectively. From the data of correlation coefficient and rate constant values, the drug release from all the formulations, was found to obey the first order release followed by the Korsmeyer Peppas kinetic model.

TABLE IX- CORRELATION COEFFICIENT (r^2) & RATE CONSTANT (K) VALUES OF ATORVASTATIN CALCIUM

KINETIC MODEL		F1	F2	F3	F4	F5
ZERO ORDER	K	1.0928	1.0997	1.2262	1.3193	1.1156
	r^2	0.9181	0.9208	0.9726	0.9663	0.9575
FIRST ORDER	K	0.0167	0.0149	0.0089	0.0096	0.0163
	r^2	0.9633	0.9347	0.9102	0.892	0.9942
HIGUCHI	K	12.208	12.393	13.668	14.741	12.48
	r^2	0.9446	0.9642	0.9962	0.9946	0.9878
PEPPAS	K	1.0463	0.5441	0.6081	0.6588	0.5543
	r^2	0.8949	0.9745	0.9965	0.9933	0.9897

TABLE X - CORRELATION COEFFICIENT (r^2) & RATE CONSTANT (K) VALUES OF BISOPROLOL FUMARATE

KINETIC MODEL		F1	F2	F3	F4	F5
ZERO ORDER	K	0.7718	0.9239	0.9514	0.9797	0.9156
	r^2	0.7704	0.8497	0.8963	0.9355	0.8632
FIRST ORDER	K	0.0111	0.0137	0.0162	0.0127	0.0144
	r^2	0.9107	0.9762	0.9938	0.999	0.9802
HIGUCHI	K	8.9934	10.623	10.863	11.059	10.503
	r^2	0.8623	0.924	0.9598	0.9827	0.9366
PEPPAS	K	0.3945	0.4715	0.45	0.4496	0.391
	r^2	0.8914	0.9318	0.9673	0.9879	0.8398

CONCLUSION

The combination tablet of Atorvastatin Calcium and Bisoprolol Fumarate was formulated successfully by direct compression method. Direct compression method is more feasible and less time consuming. Combination tablets were formulated to increase patient compliance and prevent intake of multiple drug therapy. Precompression parameter confirmed that, there was no interaction observed between drug-drug and drugs with various excipients which was used in the development of the formulations. The values of angle of repose indicated satisfactory flow behavior. The prepared formulation were within the specifications as per USP for the post compression parameter. Maximum drug release was observed for formulation F3 and F4 in 60 minutes. Both formulations F3 and F4 can be considered for further studies and development of the formulation. The release exponent (n) was calculated to be close to 1 in both first order and korsmeyer peppas release kinetics. The mechanism

for drug release was found to be through first order release followed by Korsmeyer peppas drug release kinetic model (Table 9 and 10). Thus from the results obtained, it can be concluded that the immediate release tablets of 230 mg of Atorvastatin Calcium and Bisoprolol Fumarate has successfully developed. Further long term stability studies are required to establish stable tablet formulation and to establish its efficacy in the treatment of hyperlipoproteinemia and hypertension. The study resulted in developing a Atorvastatin Calcium and Bisoprolol Fumarate commercially by reducing formulation cost. Hence such tablets can be exploited for use in obesity treatment.

CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

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