IJPSR (2020), Volume 11, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 July 2019; received in revised form, 02 January 2020; accepted, 29 February 2020; published 01 June 2020

FORMULATION AND EVALUATION OF FIXED DOSE COMBINATION OF ATORVASTATIN CALCIUM AND AMLODIPINE BESYLATE IMMEDIATE RELEASE FILM-COATED TABLETS

Sonia Pahuja, Nancy Sharma and Prerna Sarup *

Swami Vivekanand College of Pharmacy, Banur - 140601, Punjab, India.

Keywords:

Atorvastatin calcium, Amlodipine besylate, Immediate release, Superdisintegrant and film coated

Correspondence to Author:
Dr. Prerna Sarup

Principal,
Swami Vivekanand College of Pharmacy, Banur - 140601, Punjab, India.

E-mail: psarup_pu@hotmail.com

ABSTRACT: The present research work was envisaged to develop immediate release film-coated tablets of a fixed-dose combination of Atorvastatin calcium and Amlodipine besylate used to treat the hyperlipidemia, angina pectoris, atherosclerosis, hypertension and symptoms of cardiac risk. Additionally, fixed-dose combination therapy of both drugs tends to provide a synergetic effect and reduce the pill burden. Immediate-release tablets are mostly recommended for fast upgrading drug delivery systems, and thus, an effort was made to improve the onset of action of the drug. The concept of formulating immediate-release tablets using superdisintegrants like CCS offers a suitable and practical approach to faster disintegration and dissolution characteristics. In the current investigation two methods were adopted namely direct compression and wet granulation for formulation development. Based on the drug content and dissolution results, the direct compression method was used for further study. The prepared dosage forms were also subjected to pre and post compression evaluations. The results of *in-vitro* drug release suggested that CF6 was the ideal formulation among all the other formulations. *In-vitro* drug release ATO (101.4%) and AMLO (100.3%) obtained within 30 min. The optimum concentration of superdisintegrant (CCS) was found to be 4.2% w/w in CF6 with disintegration time 21 sec. The best formulation (CF6) was made to undergo kinetic analysis followed by stability studies and shelf-life determination, which was found to be 22 months. For the protection of sensitive the drug from an external environment, the film coating method was also applied to ensure the stability of the developed formulation.

INTRODUCTION: The Oral route is one of the most sought-after routes for systemic effect due to its ease of ingestion, simple, safest, convenient, non-invasive, versatility and most importantly, patient compliance [1]. Tablet dosage forms are intended to be swallowed, disintegrate, and release their medicaments readily in the gastrointestinal tract [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2937-47

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2937-47

Immediate-release tablets are intended to disintegrate and release their dosage form with no special rate controlling features, such as special coatings and other techniques. Immediate-release tablets are those which disintegrate swiftly and get dissolved to release the medicaments [3]. An immediate release dosage form helps a manufacturer to diversify the market and simultaneously offering patients a convenient dosage form or dosage regimen [4].

The present investigation was commenced with an objective to develop a fixed-dose combination of immediate-release film-coated tablets of numerous cardiovascular diseases like hypertension, angina pectoris, and hyperlipidemia.

The formulation of two drug combination comprised of Atorvastatin calcium and Amlodipine besylate. The drug molecule Atorvastatin calcium is a potent blocker of HMG-CoA reductase which is an early rate limiting step in cholesterol biosynthesis which is indicated for treatment of broadly atherosclerosis, strokes, coronary artery diseases, hypercholesterolemia [5]. The drug molecule Amlodipine besylate is third generation dihydropyridine derivative of calcium channel blocker that prevents the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle which is indicated for the treatment of chronic stable angina pectoris, prinzmetal variant angina and hypertension [6]. This formulation also relates to producing additive and synergistic effect of Atorvastatin calcium and Amlodipine besylate, thereby these synergistic combinations are helpful in treating patients that are suffering from angina pectoris, atherosclerosis, hypertension, and hyperlipidemia.

A study reported that the rate and extent absorption of Atorvastatin and Amlodipine after the administration of a fixed-dose combination tablet has shown similar results as compared with single dose of each drug component agent [7]. In another study reported that the Amlodipine and Atorvastatin single pill formulation showed improved patients compliance and decreased cardiovascular events in hypertensive patients and managed triglyceride profile. Hence, single-pill formulation efficiently improve adherence and reduce prescription costs [8]. A new and improved suitable dosage form of drugs allows the manufacture to enhance the market exclusivity by offering a more convenient dosage regimen [9].

MATERIALS AND METHODS: Atorvastatin calcium, Amlodipine besylate, and all excipients were obtained as gift samples from Ind-Swift Ltd. Derabassi, Punjab.

Preformulation Studies:

Drug and Compatibility Studies by FTIR: Separately weighed amount of drug Atorvastatin calcium (ATO) and Amlodipine besylate (AMLO) (2 mg) was mixed with 300-400 mg of Potassium Bromide. Then the triturated samples Atorvastatin calcium and Amlodipine besylate was spread uniformly in a suitable die and then die was placed in hydraulic press and pressure (800 MPa) was applied to form a disc. The disc was mounted in the suitable holder of the detector in the FTIR spectrometer. The IR spectrum was recorded by scanning the wavelength 4000 to 650 cm^{-1}. Both the drug samples were compared with reference working standards. A similar procedure was followed for all relevant excipients used.

Preparation of Immediate Release Film-Coated Tablets by Direct Compression Method: In this method, powders mixture of excipients and API were converted into the powder blend by using a blender, and then it was compressed to formulate tablets. Further, tablet batches were loaded with conventional coating pan to prepare the immediate release film-coated tablets.

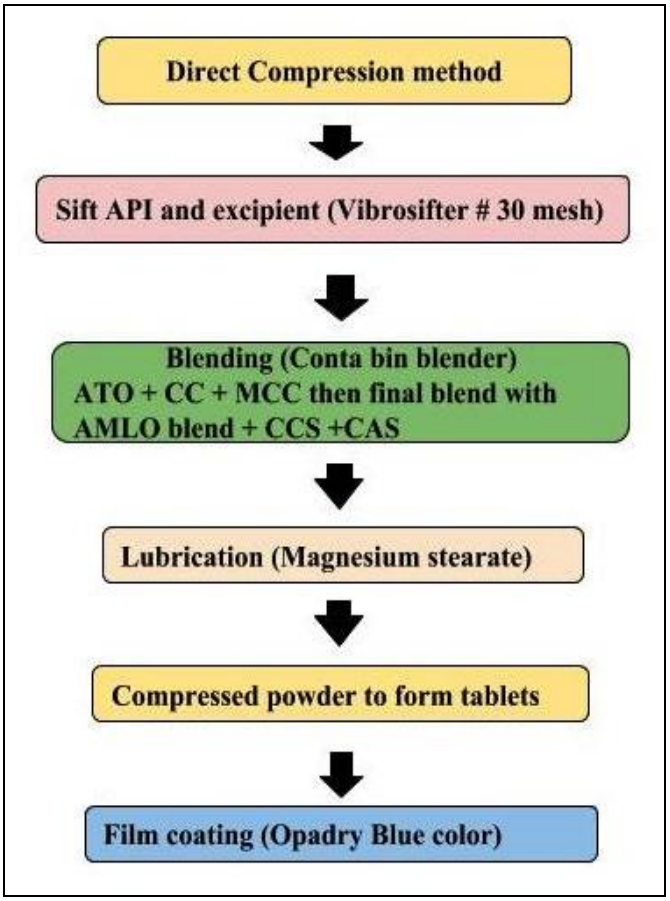

FIG. 1: FLOW CHART OF DIRECT COMPRESSION METHOD

Preparation of Immediate Release Film-Coated Tablets by Wet Granulation Method: In this method, a binder solution of HPMC and polysorbate 80 were prepared. Sifted material (API and excipients) were loaded in FBD, and granules were prepared with the help of binder solution.

Then dried granules were passed through 30# mesh sieve and mixed with fillers and lubricated with magnesium stearate which was then compressed into tablets. Then tablet batches were loaded in conventional coating pan to prepare the immediate release film-coated tablets.

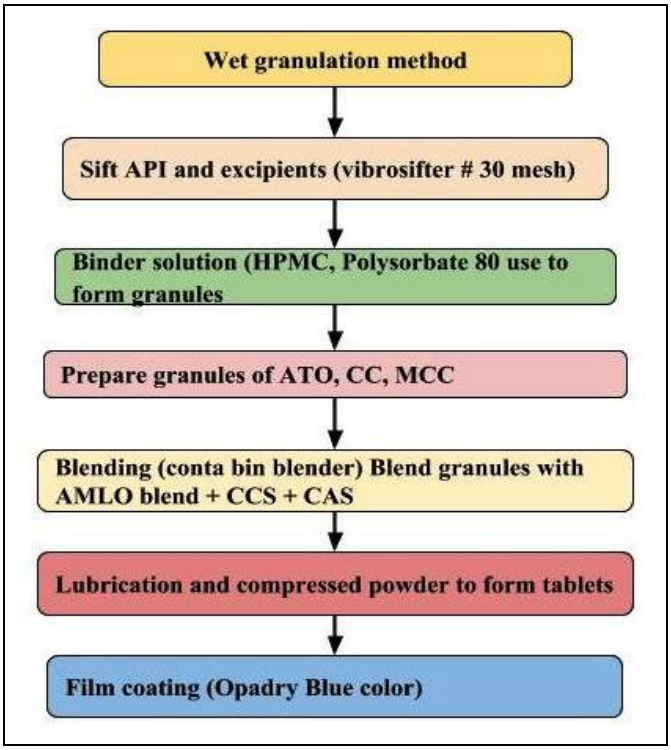

FIG. 2: FLOW CHART OF WET GRANULATION METHOD

Preliminary screening studies were carried out to choose a suitable method for the formulation development of immediate-release film-coated tablets. For this, tablets collected at random from both batches PS1 (direct compression method) and PS2 (wet granulation method) (N=50) were subjected to several routine evaluation procedures pertaining to tabletting including flow properties of powdered blend, pharmacotechnical parameters, drug release and drug content.

TABLE 1: COMPOSITIONS OF IMMEDIATE RELEASE FILM-COATED OF SELECTED COMBINATION OF TWO APIs TABLETS BY DIRECT COMPRESSION METHOD

Ingredients	Formulation composition (% w/w)
Atorvastatin calcium	2.8
Amlodipine besylate blend	32.0
Microcrystalline cellulose	43.0
Calcium carbonate	14.2
Croscarmellose sodium	4.2
Colloidal anhydrous silica	1.7
Magnesium stearate	0.8
Total weight of tablet	350.00 mg

TABLE 2: COMPOSITIONS OF IMMEDIATE RELEASE FILM-COATED OF SELECTED COMBINATION OF TWO APIs TABLETS BY WET GRANULATION METHOD

Ingredients	Formulation composition (% w/w)
Atorvastatin calcium	2.8
Amlodipine besylate blend	32.0
Microcrystalline cellulose	43.0
Calcium carbonate	14.2
HPMC E5	1.12
Polysorbate 80	1.97
Croscarmellose sodium	4.2
Colloidal anhydrous silica	1.7
Magnesium stearate	0.8
Total weight of tablet	355.00 mg

TABLE 3: COMPOSITION OF COATING DISPERSION LIQUID

Ingredient	Liquid dispersion compositions (mg)
Opadry Blue	7.0
Isopropyl alcohol	Qs
Methylene chloride	Qs

Pre-compression Parameters for Immediate Release Film-Coated Tablets: Precompression parameters of immediate release formulations were evaluated by determining the various flow properties of immediate release tablet's blend *viz.* bulk density, tapped density, compressibility index, Hausner ratio and angle of repose as per USP specifications [10].

Bulk density (g/ml) = Weight of granules / Untrapped volume of packing …..(1)

Tapped density (g/ml) = Weight of granules / Final trapped volume of packing …..(2)

Carr's compressibility index = Tapped density – Bulk density × 100 / Tapped density …..(3)

Hausner ratio = Tapped density / Bulk density …..(4)

Post Compression Parameters for Immediate Release Film-Coated Tablets: The general appearance of tablet, it's visual identity and overall elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet to tablet uniformity and for monitoring trouble free manufacturing [10]. In light of the above-cited deliberations, the tablet formulations developed during the present study were evaluated for various post compressions pharmacotechnical parameters like description, thickness, weight variation, hardness, friability, disintegration time, drug content and drug release profile [11].

Drug Contents (Assay): The areas of Atorvastatin calcium and Amlodipine besylate peak were quantified, and the drug content of each tablet was calculated using equations 5 and 6, respectively.

Drug Content (mg/tablet) = A_T / A_S × W_S / 25 × 10 / 50 × 50 / 1 × P / 100 × 1 / 1.034 × 100 / 10 (labeled claim) …..(5)

Where, A_T = Peak area of Atorvastatin calcium peak in each test preparation. A_S = Mean peak area of Atorvastatin calcium peak six injections in standard preparation-I. W_S = Weight of working standard of Atorvastatin calcium (in mg). P = Potency of working standard of Atorvastatin calcium used in percent on as such basis.

Drug Content (mg/tablet) = A_T / A_S × W_S / 25 × 10 / 15 × 50 / 1 × P / 100 × 1 / 1.386 × 100 / 10 (labeled claim) …..(6)

Where, A_T = Peak area of Amlodipine besylate peak in each test preparation. A_S = Mean peak area of Amlodipine besylate peak six injections in standard preparation-I. W_S = Weight of working standard of Amlodipine besylate (in mg). P = Potency of working standard of Amlodipine besylate used in percent on as such basis.

Pre-optimization Studies: The main objective of conducting pre-optimization studies was to select appropriate concentration or ratio (wherever applicable) of disintegrant in each immediate-release technique, to obtain the desired drug product characteristics for fixed-dose combination immediate-release film-coated tablets formulated by direct compression method followed by conventional film coating technique. Croscarmellose sodium ascribed as swelling 4-8 folds in < 10 sec, which enhances drug dissolution [12]. Various tablet formulations (CF1-CF6) prepared by physical bends were prepared to choose an appropriate concentration range of disintegrants and glidants to formulate the best one formulation in **Table 4**.

TABLE 4: FORMULATION COMPOSITION OF IMMEDIATE RELEASE FILM-COATED TABLETS PREPARED FOR OPTIMIZATION OF DISINTEGRATION AND GLIDANT CONCENTRATION

Ingredient	Formulation composition (% w/w)					
	CF1	CF2	CF3	CF4	CF5	CF6
ATO	2.8	2.8	2.8	2.8	2.8	2.8
AMLO	1.4	1.4	1.4	1.4	1.4	1.4
MCC	40.0	41.0	41.7	42.2	42.8	43.0
CC	17.0	17.1	16.5	16.0	15.0	14.2
CCS	1.4	1.1	2.5	3.1	3.7	4.2
CAS	4.5	4.0	3.4	3.1	3.7	1.7
Mg	0.8	0.8	0.8	0.8	0.8	0.8
Total weight of tablet = 350.00 mg						

ATO = Atorvastatin calcium, AMLO = Amlodipine besylate, CC=Calcium carbonate, CCS = Croscarmellose sodium, CAS = Colloidal anhydrous silica, MCC = Microcrystalline cellulose, Mg = Magnesium stearate

Optimization: The word optimize is defined as to create a perfect, functional, and effective as possible. During the development of a new project, one generally experiments by a sequence of rational steps carefully controlling the variable and changing one at a time until a satisfactory result is obtained [13].

In current studies, on the basis of results of pre-optimization studies, the formulation CF6 was further selected for optimization studies.

Optimization of Process Variable: Process optimization is the exercise of adjusting a process to optimize some specified set of parameters without violating some constraint(s). The most common goals are minimizing cost, maximizing throughput and/or efficiency. This is one of the major quantitative process in decision making [14].

TABLE 5: OPTIMIZATION OF PROCESS VARIABLES OF FORMULATION CF6

Formulation code	Process factor	Optimizing level
AT1	Blending time (min)	15-17
AT2	Lubrication time (min)	5-10
AT3	Compression speed machine (rpm)	15-50

TABLE 6: OPTIMIZATION OF PROCESS VARIABLES FOR COATING PARAMETER OF FORMULATION CF6

Formulation code	Process factor	Optimizing level
BT1	Inlet air temperature (˚C)	40-75
BT2	Spray rate (g/min)	10-100
BT3	Rotating speed of pan (rpm)	4-34

TABLE 7: OPTIMIZATION OF FORMULATION VARIABLE

Factor levels in coded form		
Formulation code	**X_1**	**X_2**
CF6	+1	-1
CT1	-1	-1
CT2	-1	+1
CT3	+1	+1

TABLE 7A: TRANSLATION OF CODED LEVELS IN ACTUAL UNITS

Factor level	+1	-1
Concentration of DTS (CCS) in % w/w	4	2
Concentration of glidant (CAS)	2	1

DTS: Disintegrants (CCS) and glidant (CAS); tablet weight and other process parameters were kept constant as that of formulation CF6

***In-vitro* Dissolution Studies:** Dissolution studies were carried out for all formulations in triplicate, employing USP Paddle apparatus (Type 2) using phosphate buffer (pH 6.8) as the dissolution medium. The apparatus was programmed for 60 minutes at 75 rpm and 37 ± 0.5 °C. An aliquot (10ml) of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of fresh dissolution medium.

The samples were collected in clean and dry test tubes and then analyzed using HPLC. Dissolution efficiency was calculated for CF6 and optimized batches (AT1-AT3, BT1-BT3, and CT1-CT3) by using the following formula and percent dissolution (PD) and dissolution efficiency (DE) data is also analyzed by ANOVA analysis.

$$\% DE = \int_0^t \frac{y.dt}{y100.t} \times 100 \quad \ldots\ldots(7)$$

Dissolution efficiency (DE) parameter, defined as the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of the rectangle arising from 100% dissolution at the same time [15].

Stability Studies of Final Formulation: Stability studies ensure the maintenance of product quality, safety, and efficacy throughout the shelf life, and therefore considered as a prerequisite for the acceptance and approval of any pharmaceutical product [16]. Thus, it was thought worthwhile to carry out stability study. The stability studies as per ICH guidelines were designed for the final optimized formulation CF6 at distinct storage conditions (25 ± 2 °C / 60 ± 5% RH, 30 ± 2 °C / 75 ± 5% RH, 40 ± 2 °C / 75 ± 5% RH). The sample was packed in an Alu-Alu blister pack and kept in stability chambers for a period of six months. Various other critical parameters were also evaluated (appearance, mean drug release, drug content and total impurities). Furthermore, the shelf life prediction of the final formulation was performed [17] (equations 8, 9, and 10).

$$\ln k = -Ea / RT + \ln A \quad \ldots..(8)$$

$$\log k = - Ea / 2.303RT + \log A \quad \ldots..(9)$$

Shelf life = Specification limit of impurity – Initial level of impurity/ Rate of change of impurity per month …..(10)

RESULTS AND DISCUSSION: The FTIR spectrum of Atorvastatin calcium and Amlodipine besylate was interpreted for different characteristic peaks. The results inferred that the IR spectrum of pure drug Atorvastatin calcium and Amlodipine besylate was concordant with that of Atorvastatin calcium and Amlodipine besylate working standard (W.S).

Drug Excipient Compatibility Study: Excipient compatibility was evaluated using FTIR spectrum studies. IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1}. The spectrums of the physical mixture were observed for characteristic peaks of Atorvastatin calcium (ATO) and Amlodipine besylate (AMLO).

TABLE 9: INTERPRETATION OF FTIR SPECTRA OF PURE DRUG ATORVASTATIN CALCIUM

Reported peaks (cm^{-1})	Observed peak (cm^{-1})	Inference
3500-3300	3365	Amine N-H stretching
1690-1630	1651	Amide C=O stretching
1700-1500	1579	Aromatic C=C bending
1400-1000	1358	Fluoro compound C-F bending
1440-1395	1435	O-H bending

TABLE 10: INTERPRETATION OF FTIR SPECTRA OF PURE DRUG AMLODIPINE BESYLATE

Reported peaks (cm^{-1})	Observed peak (cm^{-1})	Inference
1700-1500	1558	Aromatic C=C bending
1690-1630	1675	Amide C=O stretching
1845-1800	1842	Anhydride C=O stretching
1495-1440	1493	CH_2 bending
1250-1050	1248	C-O-C stretching

A physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics.

From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Atorvastatin calcium (ATO) and Amlodipine besylate (AMLO) was found to be unaltered in the drug-excipient physical mixtures, indicating they were compatible chemically.

TABLE 11: INTERPRETATION OF FTIR SPECTRA OF PURE COMBINED DRUG (AMLO+ATO)

Reported peaks (cm^{-1})	Observed peak (cm^{-1})	Inference
3500-3100	**3149**	Amine N-H stretching
1690-1630	1674	Amide C=O stretching
1700-1500	1579	Aromatic C=C bending
1495-1440	1494	CH_2 bending
1400-1000	1301	Fluoro compound C-F bending
1270-1050	1265	C-O-C stretching

TABLE 12: PHYSICAL APPEARANCE OF SAMPLES APIs AND EXCIPIENTS KEPT FOR DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Sample details	Sample code	25°C/60% RH (initial)	40°C/75% RH (1 week)	40°C/75% RH (2 week)	40°C/75% RH (1 month)
AMLO + ATO	AMAT	White	White	Off white	Off white
AMLO + ATO + Microcrystalline cellouse	AAMCC		White	White	
AMLO + ATO + Croscarmellose sodium	AMATC		Off white	Off white	
AMLO + ATO + Magnesium stearate	AAMS		Off white	Off white	
AMLO + ATO + Calcium carbonate	AACC		Off white	White	
AMLO + ATO + Colloidol anhydrous silica	AACAS		White	Off white	
Physical mixture of APIs and excipients	AAF1		Off white	Off white	

Pre-compression Parameters for Immediate Release Film-Coated Tablets: The bulk and tapped density data was used to calculate Carr's compressibility and Hausner ratio. The results are shown in **Fig. 3, 4** and **5**.

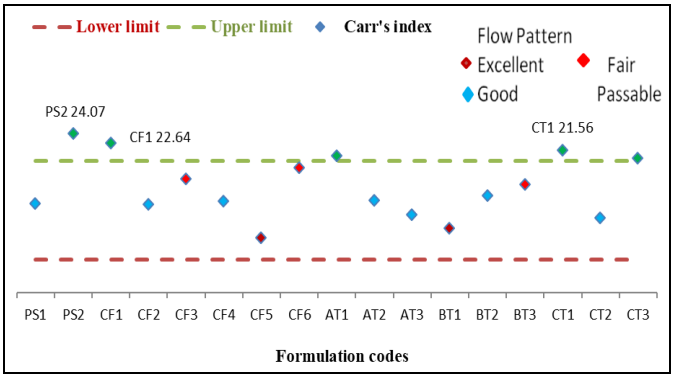

FIG. 3: COMPARISON OF CARR'S INDEX OF IMMEDIATE RELEASE FILM-COATED FORMULATION

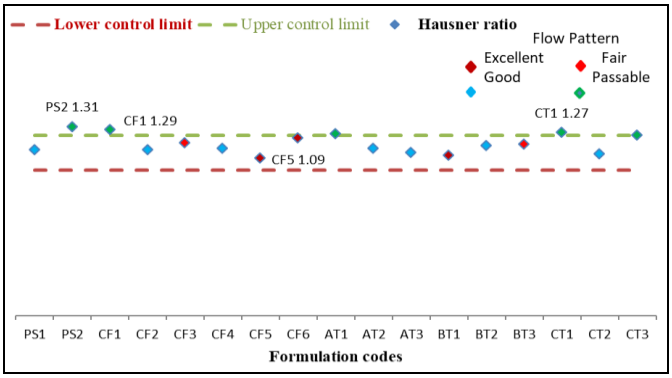

FIG. 4: COMPARISON OF HAUSNER RATIO OF IMMEDIATE RELEASE FILM COATED FORMULATION

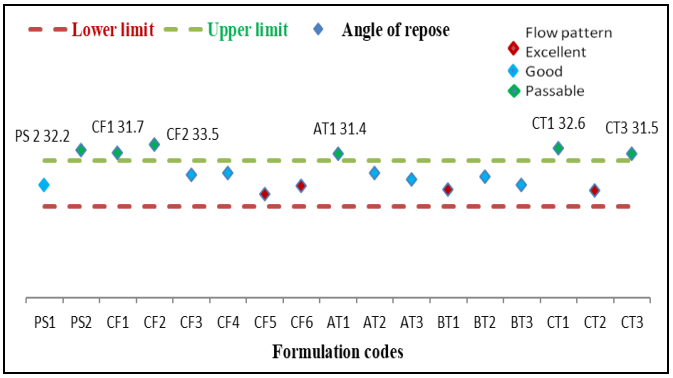

FIG. 5: COMPARISON OF ANGLE OF REPOSE OF IMMEDIATE RELEASE FILM COATED FORMULATION

Post-compression Evaluation Parameter: Thus to ensure the quality, several post compression parameters were evaluated for all developed immediate release film coated tablets and their data have been concisely compiled in the **Table 13** and **Fig. 10**.

TABLE 13: POST COMPRESSION PARAMETERS OF IMMEDIATE RELAEASE FILM COATED TABLETS

F. C	Weight variation Mean ± S.D (n=20)	DT (s) Mean ± S.D (n=20)
PS1	350.5±0.45	45±0.14
PS2	360.7±0.68	429±0.45
CF1-CF6	349.7±0.25 - 357.6±0.22	21±0.17 - 52±0.15
AT1-AT3	352.6±0.45 - 353.9±0.87	31±0.45 - 35±0.27
BT1-BT3	349.0±0.17 - 358.0±0.66	42±0.16 - 48±0.15
CT1-CT3	355.9±0.81 - 357.0±0.15	49±0.44 - 52±.012

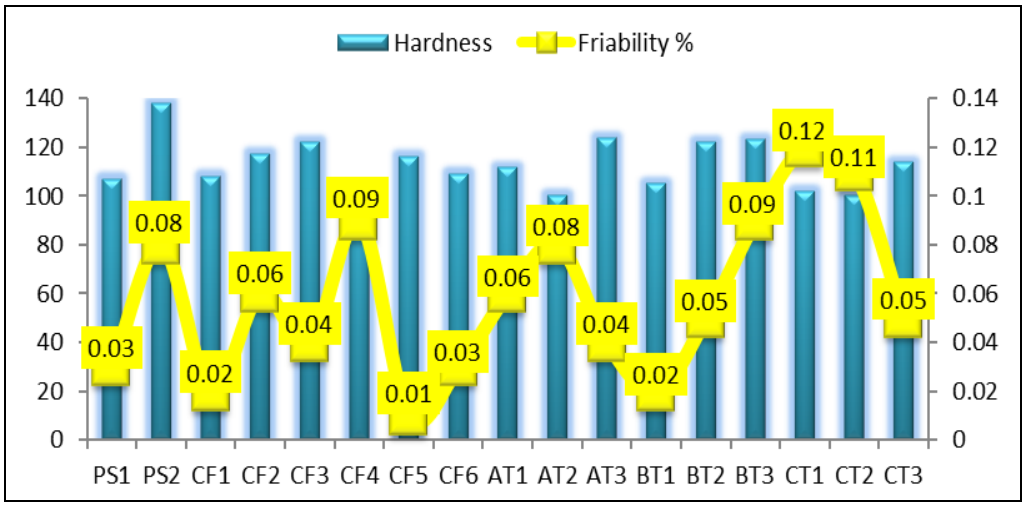

FIG. 6: HARDNESS AND FRIABILITY OF IMMEDIATE RELEASE FILM-COATED FORMULATIONS

Drug Content: The range of drug content for all formulation was for AMLO 93.5-103.6 and ATO 91.3-100.8 w/w, respectively. PS1 (DC) batch showed maximum drug content as compared to PS2 (WG) batches. Thus, the DC method was chosen as a suitable method for further formulation trials (CF1-CF6).

TABLE 14: PERCENT DRUG CONTENT OF TABLET FORMULATIONS

F.C	Drug content of AMLO Mean ± S.D	Drug content of ATO Mean ± S.D
PS1	100.6±0.48	98.8±052
PS2	93.5±0.032	91.3±0.22
CF1-CF6	95.2±0.36 - 103.6±0.77	94.9±0.44 - 100.5±0.65
AT1-AT3	101.5±0.68 - 102.8±0.70	98.2±0.53 - 99.9±0.60
BT1-BT3	100.5±0.63 - 99.3±0.49	98.4±0.64 - 97.9±0.55
CT1-CT3	100.4±0.47 - 99.5±0.52	98.9±0.66 - 97.5±0.53

***In-vitro* Dissolution Studies:** All the tablet formulations were evaluated for their *in-vitro* drug release and the results are shown in **Fig. 7** and **8**. The maximum drug release of ATO 101.2% and AMLO 102.6% was obtained at 60 min from formulation CF6 and minimum drug release of ATO 89.9% and AMLO 92.8% shown by CF1. The formulation CF6 containing superdisintegrants croscarmellose sodium 4.2% enhanced the dissolution rate of immediate-release film-coated tablets. Furthermore, the salient dissolution parameters *viz.* PD_{10}, PD_{30}, DE_{10}, and DE_{30} were also computed for Atorvastatin calcium and Amlodipine besylate CF6 and optimized batches AT1-AT3, BT1-BT3, and CT1-CT3 and also ANOVA analysis result tabulated in **Table 15** and **16**.

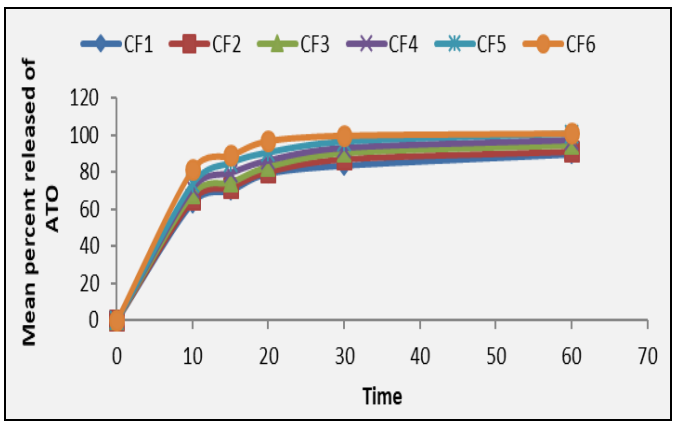

FIG. 7: DRUG RELEASE PROFILE OF CF1-CF6 (ATO)

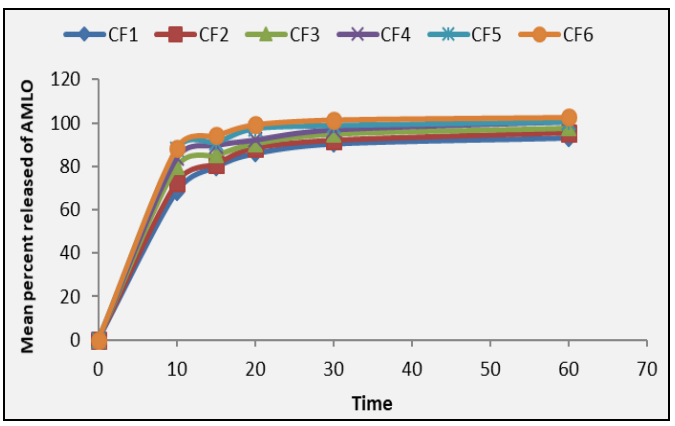

FIG. 8: DRUG RELEASE PROFILE OF CF1-CF6 (AMLO)

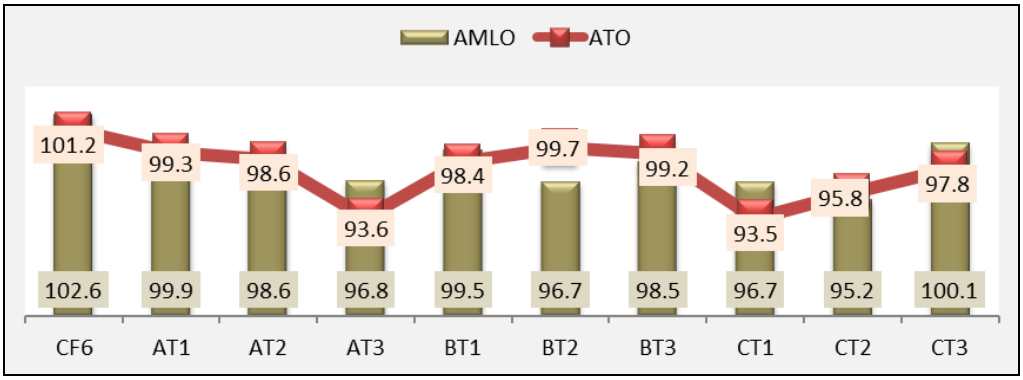

FIG. 9: MAXIMUM DRUG RELEASE OF CF6 AND OPTIMIZED BATCHES (AT1-AT3, BT1-BT3 AND CT1-CT3) AT 60 min

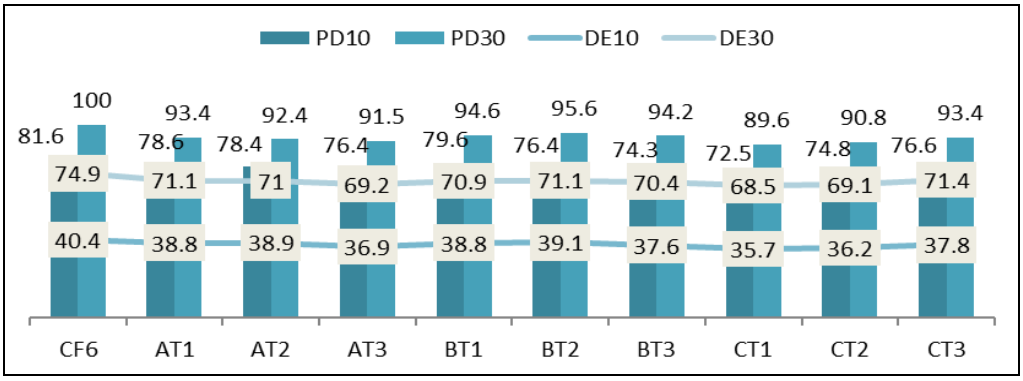

FIG. 10: COMPARATIVE DISSOLUTION PARAMETERS OF ATO FORMULATIONS CF6 OPTIMIZED BATCHES (AT1-AT3, BT1-BT3 AND CT1-CT3)

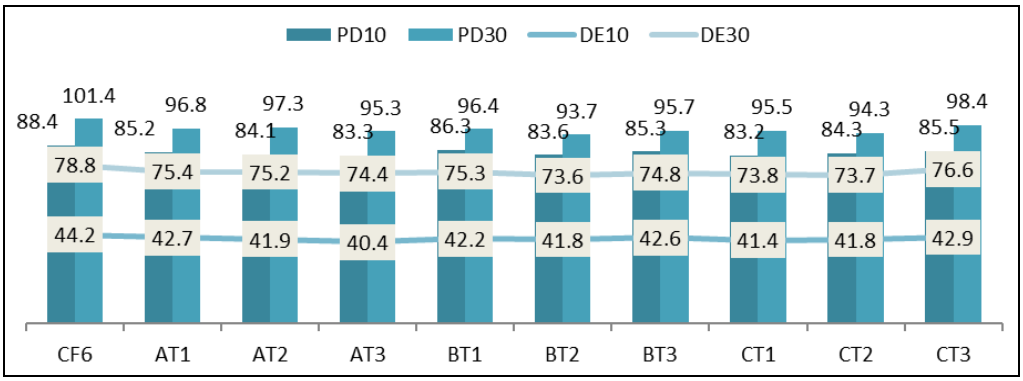

FIG. 11: COMPARATIVE DISSOLUTION PARAMETERS OF ATO FORMULATIONS CF6 OPTIMIZED BATCHES (AT1-AT3, BT1-BT3 AND CT1-CT3)

TABLE 15: ANALYTICAL VARIANCE DETERMINATION OF CF6, AT1-AT3, BT1-BT3 AND CT1-CT3 (AMLO)

Summary						
Groups	**Count**	**Sum**	**Average**	**Variance**		
CF6	4	312.8	78.2	599.5467		
AT1	4	300.1	75.025	540.9092		
AT2	4	298.5	74.625	558.3958		
AT3	4	293.4	73.35	555.87		
BT1	4	300.2	75.05	553.8567		
BT2	4	292.7	73.175	504.8425		
BT3	4	298.4	74.6	527.9133		
CT1	4	293.9	73.475	536.1958		
CT2	4	294.1	73.525	518.0692		
CT3	4	303.4	75.85	562.63		
ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	83.37625	9	9.264028	0.016973	1	2.210697
Within Groups	16374.69	30	545.8229			
Total	16458.06	39				

ANOVA: Single factor, Note: F value from the table, at 0.05 level of significance is 0.01

TABLE 16: ANALYTICAL VARIANCE DETERMINATION OF CF6, AT1-AT3, BT1-BT3 AND CT1-CT3 (ATO)

Summary						
Groups	**Count**	**Sum**	**Average**	**Variance**		
CF6	4	296.9	74.225	621.1092		
AT1	4	281.9	70.475	531.7558		
AT2	4	280.7	70.175	513.4692		
AT3	4	274	68.5	530.1533		
BT1	4	283.9	70.975	555.9225		
BT2	4	282.2	70.55	550.3767		
BT3	4	276.5	69.125	550.3292		
CT1	4	266.3	66.575	507.4092		
CT2	4	270.9	67.725	526.0758		
CT3	4	279.2	69.8	543.2533		
ANOVA						
Source of Variation	SS	Df	MS	F	P-value	F crit
Between Groups	155.8813	9	17.32014	0.031898	0.999996	2.210697
Within Groups	16289.56	30	542.9854			
Total	16445.44	39				

ANOVA: Single-factor, Note: F value from the table, at 0.05 level of significance is 0.03

Discussion about Kinetic Models: Different kinetic equations[18] (Zero order, First order, Higuchi's, Hixon-Crowell, and Korsmeyer-Peppas equation) were applied to interpret the release rate of CF6. The release obeyed Hixon crowell kinetics and the results of this investigation showed a high correlation coefficient among the formulation and the probable release mechanism was initial diffusion and the value of release exponent (R^2) was found to be a 0.962 for both drug Atorvastatin calcium and Amlodipine besylate followed with non-fickian release.

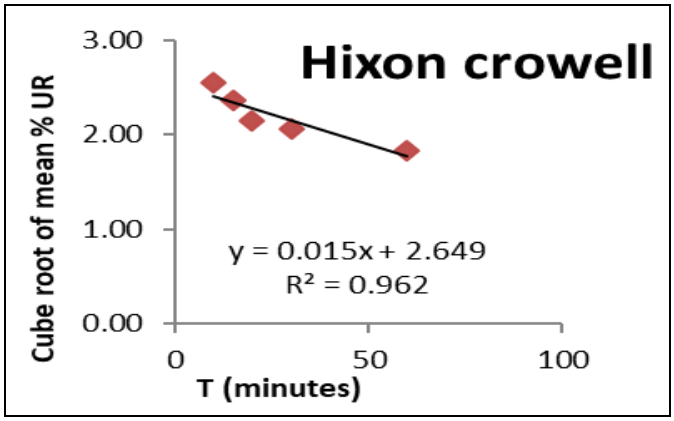

FIG. 12: HIXON CROWELL MODEL (ATO)

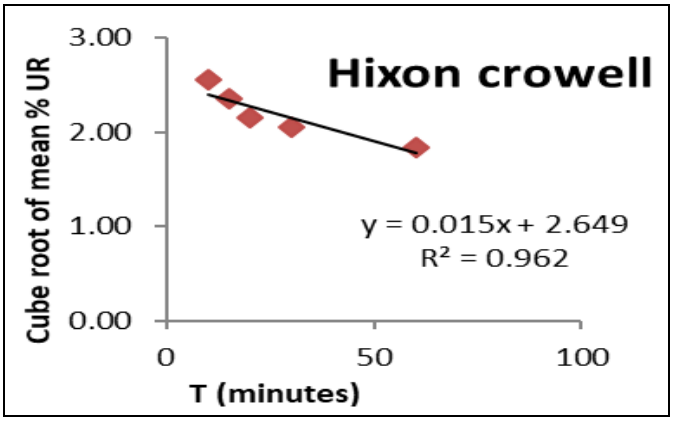

FIG. 13: HIXON CROWELL MODEL (AMLO

Stability Studies Results: Stability study was conducted for the best formulations (CF6) selected based on *in-vitro* disintegration time and *in-vitro* drug release. There was no significant reduction in the drug release profile of formulation CF6. The results found to be satisfactory. The result was shown in **Table 17**. Furthermore, the energy of activation (E_a= 21652.3412) and rate constant (In A = 32.2647) was calculated using equations 8 and 9. Eventually, the values of E_a and log A was put into Arrhenius equation (equations 8 and 9) at 25°C (0.135 K) to estimate the shelf life of the final formulation in long term condition which was found to be 22 months **Table 18.**

TABLE 17: STABILITY STUDY DATA OF FINAL OPTIMIZED CF6

Stability study data of ATO in final optimized formulation						
Storage condition	**Time Period**	**MDR (%) Mean± S.D (n=3)**	**DC (%) Mean± S.D (n=3)**	**WC Mean± S.D (n=3)**	**TI (%) Mean± S.D (n=3)**	**DT (s) Mean± S.D (n=3)**
Initial		102.1±0.08	100.2±0.03	3.2±0.02	0.43±0.01	46±0.03
25±2°C/60±5% RH	3M	95.9±0.17	98.4±0.048	3.4±0.32	0.60±0.12	52±0.07
	6M	97.2±0.06	98.3±0.012	3.5±0.04	0.63±0.08	58±0.19

30±2°C/75±5% RH	3M	100±0.23	97.5±0.020	3.2±0.22	0.73±0.12	35±0.63
	6M	94.5±0.25	96.8±0.010	3.6±0.04	0.71±0.63	49±0.17
40±2°C/75±5% RH	1M	100.9±0.07	99.9±0.014	3.4±0.03	0.41±0.17	44±0.46
	3M	96.9±0.04	97.4±0.051	3.3±0.05	0.52±0.16	52±0.09
	6M	95.5±0.05	96.5±0.016	3.7±0.13	0.90±0.01	55±0.06
Stability study data of AMLO in final optimized formulation						
Initial		99.0±0.03	102.9±0.17	3.2±0.10	0.03±0.03	46±0.08
25±2°C/60±5% RH	3M	95.1±0.31	102.3±0.34	3.4±0.46	0.04±0.14	52±0.23
	6M	97.3±0.11	101.8±0.29	3.5±0.37	0.06±0.20	58±0.58
30±2°C/75±5% RH	3M	94.4±0.09	102.5±0.15	3.2±0.53	0.05±0.14	35±0.25
	6M	95.8±0.04	101.6±0.19	3.6±0.16	0.06±0.06	49±0.19
40±2°C/75±5% RH	1M	97.9±0.37	101.3±0.03	3.4±0.13	0.03±0.03	44±0.17
	3M	94.6±0.25	100.9±0.22	3.3±0.34	0.06±0.08	52±0.26
	6M	95.2±0.14	99.5±0.04	3.7±0.17	0.09±0.19	55±0.18

Alu-Alu blister packing was used for each sample during storage; DC: Drug content; DT: Disintegration Time; F.C: Formulation code; M: Months; MDR: Mean drug released; RH: Relative humidity; s: Second; TI: Total Impurities; WC: Water content. Note: In the entire course of stability studies the appearance of the tablets remained light blue colored (as initial)

TABLE 18: SHELF LIFE ESTIMATION OF FINAL FORMULATION CF6

Storage conditions	Initial percent impurity in formulation T2H5 (%)	Limit (as per USP)	Percent impurity (in 6 months)	Value of E_a, log A and K
40±°C/75±5% RH			0.90	E_a = 21652.3412
30±2°C/75±5% RH	0.43	NMT 1 %	0.71	Log A = 32.2647
				K = 0.135
		Shelf life = 22 months		

E_a: Energy of Activation; K: Rate of change of impurity per month; log A: logarithmic scale of Rate constant; RH: Relative humidity

CONCLUSION: Immediate release film-coated tablets of fixed-dose combination of Atorvastatin calcium and Amlodipine besylate of 350 mg were prepared using superdisintegrants like croscarmellose sodium (CCS) with 1.4-4.2% by direct compression method. On the basis of drug content result, direct compression method was used for further development CF1-CF6 batches. The pre-optimization process was employed to optimize the appropriate concentration of superdisintegrants and glidant to achieve a desired immediate release of drug from the dosage form and CF6 batch was found as best formulation and it was further optimized for process variable and formulation variable.

The following conclusions can be drawn from the results obtained. FTIR studies revealed no chemical interaction of the drug with excipients. The tableting properties like Angle of repose, Bulk density, tapped density; Hausner's ratio and Carr's index of all the formulations were found to be within the standard limits. All the physical characteristics of the formulations like thickness, hardness, friability, drug content, *in-vitro* disintegration time and *in-vitro* dissolution studies were found to be well within the limits of official standards. All the formulations get disintegrated within a time period of 65 sec except PS1 429 (sec) when tested for *in-vitro* disintegration time. The CF6 formulation containing croscarmellose sodium (4.2%) was found to have a higher percentage of drug release compared with other formulations and also noticed that as the concentration of superdisintegration was increased resulted in increase disintegration time and dissolution rate.

Stability studies of the tablets were checked at varied storage conditions (25 ± 2 °C / 60 ± 5% RH, 30 ± 2 °C / 75 ± 5% RH, 40 ± 2°C / 75 ± 5% RH) for a period of 6 months. It can be concluded from the present work that the concentration of croscarmellose sodium 4.2% is superior to achieve immediate disintegration of tablets by direct compression method and also observed coating material does not interfere with the disintegration process. The fixed-dose combination of Atorvastatin calcium and Amlodipine besylate immediate-release film-coated tablets were found to have enhanced dissolution rate.

ACKNOWLEDGEMENT: Authors are thankful to the management of Swami Vivekanand Group of Institutions (SVGOI) for providing financial support and conducible environment to carry out the current research project.

CONFLICTS OF INTEREST: The authors declared no conflict of interest.

REFERENCES:

1. Mahboob MBH, Tehseen R, Jamshaid M, Irfan B and Zulfiqar AS: Oral films: A comprehensive review. Int Current Pharmaceutical J 2016; 5(12): 111-17.
2. Bushra R, Rehman A, Ghayas S, Zafer F, Ali H, Shafiq Y, Khan MA, Hanief A and Mustpha O: Formulation design, Characterization and Optimization of Cinitapride (1mg) immediate release tablets using direct compression technology. Pakistan Journal of Pharmaceutical Sciences 2018; 31(6): 2725-31.
3. Karad BB and Shinde AD: Formulation and evaluation of immediate release tablets of Levonorgestrel. Indo American J of Pharmaceutical Res 2017; 7(8): 471-79.
4. Upadhyay CP and Gupta T: Formulation & Characterization Study of immediate release Progestrin Tablet and its comparative study with Innovator Drug: SGVU Journal of Pharmaceutical Research & Education 2018; 3(1): 279-06.
5. Brunton LL, Lazo JS and Parker K: Goodmann & Gillman's, The Pharmacological Basic of Therapeutics. McGraw Hill Education, Eleventh Edition 2005.
6. Katzang BG: Basic & Clinical Pharmacology. Mc Graw Hill, Ninth Edition 2004.
7. Devabhaktuni M and Bangalore S: Fixed combination of Amlodipine and Atorvastatin in cardiovascular risk management: Patient perspectives. Vascular Health Risk Management 2017; 5: 377-87.
8. Blank R, Hobbs FD, Zamorano J and Girerd X: A single-pill combination of Amlodipine besylate and Atorvastatin calcium (update). Drug of Today 2016; 3: 155-77.
9. United States Pharmacopeia and National Formulary (USP 41-NF 36). Rockville, MD: United States Pharmacopeial Convention, Thirty Edition 2018.
10. Neeraj B, Abhishek K, Abhilash C, Rubia C and Rajni B: A review on immediate release drug delivery system. International Research Journal of Pharmaceutical and Applied Sciences 2014; 4: 78-87.
11. Augsburger LL, Larry LA, Lachman L and Schwartz JB: Pharmaceutical Dosage Forms: Tablets, Taylor & Francis, Second Edition -Volume 2 1990.
12. Rowe RC, Sheskey PJ and Owen SC: Handbook of Pharmaceutical Excipients. Pharmaceutical Press and American Pharmacists Association, Fifth Edition 2005.
13. Patil DA: Optimization techniques: An introductory overview. Journal of Pharmacy Research 2013; 2: 144-47.
14. Amir AS, Praveen DC and Sagar SH: A design of Experiment Approach for Optimizing and Characterization of Etodolac Ternary System using Spray Drying: International Journal of Pharmacy and Pharmaceutical Sciences 2017; 9(2): 233-40.
15. Cutrignelli A, Trapani A, Lopedota A, Franco M, Delia M, Denora N, Laquintana V and Trapani AG: Griseofulvin/Carrier blends: Application of partial least squares (PLS) regression analysis for estimating the factors affecting the dissolution efficiency. American Association of Pharmaceutical Scientists 2011; 12: 1019-30.
16. Baishya H, Chidambaram A and Haitho AZ: Optimization of various process parameters for formulation of model anti-hyperlipidemic drugs by using dry granulation method. International Journal of Pharmaceutical Sciences and Research 2016; 7: 3959-70.
17. Waterman KC and Adami RC: Accelarated aging: Prediction of chemical stability of pharmaceuticals. International Journal of Pharmaceuticals 2018; 293: 101-25.
18. Dash S, Murthy PN, Nath L and Chowdhury AP: Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutical and Drug Research 2011; 67: 217-23.

How to cite this article:
Pahuja S, Sharma N and Sarup P: Formulation and evaluation of fixed dose combination of atorvastatin calcium and amlodipine besylate immediate release film coated tablets. Int J Pharm Sci & Res 2020; 11(6): 2937-47. doi: 10.13040/IJPSR.0975-8232.11(6).2937-47.