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FORMULATION AND EVALUATION OF BILAYERED TABLET OF ATORVASTATIN

B. Kalpana*, P. Prasuna Sundari and Dr. M. Bhagavan Raju

Sri Venkateshwara College of Pharmacy, 86, Hi-Tech City Road, Madhapur, Hyd 500081, Telangana State.

***Corresponding Author: B. Kalpana**

Sri Venkateshwara College of Pharmacy, 86, Hi-Tech City Road, Madhapur, Hyd 500081, Telangana State.

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ABSTRACT

Piperine is an alkaloid isolated from piper nigrum Linn (family: piperaceae) a natural bioenhancer. It enhances the bioavailability of drugs by inhibiting cytochrome p450 enzyme. Atorvastatin is a lipid lowering agent. It has approximately 12% bioavailability. Hence, the objective of present study is to enhance bioavailability of atorvastatin using piperine as a bioenhancer. The study was carried out to formulate bilayered tablets of atorvastatin with different concentration of piperine using superdisintegrants (sodium starch glycolate, croscarmellose sodium, crospovidone) by direct compression method. The prepared formulation was subjected to evaluation for hardness, weight variation, friability, content uniformity, invitro release studies. Among all the formulation F3 containing piperine (15mg), sodium starch glycolate, microcrystalline cellulose and magnesium stearate is considered as the best formulation when compared to all other formulations and compared with the marketed formulation of atorvastatin (Lipitor)

KEYWORDS: Piperine, Bioenhancer, Atorvastatin, Bioavailability.

INTRODUCTION

Bilayer tablets can be a primary option to avoid incompatibilities between API by physical separation and to enable the development of different drug release profiles. Bilayered tablet is suitable for- sequential release of two drugs in combination, separate two incompatible substances and for sustained release in which one layer is immediate and the second layer is maintenance dose.[1,2]

Bioenhancers are the agents, which, when combined with an active drug lead to the potentiation of the pharmacological effect due to increase in the bioavailability of the drug. One such example is piperine, an alkaloid obtained from piper nigrum. Piperine has the ability to increase drug bioavailability by increasing blood supply to the gastrointestinal tract, decreasing hydrochloric acid secretion which prevent breakdown of some drugs, increasing content of the gut, increasing enzymes like gamma-glutamyl transpeptidase which participate in active and passive transport of nutrients to the intestinal cells and inhibiting enzymes (CYP450, P-gp) participating in biotransformation of drugs, preventing their inactivation and elimination.[3] Hence from the reviews piperine is used as a bioenhancer, it showed enhanced bioavailability of various drugs such as rifampicin, isoniazid, simvastatin, theophylline, propranolol etc.[4,5] The objective of this research was to formulate and evaluate bilayered tablets of atorvastatin using piperine as a bioenhancer.

In the present work, the goal was to formulate bilayered tablets of atorvastatin with different concentrations of piperine using super disintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone) microcrystalline cellulose and magnesium stearate.

Atorvastatin is a novel semi synthetic and potent HMG-CoA inhibitor in statins family primarily used for the treatment of dyslipidemia and the prevention of cardiovascular disease.[6] Atorvastatin lowers plasma cholesterol and the lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver.[7] It has low oral bioavailability of 15% because of extensive first pass metabolism.[8] Thereby bioavailability of atorvastatin was enhanced by piperine. Hence an attempt was made to formulate and evaluate bilayered tablets of atorvastatin.

MATERIALS AND METHODS

Materials

Atorvastatin was obtained as gift sample from Ajanta pharma Ltd, Hyderabad. Piperine was obtained as gift sample from Ramini bio nutrition pvt limited. Hyderabad. Sodium starch glycolate, Croscarmellose sodium, Crosprovidone was obtained from Arcot chemicals, Hyderabad. Microcrystalline cellulose was obtained from Sri Krishna pharmaceutical Ltd., Hyderabad. Magnesium stearate was purchased from SD fine chemicals, Mumbai. All materials used in the study were of analytical grade.

Preformulation studies

Preformulation study of the drug was carried out to establish its identity and purity which includes λmax of the drug. An absorption maxima of atorvastatin was determined using Phosphate buffer, pH 6.8 solution ranging from 4-20µg/ml were scanned from 200-400 nm using UV spectrophotometer.

Preparation of Tablets

The tablets were prepared by direct compression method.[9]

Accurately weighed quantity of atorvastatin, piperine, super disintegrants (sodium starch glycolate, croscarmellose, Crosprovidone) and mcc mixed thoroughly and passed through # 40 mesh and collected. Magnesium stearate was passed through # 60 mesh and collected. Then the major raw materials were mixed with the lubricant. Lubricated blend was compressed using 6mm flat round shaped punches plain on both sides in compression machine.

Table No. 1: Composition of Atorvastatin Layer.

S.No	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1	Atorvastatin	20	20	20	20	20	20	20	20	20	20	20	20
2	Sodium starch glycolate	3	3	3	3	-	-	-	-	-	-	-	-
3	Croscarmellose	-	-	-	-	3	3	3	3	-	-	-	-
4	Crosprovidone	-	-	-	-	-	-	-	-	3	3	3	3
5	Micro crystalline cellulose	51.8	51.8	51.8	51.8	51.8	51.8	51.8	51.8	51.8	51.8	51.8	51.8
6	Magnesium stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Table No.2: Composition of Atorvastatin Layer.

S.NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1	Piperine	5	10	15	20	5	10	15	20	5	10	15	20
2	Sodium starch glycolate	3	3	3	3	-	-	-	-	-	-	-	-
3	Croscarmellose	-	-	-	-	3	3	3	3	-	-	-	-
4	Crosprovidone	-	-	-	-	-	-	-	-	3	3	3	3
5	Micro crystalline cellulose	66.8	61.8	56.8	51.8	66.8	61.8	56.8	51.8	66.8	61.8	56.8	51.8
6	Magnesium stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

PRECOMPRESSION EVALUATION[10,11]

Angle of repose (θ): it is defined as maximum angle possible between the surface pile of powder and the horizontal plane.

The powder mixture was allowed to flow onto the surface through the funnel fixed to a stand at definite height (h). The angle of repose was calculated by measuring the height and radius of the heap of powder formed.

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

Where, θ is the angle of repose,

h is the height in cms,

r is the radius in cms.

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder and initial weight will be noted. This initial volume is called bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Bulk density (g/ml) = Mass of the powder/Tapped volume.

Tapped Density (Dt): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 taps and after that the volume was measured and continued operation till the two consecutive readings were equal and the tapped volume will be noted. It is expressed in g/ml and is given by

Tapped density (g/ml) = Mass of powder/bulk volume.

Carr's index (or) %compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

Carr's index (%) = [(Tapped Density-Bulk density)/Tapped density] ×100

Hausner's ratio: Hausner's ratio is the measurement of frictional resistance of the drug and the ideal range

should be 1.2-1.5 it is calculated by the following formula.
Hausner's Ratio = Tapped density/Bulk density

POST COMPRESSION EVALUATION[12-15]
All the above formulations were compressed and subjected for evaluation such as Hardness, Weight variation, Friability, Thickness and Drug content.

Hardness
The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The hardness was measured in terms of kg/cm2.

Weight variation
Formulated tablets were tested for weight uniformity. Twenty tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.
% weight variation = Average weight- Individual weight/Average weight×100

Friability
The Roche friability test apparatus was used to determine the friability of the tablets. Ten pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.
Friability = Initial weight- Final weight / Initial weight×100

Thickness and diameter
Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of then tablet was measured using screw gauge. It is measured in mm.

Drug Content
Two tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. Then the samples were transferred to a 100ml volumetric flask and the volume was made up to the mark with distilled water. The content was shaken periodically and kept for one hour to allow the drug to dissolve completely. The mixtures were filtered and appropriate dilutions were made by taking aliquots of 2.5ml and 5ml to give a concentration of 25 ppm and 50 ppm respectively. The drug content in each tablet was estimated at λmax of 246nm against blank reference.

In Vitro Drug Release Studies
In-vitro release studies was carried out using pH 6.8 buffer containing tween (1%) as dissolution medium at 37ºc and rotational speed of 75 rpm for 1h.5ml of dissolution medium was withdrawn at every 5min time intervals and then estimated spectrophotometrically. Dissolution mechanism of the formulations was analyzed by plotting drug release versus time plot.

RESULTS AND DISCUSSION
Determination of absorption maxima of atorvastatin
The absorption maximum of atorvastatin was found to be 246nm.

PRECOMPRESSION EVALUATION
Table No: 3 Pre-Compression Data of Atorvastatin Powder Blend.

Formulation code	Bulk density (gm/ml) ±SD	Tapped density (gm/ml) ±SD	Hausner's ratio ±SD	Carr's compressibility Index (%)±SD	Angle of repose(º) ±SD
SSG	0.39±0.06	0.49±0.05	1.18±0.06	12.24±0.10	26.56±0.25
CS	0.31±0.03	0.40±0.04	1.29±0.08	10.25±0.09	30.00±0.24
CP	0.34±0.04	0.38±0.05	1.13±0.02	13.8±0.24	29.24±0.21

From the results listed in the table 3, the formulation is shown to have bulk density was 0.34gm/ml, tapped density was 0.38gm/ml, carr's index was 13.8, Hausner's ratio was 1.13 the values showed low intra particulate friction between the powdered blend. The angle of repose was found to be 29.24 indicating good flow properties of the blend. The powdered blend was found to be free flowing with no intra and inter particulate friction and can be efficiently suitable to compress in to tablets.

Table No 4: Pre-Compression Data of Piperine Powder Blend.

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's compressibility Index (%)	Angle of repose(°)
F1	0.34±0.03	0.25±0.03	1.06±0.04	12.76±0.15	25.48±0.14
F2	0.29±0.05	0.27±0.05	1.20±0.06	16.58±0.12	30.27±0.21
F3	0.31±0.04	0.38±0.04	1.11±0.08	12.79±0.07	26.52±0.18
F4	0.39±0.06	0.49±0.06	1.18±0.04	12.24±0.16	28.79±0.22
F5	0.42±0.05	0.40±0.05	1.25±0.07	8.39±0.14	34.76±0.19
F6	0.37±0.04	0.57±0.06	1.09±0.02	10.43±0.13	24.89±0.16
F7	0.30±0.02	0.19±0.03	1.12±0.03	16.72±0.15	31.47±0.18
F8	0.44±0.05	0.46±0.04	1.27±0.05	12.46±0.11	33.29±0.20
F9	0.43±0.06	0.45±0.05	1.19±0.04	17.29±0.23	27.38±0.21
F10	0.35±0.04	0.52±0.04	1.32±0.06	17.1±0.21	27.73±0.15
F11	0.30±0.03	0.19±0.02	1.12±0.03	18.72±0.18	31.47±0.23
F12	0.39±0.05	0.49±0.04	1.18±0.04	12.24±0.12	34.76 ±0.24

From the results table 4, the formulation is shown to have bulk density was 0.31gm/ml, tapped density was 0.38gm/ml, carr's index was 12.79, Hausner's ratio was 1.11 the values showed low intra particulate friction between the powdered blend. The angle of repose was found to be 26.72 indicating good flow properties of the blend. The powdered blend was found to be free flowing with no intra and inter particulate friction and can be efficiently suitable to compress in to tablets**.**

Post-compression parameters

Evaluation parameters such as weight variation, thickness, hardness, friability and drug content of atorvastatin and piperine bilayered tablets were evaluated and listed in tables.

Evaluation of atorvastatin bilayered tablets.

The formulated bilayered tablets were subjected to various evaluation parameters such as.

Hardness: The Hardness of bilayered tablets was determined by using Mansatto hardness tester. The data obtained is represented below in Table No: 5.

Weight variation: The weight of the bilayered tablets was determined by using Sartorius balance. The data obtained is represented below in Table No: 5.

Friability: The friability of bilayered tablets was determined by using Roche friability test apparatus. The data obtained is represented in the Table No: 5.

Thickness: Thickness of the tablets was measured using digital screw gauge. The data obtained is represented in Table No: 5.

Drug content: atorvastatin bilayered tablets (F1 –F12). From each formulation of prepared tablets, 2 tablets were randomly collected and powdered and transferred separately to a 100ml volumetric flask. Volume was made up to 100ml with pH 6.8 phosphate buffer and subjected for vortex mixing and bath sonication for dissolving the drug. Appropriate dilutions were made with pH 6.8 buffer and the amount of atorvastatin was analyzed using a UV visible spectrophotometer at 246nm.The data obtained is represented in the Table No: 6.

Table No 5: Evaluation Data Of Atorvastatin Bilayered Tablets.

Formulation code	Hardness (kg/cm^2)±SD*	Friability (%)±SD*	Weight variation (%)±SD*	Thickness (nm)±SD*
F1	4.5±0.16	0.65±0.04	0.29±0.01	2.50±0.02
F2	4.0±0.18	0.57±0.03	0.14±0.01	2.48±0.04
F3	4.5±0.21	0.68±0.05	0.56±0.02	2.50±0.05
F4	4.3±0.5	0.53±0.04	0.13±0.03	2.48±0.04
F5	5.2±0.34	0.66±0.03	0.23±0.05	2.49±0.04
F6	4.5±0.14	0.59±0.06	0.28±0.02	2.50±0.03
F7	3.8±0.38	0.60±0.04	0.29±0.01	2.50±0.03
F8	5.0±0.13	0.55±0.07	0.33±0.03	2.50±0.03
F9	4.8±0.34	0.54±0.01	0.27±0.04	2.48±0.02
F10	4.7±0.21	0.50±0.04	0.27±0.01	2.50±0.03
F11	4.7±0.21	0.50±0.04	0.27±0.01	2.50±0.03
F12	5.0±0.15	0.46±0,03	0.33±0.01	2.48±0.04

The prepared bilayered tablets were evaluated for their weight variation, hardness, friability. The weight variation was within the specified limits and it was varied between 0.13 to 0.33%. Hardness of the tablet

should be 3 to 5 kg/cm2. Friability of tablets should be not more than 1%. Hence the friability is less than 1% in all the batches which indicates tablet's ability to withstand stock during time of transportation and handling. It is clear from the above factors that the physical parameters evaluated for the different batches of bilayered tablets were within the specified limits.

Table No: 6 drug content data of atorvastatin bilayered tablets.

Formulation code	Drug content (%) ±SD*	Formulation code	Drug content (%) ±SD*
F1	84.15±2.06	**F7**	90.15±2.21
F2	83.36±2.5	**F8**	89.76±4.08
F3	92.42±4.04	**F9**	86.14±2.5
F4	80.36±1.35	**F10**	90.15±2.27
F5	88.76±2.27	**F11**	85.10±2.14
F6	85.73±2.24	**F12**	84.12±2.3

The prepared bilayered tablets of all formulations were evaluated for drug content uniformity. The drug content of F3 formulation was found to be 92.42%.

In Vitro Drug Release Studies

In vitro drug release studies of formulated bilayered tablets were determined by using dissolution type 2 apparatus. The data obtain Table No. 4.5

- Type of model : Dissolution type II (paddle type)
- Medium : pH 6.8buffer containing tween (1%)
- Temperature : 37°c
- Time : 1hour

Table No 7: Cumulative % drug release profile of formulations (F1-F4).

Time (min)	Cumulative% drug release			
	F1±SD*	F2±SD*	F3±SD*	F4±SD*
0	0	0	0	0
5	26.48±0.05	30.54±0.05	28.12±0.04	50.13±0.04
10	36.25±0.04	49.35±0.03	46.34±0.05	56.44±0.03
15	46.31±0.05	60.55±0.04	68.72±0.04	73.43±0.04
30	55.30±0.03	73.90±0.02	79.67±0.03	80.54±0.03
45	66.02±0.02	77.80±0.03	96.24±0.02	89.34±0.02

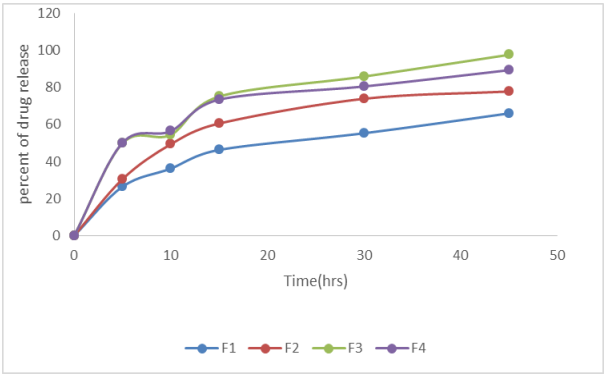

Figure No: 1 In Vitro Drug Releases of Atorvastatin Bilayered tablets (F1- F4).

Graph showing comparative drug release data of atorvastatin bilayered tablets formulated with different concentration of piperine using sodium starch glycolate (F1-F4) is shown in figure1. The results in vitro dissolution studies of atorvastatin bilayered tablets were formulated with different concentrations of piperine using sodium starch glycolate. Formulation F1, F2, F3, F4 containing different ratios of piperine showed the percentage cumulative drug release of 66.02%, 77.80%, 97.63%, and 89.34%.

Table No: 8 cumulative % drug release profile of formulations (F5-F8).

Time (min)	Cumulative % of drug release			
	F5±SD*	F6±SD*	F7±SD*	F8±SD*
0	0	0	0	0
5	25.34±0.04	45.16±0.05	35.25±0.04	46.25±0.04
10	30.13±0.05	50.66±0.04	48.47±0.05	55.32±0.4
15	50.19±0.03	58.49±0.03	50.31±0.03	66.09±0.05
30	54.80±0.04	65.50±0.04	65.02±0.04	74.38±0.03
45	70.90±0.02	75.90±0.03	76.88±0.02	80.88±0.02

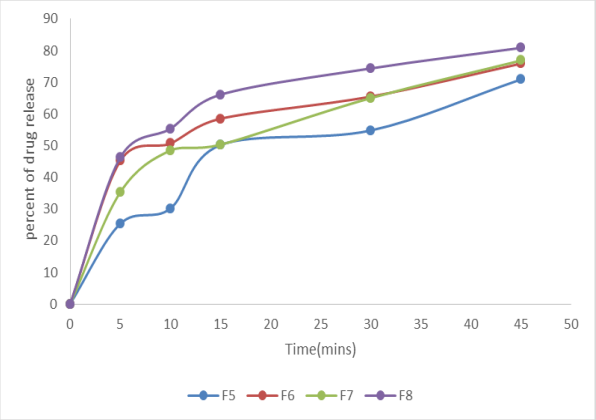

Figure No: 2 in Vitro Drug Release of Atorvastatin Bilayered tablets (F5- F8).

Graph showing comparative drug release data of atorvastatin bilayered tablets formulated with different concentration of piperine using croscarmellose sodium (F5-F8) is shown in figure 2.

The results in vitro dissolution studies of atorvastatin bilayered tablets were formulated with different concentrations of piperine using croscarmellose sodium. Formulation F5, F6, F7, F8 containing different concentrations of piperine showed the percentage cumulative drug release of 70.90%, 75.90%, 76.88%and 80.88%.

Table No: 9 Cumulative % drug release profile of formulations (F9-F12).

Time (min)	Cumulative % drug release			
	F9±SD*	F10±SD*	F11±SD*	F12±SD*
0	0	0	0	0
5	28.39±0.04	35.48±0.04	40.14±0.05	42.51±0.04
10	36.89±0.05	49.51±0.05	52.17±0.04	55.14±0.03
15	46.09±0.03	67.47±0.03	65.32±0.03	69.32±0.04
30	58.21±0.04	72.12±0.04	76.13±0.04	74.13±0.03
45	67.80±0.02	79.13±0.03	80.15±0.02	81.65±0.02

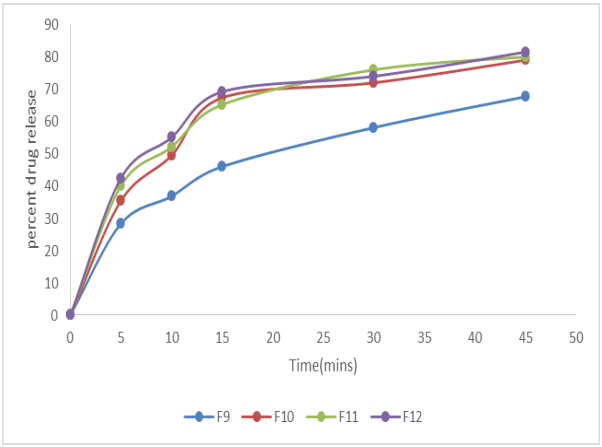

Figure No: 3 in vitro drug release of atorvastatin bilayered tablets (F9- F12).

Graph showing comparative drug release data of atorvastatin bilayered tablets formulated with different concentration of piperine using crospovidone (F9-F12) is shown in figure 3.

The results in vitro dissolution studies of atorvastatin bilayered tablets were formulated with different concentrations of piperine using Crosprovidone. Formulation F9, F10, F11, F12 containing different concentrations of piperine showed the percentage cumulative drug release of 67.80%, 79.13%, 80.15%, and 81.65%.
The percentage cumulative drug release of 28.12 to 96.24% highest percentage of drug release 96.24% was observed from the formulation F3.

Comparison of In-vitro dissolution studies of optimized bilayered tablets of atorvastatin with the In-vitro dissolution studies of marketed formulation of atorvastatin tablet (Lipitor 20mg)

The drug releases of the optimized bilayered tablets of atorvastatin are compared with the drug release of the marketed formulation of atorvastatin (Lipitor (20mg)). From the figure No:1.it was found that the drug release of the optimized bilayered tablets of atorvastatin drug release was found to be 96.24% in 45 mins and the marketed formulation tablet was found to be 92.41% in 45mins.

Table No: 10 in-vitro release profile of F3 and marketed formulation.

Time (mins)	% DR of F3	%DR of MF
0	0	0
5	28.12	24.75
10	46.34	31.86
15	68.72	55.25
30	79.67	74.12
45	96.24	92.41

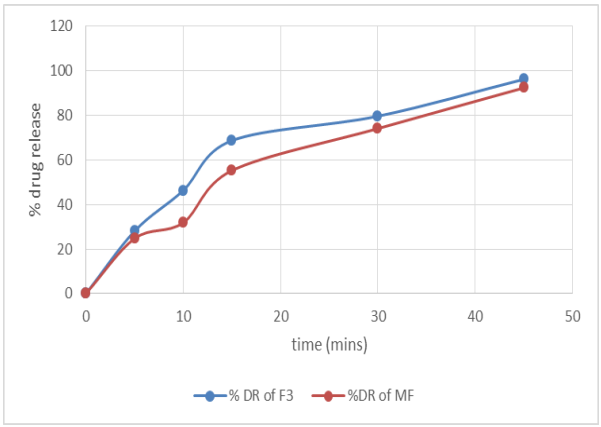

Figure No: 4 in-vitro release profile of F3 and marketed formulation.

CONCLUSION

Bilayered tablets of atorvastatin were successfully prepared with different concentrations of piperine using super disintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone) microcrystalline cellulose and magnesium stearate. Bilayered tablets of atorvastatin were formulated and formulations were evaluated for Hardness, weight variation, friability, drug content and invitro dissolution studies. Formulation F3 containing piperine (15mg) and sodium starch glycolate were selected as best formulation based on invitro dissolution studies. Best formulation selected based on the invitro release studies and compared it the marketed formulated of atorvastatin (Lipitor)**.** The co-administration of piperine with atorvastatin improved the oral bioavailability of atorvastatin.

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