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DESIGN OF DUAL RELEASE DRUG DELIVERY SYSTEM OF ASPIRIN AND ATORVASTATIN FOR CARDIOVASCULAR DISEASES

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ABSTRACT

Combined drug therapy (CDT) is favoring for most of the treatment, and aim of the therapy is to decrease or reduce dose dependent adverse drug reactions and side effects. The present work an attempt to design bilayer tablets of Atorvastatin immediate release and Aspirin Pulsatile release for the treatment of cardiovascular diseases. Four formulations were prepared for immediate release layer of atorvastatin using different concentrations of Microcrystalline cellulose and Talc by direct compression method. For aspirin pulsatile release layer, the four formulations of core tablets were prepared using Microcrystalline cellulose, Talc. The different concentrations of Cross carmellose sodium and Sodium starch glycolate were selected as superdisintegrants in F1, F2 and F3, F4 formulations. Then the core tablets were coated with Eudragit S 100 as enteric polymer. Physico chemical parameters of bilayer tablets were performed and it has shown a good drug release profile. The work reveals that F3 formulation was the best formulation and they are the good candidate for lowering the risk of heart attack. Pattern like one layer of the formulation as immediate release to reduce the cholesterol level and the second layer to deliver the drug at right time and in right amount, to reduce the risk of heart attack.

KEYWORDS: Combined drug therapy, Pulsatile drug release, Aspirin, Atorvastatin, Cardiovascular diseases, Bilayer tablets.

INTRODUCTION

Now a days various developed and developing countries move towards a combination therapy for treatment of various diseases and disorders requiring a long term therapy such as hypertension, diabetes and cardiovascular diseases. Over 90% of the formulation manufactured today are ingested orally. It shows that this class of the formulation is the most

popular worldwide and the major attention of the researcher is towards this direction. The major aim of controlled drug delivery is to reduce the frequency of dosing. The design of modified release drug product is to optimize a therapeutic regimen by providing slow and continues delivery of drug over the entire dosing interval providing greater patient compliance and convenience. Bilayer tablet is a newer for the successful development of controlled release formulation and better than the traditionally used dosage forms. Bilayer tablet is suitable for sequential release of two drugs in combination. It is also capable of separating the two types of incompatible substances and also for sustained release tablet in which one layer is immediate release tablet as initial dose and second layer is maintenance dose. In certain cases bilayer tablet have two sustain release layer of different drugs.[1,2]

The current research work is to develop the immediate release layer of atorvastatin and Pulsatile release layer of aspirin tablets. Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques. Despite a rising interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract. A Disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, Thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action.[2]

Pulsatile drug delivery systems are developed to deliver drug in a programmed manner according to circadian behavior of diseases resulting in improved therapeutic efficacy as well as patient compliance These systems are designed for diseases showing chronopharmacological behavior and where the drug dose is required for extended day time or night time activity or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity.

Diseases wherein pulsatile drug delivery system are likely to be successful for diseases such as asthma, peptic ulcer, cardiovascular diseases, arthritis, hypertension, and hypercholesterolemia. Here atorvastatin act as immediate release layer and aspirin act as Pulsatile release layer. Statins are the most commonly prescribed lipid-lowering agents because they are effective, well tolerated and easy to administer. They are generally effective, are supported by favorable outcome studies and have relatively few adverse effects. The six

statins currently available are atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor).

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase and is commonly used as atorvastatin calcium. Atorvastatin calcium is a white to off white amorphous powder that is insoluble in aqueous solutions of pH 4 and below, which are the conditions typically present in the stomach of a subject. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.[2] Atorvastatin is rapidly absorbed after oral administration, with time to reach peak concentrations (tmax) within 1–2 h. The fraction absorbed (%) and absolute bioavailability of atorvastatin are approximately 30% and 12%, respectively.[3] The low systemic availability is attributed to pre systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.[3-5]

Aspirin's efficacy in preventing myocardial infraction is related to preventing thrombus formation by decreasing platelet aggregation. Aspirin is a non-steroidal anti-inflammatory drug (NSAIDS) that permanently inactivates the cyclooxygenase (COX) mediated activates of prostaglandins through irreversible binding there are two forms of COX: COX 1 & COX 2. COX 1 is responsible for the synthesis of thromboxane A2 in platelets and the production of prostacyclin in vascular walls. Thromboxane A2 is a vasoconstrictor & platelet aggregating agent, while prostacyclin's act as a vasodilator and platelet inhibitor. The major drawback of aspirin G.I mucosa ulceration can be avoided by providing the effective enteric coating. In this study an attempt was made to formulate aspirin pulsatile release tablet with the use of enteric polymer Eudragit S 100 to produce the effective enteric coating.[4]

MATERIALS AND METHODS

Material

Aspirin, Atorvastatin, Microcrystalline cellulose, Sodium starch Glycolate, Cross carmellose Sodium, Talc, Eudragit S 100 was purchased from Yarrow chem products, Mumbai. PEG (poly ethylene glycol) was purchased from SDFCL Sd fine Chem Ltd. Titanium dioxide was purchased from Prowess Lab chemicals, Palakkad. All ingredients were of analytical grade.

Method

Compatibility study

Compatibility study of drug with polymer was determined by FT-IR spectroscopy using

Shimadzu spectrophotometer. The pellets were prepared by gently mixing 200mg of Potassium bromide with 1mg of Sample. The prepared pellets were analyzed for individual drug, for individual polymers and for drug polymer mixture. The drug and polymer interaction were analyzed by comparing IR spectra of Drug Sample mixture.

Design of Immediate release tablets of Atorvastatin and Pulsatile release tablets of Aspirin.

Table 1: Composition of Immediate release tablets of Atorvastatin Pulsatile release tablets of Aspirin.

SL.No.	Ingredients (mg)	F1	F2	F3	F4
Immediate release layer					
1	Atorvastatin	10	10	10	10
2	Microcrystalline cellulose	138	137	136	135
3	Talc	2	3	4	5
4	Total weight	150	150	150	150
Pulsatile release layer					
5	Aspirin	75	75	75	75
6	Microcrystalline cellulose	100	100	100	100
7	Cross carmellose sodium	1.5	2	-	-
8	Sodium Starch Glycolate	-	-	1.5	2
9	Talc	2	2	2	2
10	Total weight	180	180	180	180

Preparation of the bilayer tablets[6]

Preparation of Atorvastatin immediate release layer

The tablets containing 10 mg of the drug were prepared by direct compress method and the various formulae used in the study are shown in Table 1. The drug, diluents, were passed through sieve No 40. All the above ingredients were properly mixed together. Talc was passed through sieve No 80, mixed and blended with initial mix. The powder blend was compressed into tablets on a ten station rotary punch tablet machine using 8 mm convex punch.

Preparation of Aspirin Pulsatile release layer (core tablet)

The tablets containing 75 mg of the drug were prepared by direct compress method and the various formulae used in the study are shown in Table 1. The drug, diluents, superdisintegrants were passed through sieve No 40. All the above ingredients were properly mixed together. Talc was passed through sieve No 80, mixed and blended with initial mix. The powder blend was compressed into tablets on a ten station rotary punch tablet machine using 8 mm convex punch.

Preparation of coated tablets of Aspirin

The coating solution was developed by dissolving Eudragit S 100 (20%) in acetone and isopropyl alcohol mix solvents and then Polyethylene glycol (2%), Titanium dioxide (5%) was added and stirring. The resulting solution was adjusted with acetone and isopropyl alcohol mixed solvents. The core tablets were coated using dipping and drying method and increase in weight percent after coating was determined as the coating level.

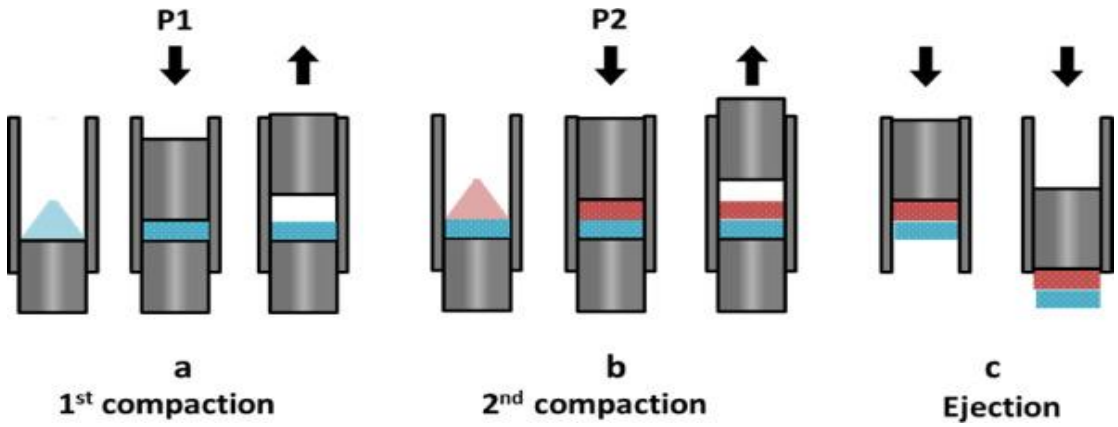

Fig. 1: Schematic Presentation for Compression of Bi-Layer Tablet.[7]

1. Filling of first layer.
2. Compression of first layer.
3. Ejection of upper punch.
4. Filling of second layer.

Evaluation of Bilayer tablets of Aspirin and Atorvastatin

Preparation of 0.1N HCl

Dissolving 0.85 ml of concentrated hydrochloric acid in 100 ml of distilled water will give acid buffer of pH 1.2 having a concentration of pH 1.2.

Preparation of Standard curve of Atorvastatin in 0.1N HCl

10 mg was dissolved in 60 ml 0.1N HCl and volume was made up to 100 ml in volumetric flask using 0.1N HCl to prepare stock solution (100µg/ml). From this stock solution, 0.5 ml solution was withdrawn and diluted up to 10 ml in volumetric flask (5µg/ml). In the Same way solution of 10, 15, 20, and 25µg/ml was prepared. Absorbance of each solution was measured at 243 nm using shimadzu UV-1800 UV/Visible double beam spectrophotometer using 0.1N HCl as a reference standard.

Preparation of standard curve of Aspirin in 0.1N HCl

100 mg was dissolved in 60 ml 0.1N HCl and volume was made up to 100 ml in volumetric flask using 0.1N HCl to prepare stock solution (100µg/ml). From this stock solution, 0.5 ml solution was withdrawn and diluted up to 10 ml in volumetric flask (5µg/ml). In the Same way solution of 10, 15, 20, and 25µg/ml was prepared. Absorbance of each solution was measured at 265 nm using shimadzu UV-1800 UV/Visible double beam spectrophotometer using 0.1N HCl as a reference standard.

Preparation of pH 6.8 phosphate buffer

Phosphate buffer (pH 6.8) was prepared by mixing of 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in 1000 ml distilled water.

Preparation of Standard curve of Pantoprazole sodium in pH 6.8 phosphate buffer

Aspirin (100mg) was dissolved in 60 ml phosphate buffer (pH 6.8) and volume was made up to 100 ml in volumetric flask using phosphate buffer (pH 6.8) to prepare stock solution (100µg/ml). From this stock solution, 0.5 ml solution was withdrawn and diluted up to 10 ml in volumetric flask (5µg/ml). In the Same way solution of 10, 15, 20, 25 3µg/ml was prepared. Absorbance of each solution was measured at 265 nm using shimadzu UV1800 UV/Visible double beam spectrophotometer using phosphate buffer (pH 6.8) as a reference standard.

Precompression Parameters[8]

Angle of repose

The static angle of repose "Ɵ" was measured according to the fixed funnel and free standing cone method. It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The funnel was clamped with its tip 2 cm above a paper placed on a flat horizontal surface. The tablet granules were poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation,

$\tan\Theta = h/r$, h = height of granule pile r = radius of tablet granules

Angle of repose $(\Theta) = \tan^{-1} (h/r)$

Bulk and tap density

Bulk density is ratio of total mass of powder to the bulk volume of the powder. Required quantity of powder sample was in a measuring cylinder and the volume, Vb, occupied by each of the samples without tapping the measuring cylinder was noted. After 100 taps on the table, the volume Vt was noted. The bulk and tap densities were calculated using following equations.

Bulk density = Weight of sample/Bulk volume (Vb)

Tapped density = Weight of sample/ Tapped volume (Vt)

Hausner's ratio

This was calculated as the ratio of tapped density to the bulk density

Hausner's ratio= Tapped density/Bulk density

Compressibility index

Compressibility index was calculated using the equation

Compressibility index = (Tapped density-Bulk density)/tapped density x100

Post compression parameters

Hardness[9]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined by Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Weight variation test[9]

Twenty tablets from each formulation weighed individually in Shimadzu digital balance and the test was performed according to the official method. Randomly selected pre dusted tablets weighed again and the change in the variation is noted and tabulated.

Table 2: Specification for weight variation of tablets as per IP.

Average weight of tablets	Percentage difference
125 or less	10
125-250	7.5
More than 250	5

% deviation= $Average\ weight\ of\ tablet - Individual\ weight\ /\ Average\ weight$ x100

Friability test[9]

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (Wi) and transferred into friabilator and was operated at 25 rpm for 4 min or run up to 100 revaluations. Then the tablets were weighed again (Wf). The percentage friability was then calculated by

% friability (F) = ($initial\ weight\ (Wi) - final\ weight\ (Wf)$)/$initial\ weight$ x 100

Percentage friability of tablet less than 1% are considered acceptable

Drug content Uniformity[7]

Sample preparation of Aspirin

Tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered Aspirin (100mg) was extracted in buffer. The absorbance was measured at 230 nm after suitable dilution.

Sample preparation of Atorvastatin

Tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered Atorvastatin Calcium (100mg) was extracted in buffer. The absorbance was measured at 246 nm after suitable dilution.

***In Vitro* Drug Release Studies**[7]

Dissolution parameters

Medium: 0.1 N HCl (pH1.2), Phosphate buffer pH 6.8

Apparatus: USP, XXIII-type 2 Paddle

RPM: 50

Temperature: 37±0.5ºC

Volume: 900ml

Procedure

Dissolution Studies on Atorvastatin[7]

The release of Atorvastatin tablets was studied in 900ml of 0.1N HCl for 2 hrs as dissolution medium using USPXXIII paddle dissolution apparatus at 50 rpm with 37ºC as temperature. Drug release was determined by UV-Visible spectrophotometer at 243nm. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve. The dissolution studies were performed 4 times for a period of 2 hrs and the mean values were calculated.

Dissolution Studies on Aspirin[6]

The dissolution studies of the pulsatile tablets containing aspirin was carried out using 900 ml of 0.1N HCl for 2h followed by pH 6.8phosphate buffer solution. The set condition was 37±0.5°C, 50 rpm, and paddle type USP XX111 apparatus. Aliquots withdrawn for every one hour intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable diluents were assessed spectrophotometrically at 230nm.

RESULTS AND DISCUSSIONS

The bilayer tablet formulations were prepared and evaluated with an aim of immediate release of Atorvastatin and Pulsatile release of Aspirin. The compatibility study of drug and polymer compositions was studies by FTIR. The IR spectrum of drug and polymer shown the major characteristics of absorption bands of excipients with negligible difference of absorption band values. So, FT-IR spectra shows there is no change in nature and position of absorption band indicating no chemical reaction between Aspirin and Atorvastatin Calcium and excipient combinations. A physical combination of the excipients with the aspirin was probably responsible for the pulsatile release characteristics of Aspirin. The physical characteristics of tablets were evaluated such as bulk characterization, angle of repose, weight variation, hardness and friability. All the formulations provided good weight uniformity. The parameters like hardness and friability were within the acceptable limit. The drug content of Atorvastatin Calcium and Aspirin of all formulations within the acceptable limit indicating a uniform amount of drug in all formulations. The dissolution profiles of prepared bilayer tablets are displayed in Table 9 and clearly depicted in the form of figure 10 and 11. In Atorvastatin immediate release layer F1 formulation showed that maximum drug was released at 2 hr in 0.1 N HCl. At the same time, F3 formulation also showing 90% drug release. In Aspirin Pulsatile release layer, all formulations showed that limited release in 0.1 N HCl. After 5 hrs, there was a sudden release of drug, Eudragit S 100 maintained a lag time of 5hrs and the drug was released after 5hrs. The F3 formulation showing maximum drug release (97%) at 6 hr in pH 6.8 phosphate buffer.

Table 3: Standard Plot for Atorvastatin in 0.1N HCl.

Concentration (µg/ml)	Absorbance
0	0
5	0.242
10	0.464
15	0.679
20	0.888
25	1.09

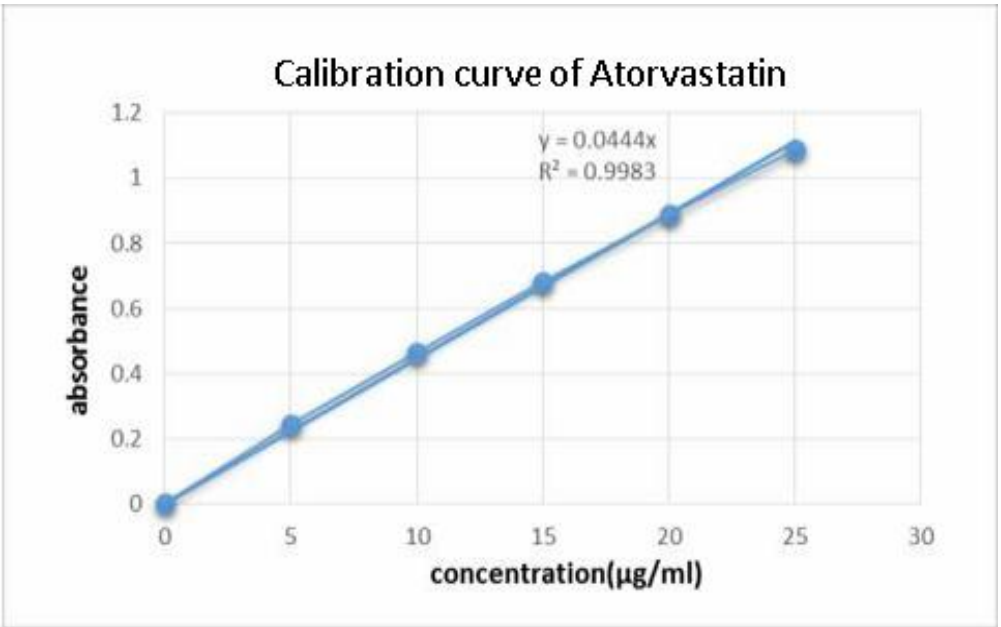

Fig. 2: Calibration curve of Atorvastatin in 0.1N HCl.

Table 4: Standard plot for Aspirin in 0.1N HCl.

Concentration (µg/ml)	Absorbance
0	0
5	0.192
10	0.38
15	0.565
20	0.752
25	0.912

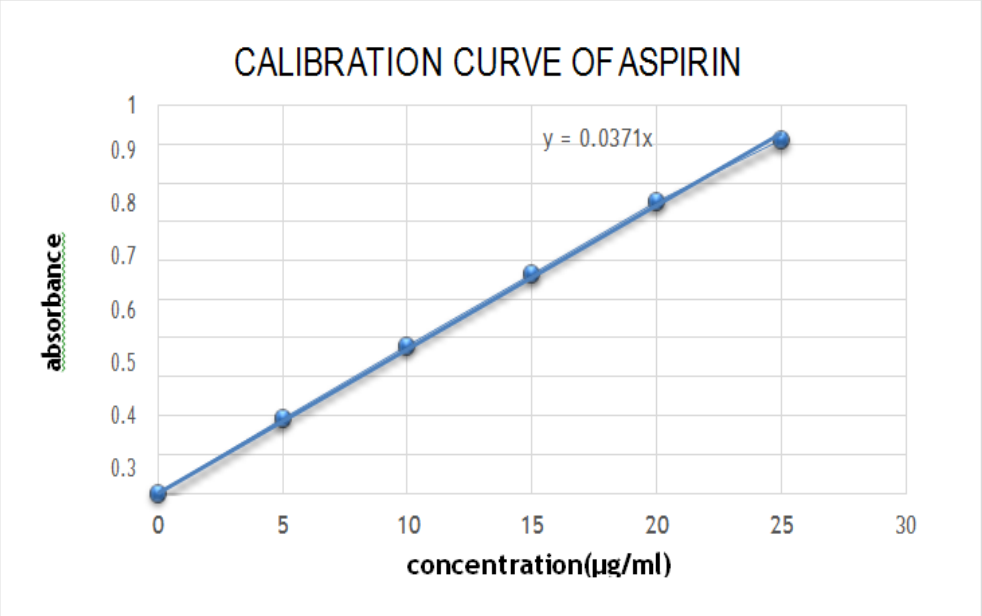

Fig. 3: Calibration curve of Aspirin in 0.1N HCl.

Table 5: Standard plot for Aspirin in 6.8 pH phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
5	0.02
10	0.036
15	0.058
20	0.075
25	0.098

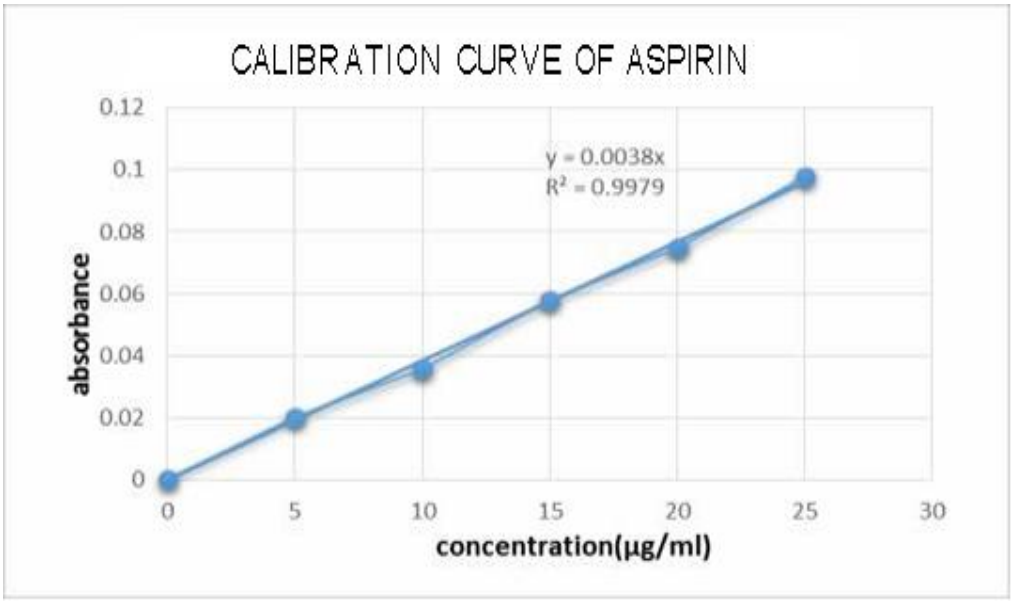

Fig. 4: Calibration curve of Aspirin in 6.8 pH phosphate buffer.

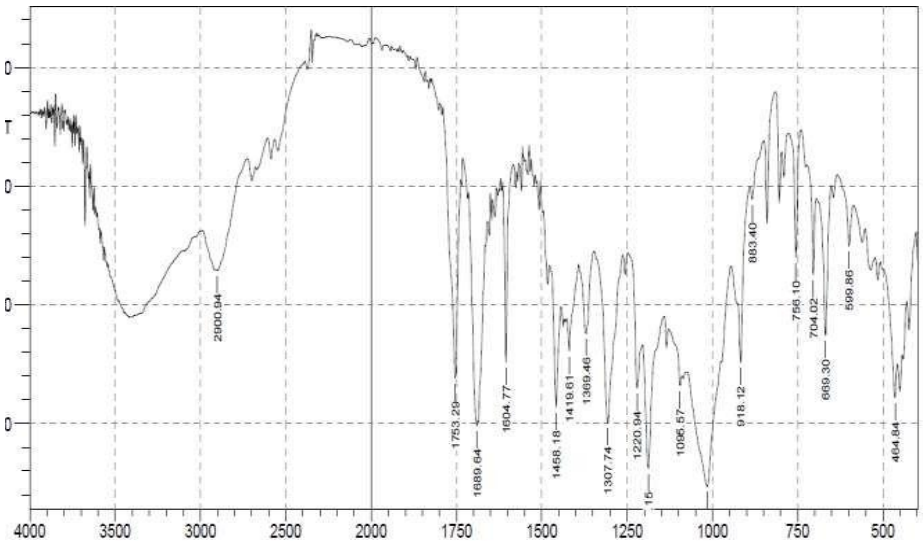

Fig. 5: FTIR study of Aspirin.

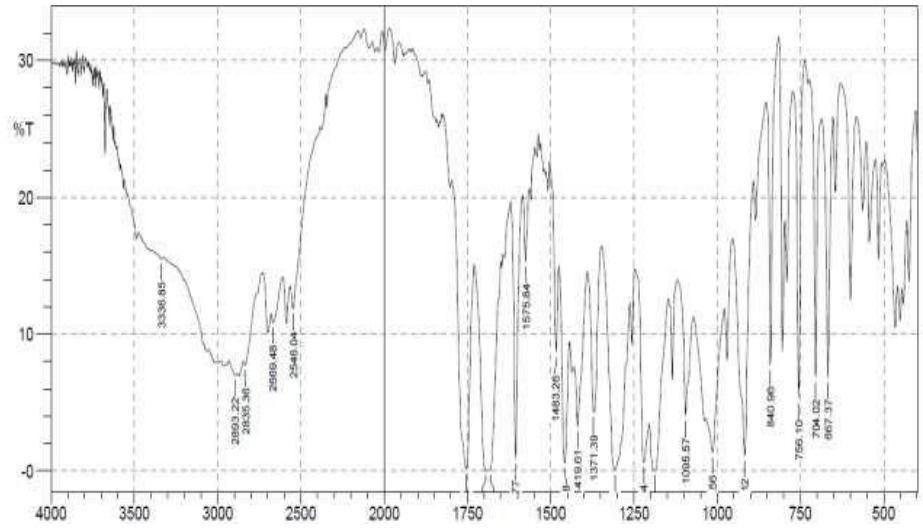

Fig. 6: FTIR study of Aspirin + MCC + CCS +SSG+ Eudragit S 100.

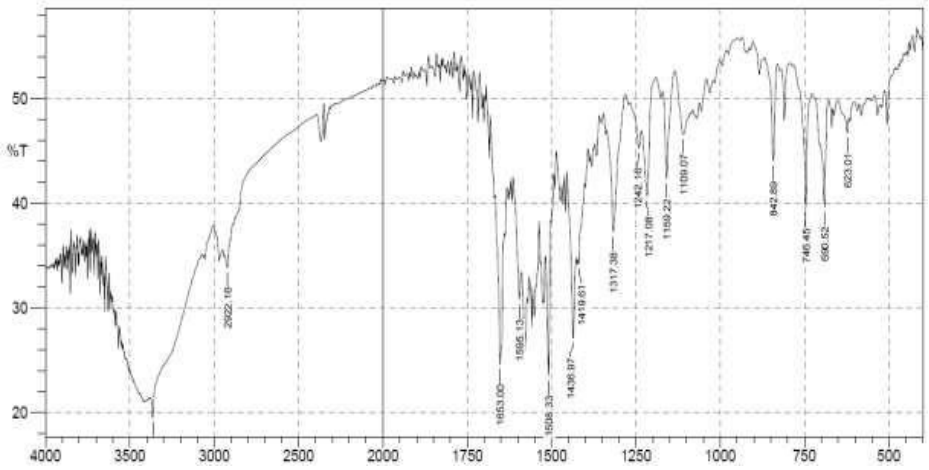

Fig. 7: FTIR study of Atorvastatin.

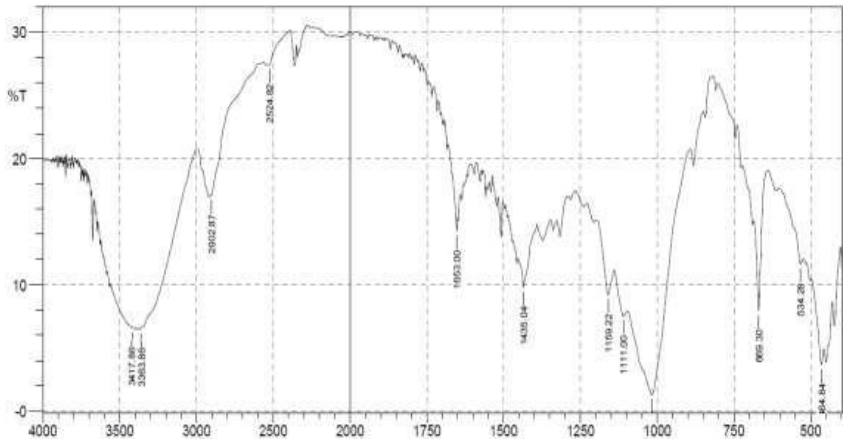

Fig. 8: FTIR study of Atorvastatin + MCC + Talc.

Fig. 9: Photographs of Bilayer tablets of Aspirin and Atorvastatin.

Table 6: Precompression parameters of Aspirin and Atorvastatin.

S.No	Parameters	F1	F2	F3	F4
Atorvastatin powder blend					
1	Bulk density(g/cm3)	0.59	0.64	0.58	0.55
2	Tapped density(g/cm3)	0.68	10.93	0.66	0.64
3	Carrs Index (%)	13.23		12.12	14.06
4	Hausner's ratio	1.15	1.12	1.13	1.16
5	Angle of repose	30.13	30.04	27.16	30.35
Aspirin powder blend					
1	Bulk density(g/cm3)	0.57	0.58	0.61	0.62
2	Tapped density(g/cm3)	0.69	0.66	0.68	0.69
3	Carrs Index (%)	17.3	12.21	10.29	10.14
4	Hausner's ratio	1.21	1.13	1.11	1.11
5	Angle of repose	31.23	30.54	29.25	31.28

Table 7: Post compression Parameters for Bilayer tablets of Aspirin and Atorvastatin.

Batch Code	Weight variation (%)	Hardness (kg/cm^2)	Friability (%)
F1	1.5	7.0±0.5	0.56±0.01
F2	1.2	7.0±0.5	0.62±0.01
F3	1.3	6.0±0.5	0.43±0.01
F4	0.9	6.5±0.5	0.48±0.01

Table 8: Drug content estimation for Bilayer tablets of Aspirin and Atorvastatin.

Batch Code	Drug Content of Atorvastatin layer (%)	Drug Content of Aspirin layer (%)
F1	76.89	79.25
F2	79.44	81.23
F3	93.27	94.45
F4	84.23	89.48

Table 9: Comparative In-Vitro Release of Bilayer Tablets of Aspirin and Atorvastatin.

S.No	Medium	Time(hr)	% drug release			
			F1	F2	F3	F4
Atorvastatin immediate release layer						
1		0	0	0	0	0
2		0.5	24.52	20.52	23.96	17.52
3		1.0	55.91	54.12	49.53	24.82
4		1.5	70.15	68.19	68.29	42.58
5		2.0	92.15	89.29	90.25	72.96
Aspirin Pulsatile release layer						
6	**0.1N HCl**	1	3.9	4.28	4.17	5.28
7		2	4.12	4.56	4.82	6.96
8	**6.8 pH phosphate buffer**	3	4.18	5.20	4.96	7.89
9		4	5.20	5.45	5.14	9.25
10		5	6.12	6.23	5.25	10.45
11		6	72.23	85.25	97.79	92.25

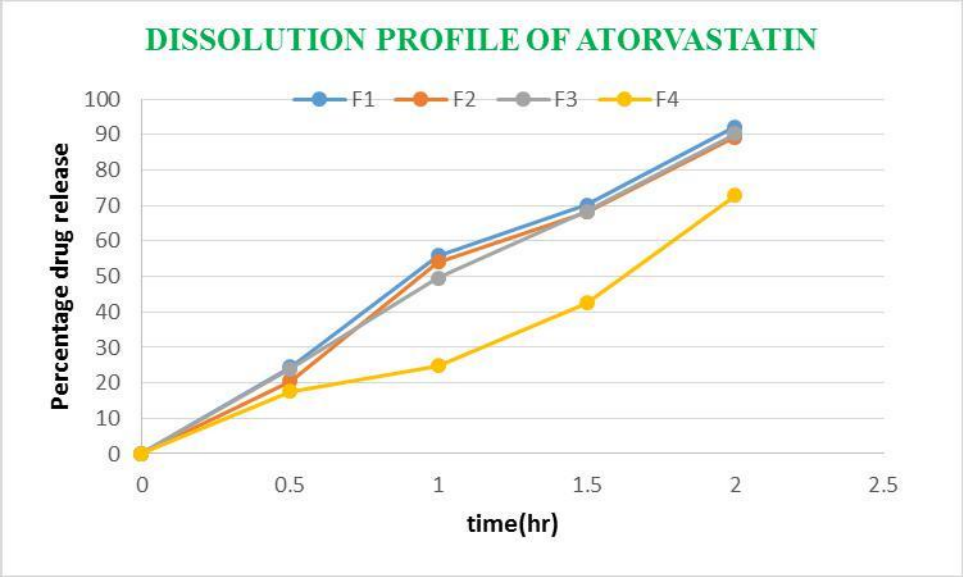

Fig. 10: Dissolution profile of Atorvastatin.

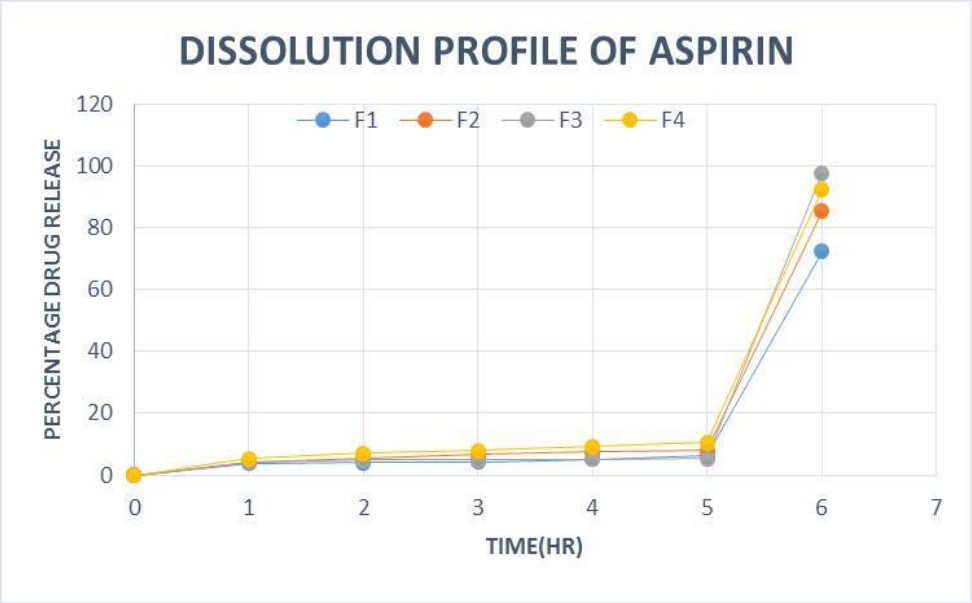

Fig. 11: Dissolution profile of Aspirin.

CONCLUSION

It was conclude that the Bilayer tablets containing immediate release layer of Atorvastatin and Pulsatile release layer of Aspirin were prepared by direct compression technique and their evaluation were carried out. The work reveals that F3 formulation was the best formulation and they are the good candidate for lowering the risk of heart attack. However stability studies and further clinical trials are needed to improve the tablet formulation by quality wise as well as efficacy wise.

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REFERENCES

1. Asha Spandana KM, Senthil kumar SK: Bilayer floating tablet – A Review, IJPSR Journal, 2013; 3(1): 1-8.
2. Anusha JSK & Karthik M: A Review on bi layered tablets, RRJPPS, 2016; 5(1): 118-119.
3. Patel Dipika, Patel Vijay: Formulation Development and evaluation of immediate release tablets containg atorvastatin calcium drug, International journal of pharmaceutical erudition, 2012; 2(1): 1-8.
4. Kalvimoorthi V. Narasimhan: Formulation Development And Evaluation of Aspirin Delayed Tablet, International journal of pharmaceutical sciences review and research, 2012; 7(1): 27.
5. Palanisami P, Jayakar B: Formulation Evaluation And Development of Immediate Release Film Coated Tablets Of Atorvastatin And Sustained Release Film Coated Tablets Of Ezetimibe In Capsules Form USP, International journal of medicine and pharmacy, 2013; 1: 33-34.
6. Reshma Fathima K, Sivakumar R: Design of Pulsatile Tablets of Pantoprazole Sodium: Factorial Design Approach, Saudi journal of medical and pharmaceutical sciences, 333-339.
7. Natarajan R, Abirami M: Combination of Aspirin, Clopidogrel Bisulphate And Atorvastatin Calcium Bilayer Tablets For Heart Diseases, wjpps, 2016; 5(2): 850-866.
8. Leon Lachman, The Theory and Practice of Industrial Pharmacy, 3rd edition, Indian edition, Varghese Publishing Home, 1987.
9. Martin A, Micromeretics, In: Martin A, Physical Pharmacy, Baltimores, MD: Lippincott Williams and Wilkins, 2001.