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FORMULATION AND *IN VITRO* EVALUATION OF METFORMIN HYDROCHLORIDE AND ATORVASTATIN CALCIUM BILAYERED TABLETS

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ABSTRACT

The present work was carried out to formulate and evaluate bilayer tablets, Sustained release of Metformin HCl and immediate release of Atorvastatin Calcium used for adjunctive therapy to diet and exercise in patients with diabetic dyslipidemia. Drug exicipient compatibility studies were conducted and show satisfactory results. The formulation were prepared as bilayer tablets using Hypromellose and sodium CMC by wet granulation process containing sustained release of Metformin HCl and immediate release layer of Atorvastatin Calcium. Hyperglycemia is the technical term for high blood glucose (sugar). It happens when the body has too little or not enough insulin or when the body can‘t use insulin properly. The tablets were prepared by wet granulation method. Granules were evaluated for pre compression parameters and the tablets were evaluated for post compression parameters. Optimized formulations were evaluated for *in vitro* dissolution test. Stability studies were conducted for F9-F11.

KEYWORDS

Metformin HCl, Atorvastatin Calcium, Bilayer tablets and Stability studies.

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INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there

for the desire time, be excluded from other site. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research. Once a day or at the most twice a day formulation is of most precious sorts for scientists working with oral dosage forms. A sustained release preparation that makes once or twice daily administration of drug possible might be an advantageous dosage form, especially in long-term therapy[1]. This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. With advancement in technology and increase in awareness, towards modification in standard tablet is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient‘s perspective and utilize an approach that is unlikely to add complexity during regulatory approval process[2].

Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is controlled release part of single or multiple actives. They are also called as bilayer tablet, multi-layer matrix tablet[3].

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site (s) of action is attainted immediately and is then maintained constant for the desired duration of the treatment[3]. Over the past 30 years as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantage of modified release per oral dosage forms, greater attention has been focused on development of sustained, controlled release and delayed release system. There are several reasons for the attractiveness of this dosage form. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting.

MATERIALS AND METHODS

MATERIALS

Metformin HCl was obtained as a gift sample from Wanbury ltd. Atorvastatin Calcium was obtained as a gift sample from Biocon ltd. Hydroxyl propyl methylcellulose Shinetsu chemicals. Povidone IP (K-30), Cross carmellose sodium, Colloidal Silicon Dioxide, Lactose, Cross povidone and Micro crystalline cellulose, Magnesium stearate were obtained from BASF, Sanmar ltd. All the ingredients used were of analytical grade.

METHODS

Formulation of bilayered tablet

Layer I: Metformin hydrochloride SR granulation

Sift Metformin Hydrochloride, HPMC K4M, HPMC 15 CPs, Sodium CMC, and DCP anhydrous through # 40 meshes. Sift Quinoline yellow lake through #100 meshes. Load the materials of stage 1 into rapid mixture granulator and mix for 15 min at slow speed. Dissolve Povidone (K-30) in Purified water. Add slow binder solution and mix for 5 min at slow speed. After complete addition of binder solution, mix until to get granules. Load the wet granules in to Tray drier; dry the granules at 50˚C till the moisture content of granules is between 2 to 3%. Mill the dried granules of stage -5 through multimills with 1.5 mm screen and sift through #20 mesh sieve. Mill the retained granules through Multimill and sift through # 20 meshes. Sift Colloidal silicon dioxide through # 40

meshes, Magnesium Stearate and Talc through #60 meshes. Load the granules of stage-6 and lubricants into octagonal blender. Mix for 3 minutes at slow speed (Table No.1).

Layer II: Atorvasatatin Calcium Granulation

Sift Atorvastatin Calcium, Calcium Carbonate (light), Lactose monohydrate, microcrystalline cellulose, Croscarmellose Sodium, Aerosil through #40 meshes. Then Load the materials into planetary mixture and mix for 15 min at fast speed. Dissolve polysorbate-80 in purified water. Add slowly binder solution and mix for 5 min at slow speed. After complete addition of binder solution, mix until to get granules. Load the wet granules into FBD; Dry the granules at 50°C till the moisture content of the granules should be between 3 to 4%. Mill the dried granules of through multimill with 1.5 mm screen and shift through # 20 mesh sieve. Mill the retained granules through multimill and sift through #20 meshes. Sift Magnesium stearate and Talc through #60 meshes. Load the granules and Lubricants into planetary mixture. Mix for 3 min at slow speed. Compress the Metformin Hydrochloride sustained release layer and Atorvastatin Calcium immediate release layer in double rotary compression machine with the specification (Table No.2).

Film coating

Coating solution preparation

Dissolve the Transparent coat ic-u-6638 of (1:1) Isopropyl alcohol and Methylene chloride. Mix it well and filter the solution to 200 mesh nylon cloth (Table No.3).

EVALUATION PARAMETERS[4-6]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMENMB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr; samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of bilayer tablet

Angle of repose

The angle of repose was determined by the funnel method (Repos gram). The accurately weighed drug or tablet blend was taken in a funnel. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\mathbf{Tan\ \theta = h / r}$$

Where h = height of the pile

r = radius of the pile.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined by passed through a #18 sieve to break the clumps, if any. Accurately weighed 50 g of the drug was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 $\pm$ 2 mm. The tapped volume (V_a) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tap volume was measured to the nearest graduated unit. The same thing was done for powder blend of the tablet. The LBD and TBD were calculated in g per ml using following formulae,

$$\mathbf{Bulk\ density = M / V_0}$$

Where M = Mass of the sample.

V_0 = Bulk volume.

Tapped density (Td)

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. The cylinder was placed in the tapped density apparatus and allowed to fall under its own weight on to a hard surface (USP-II), that provides fixed a drop of 3mm(±10%) at a nominal rate of 250 drops per minute is used. Tapping was continued until no further change in volume was noted. Td was calculated using the following equation;

$$\mathbf{D_t = m / V_i}$$

Where, m = Mass of the powder.

V_I = Tapped Volume of the powder.

Compressibility index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30 % is defined as the free flowing material.

$$C_I = (1-V_i/V_0).100$$

Where V_I = Tapped Volume of the powder.

V_0 = Bulk volume

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = D_t/D_b$$

Where, Dt = the tapped density,

Db = the bulk density.

Post compression studies of bilayer tablet

Physical appearance

The general appearance of tablets its visual identity and over all elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color presence or absence of odour, taste, surface texture and consistency of any identification marks.

Tablet size and thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity .The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter .Tablet thickness should be controlled within a + or - 5%. In addition thickness must be controlled to facilitate packaging.

Average weight of tablets

Take randomly 20 tablets and weigh accurately 20 tablets and calculate the average weight.

Average weight =weight of 20 tablets/20

Hardness test

This is the force required to break a tablet in diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel which the tablet fractures. Hardness of 5 kg considered as suitable for handling the tablet.

Uniformity of dosage units (by weight variation method)

Take randomly 30 tablets, weigh collectively and individually 30 tablets and calculate average weight of the tablets and % assay of individual dosage units by using formula:-

$$\text{Weight variation} = \frac{\text{Assay} \times \text{Individual weight}}{\text{Average wt}}$$

Friability test (As per USP)

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. After 100 rotations (4 minutes), the tablets were taken out from the friabilator. Permitted friability limit is 1.0%. The percent friability was determined using the following formula:-

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = Weight of the tablet before test.

W_2 = Weight of the tablets after test.

Drug content uniformity

The tablets were assayed for the drug content using methanol as the extracting solvent. Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml methanol. The solution was diluted appropriately using pH 6.8 phosphate buffer and The Atorvastatin Calcium and Metformin HCl was estimated spectrophotometrically at 253 nm and 232 nm using pH 6.8 phosphate buffer and 0.1N HCl as blank.

Content of active ingredients (assay)

The amount of active ingredient(s) was determined and compared with standards stated in the monograph. Twenty tablets were used for assay. All the batches should fall within the limit of 95 - 105 %.

***In vitro* dissolution**

In vitro release of the drug[5] was determined by estimating the dissolution profile. Dissolution test for Atorvastatin Calcium and Metformin HCl. *In vitro* drug release study was carried out using USP apparatus II at 37 ± 0.5^0C for 1hrs, at 100rpm.0.1N HCl (pH 1.2) was used as dissolution medium for the first hr, followed by pH 6.8 phosphate buffer for further 12hrs. 5 ml of sample was withdrawn at regular time interval and was replaced with an equal volume of fresh dissolution medium to maintain the equilibrium. Collected samples are analyzed by UV spectrophotometer at 253nm and 232nm respectively for Atorvastatin Calcium and Metformin HCl.

Stability studies

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists detoriation. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Detoriation of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

RESLTS AND DISCUSSION

In order to achieve the development of a conventional and sustained release dosage forms, currently, the Bilayer technology with multiple layer having a rapid and sustained phase has been investigated. This formulation can be used for the treatment of type-2 Diabetes Mellitus with associated Dyslipidemia. For the study, Metformin hydrochloride and Atorvastatin Calcium was used as a model drugs for the treatment of type-2 Diabetes Mellitus with associated Dyslipidemia, which was formulated by using wet granulation method where the core consist of an immediate release layer(Atorvastatin Calcium) and sustained release layer (Metformin HCl) coated by using a Transparent coat-U-6638.

Pre-formulation Studies

The IR spectrum of pure Metformin Hydrochloride and Atorvastatin Calcium was compared with the IR spectrum of formulated Metformin Hydrochloride of sustained release and immediate release of Atorvastatin Calcium bilayer tablets. The IR spectrums of the formulation where matching with IR spectrum of pure Metformin Hydrochloride and Atorvastatin Calcium. There is no appearance or disappearance of any characteristics peaks. This shows that there is no interaction between the drugs, excipients and polymer used in the tablets (Figure No.1 and 2).

Evaluation of blend materials of Bilayer tablets

Angle of repose for layer 1 granules (Metformin Hydrochloride sustained release) was found to be between 21.1° to 28.7° and layer 2 granules (Atorvastatin Calcium immediate release) was found to be between 21.2° to 28.9°, which is well within the specified limit of 20° to 30° and the flow type is good. Bulk density for layer 1 granules was found to be between 0.46 to 0.87 and layer 2 granules was found to be between 0.47 to 0.87. Tapped density for layer 1 was found to be between 0.36 to 0.74 and layer 2 granules was found to be 0.25 to 0.78. Carr's index for layer 1 was found to be in the range of 9.4 - 25.36 and for the layer 2 was found to be between 11.25 - 25.02. All the granules are well within the specification limit. Hauser's ratio for layer 1 was found to be between 1.050 - 1.321 and for the layer 2 to was found to be between 1.101 - 1.250, with this, the granules where found to be free flowing material and shows suitability to be compressed as tablets at expected weight (Table No.4).

Evaluation of Bilayer Tablets

All the batches of layer 2 tablets fulfilled the official requirement of uniformity of dosage units. The average percentage deviation of 20 tablets of each formula was less than ±3%. Drug content was found to be uniform among the three formulations and ranged from 97.5 and 99.45. The thickness of tablet ranged from 5.8 - 5.9 mm. The hardness and percentage friability of all batches ranged from 9.5 -

11.0 Kg / Cm^2 and 0.11 - 0.18 % respectively (Table No.5 and 6).

Layer 1 Metformin Hydrochloride

Based on the pre-formulation data, HPMC K4M and HPMC 15 CPs was taken us drug release retardants for sustained release layer of Metformin Hydrochloride. The formulation consists of two layers immediate release layer of Atorvastatin and a sustained release layer of Metformin Hydrochloride. In Formulation F1, F2 and F3 the sustained layer consists of HPMC K4M in the ratio of 2.4%, sodium CMC in the ratio of 23.6% and HPMC 15 CPs in the ratio of 0 %, 0.6% w/w and 1.2% w/w respectively, where the weight of tablets was adjusted with dicalcium phosphate anhydrous to 845mg. Here the release of drug F1, F2 and F3 was not within the specification limits i.e. the release of drug at first and fourth hour was more than the limits.

In order to retard the release of drug to be meet the specification limits, the polymer concentration (HPMC K4M and HPMC 15 CPs) was increased from 2.4% to 4.8% and HPMC15 CPs in the ration of 0%, 0.6% and 1.2 % w/w respectively in formulation F4, F5 and F6 where the weight of tablets was adjusted with Dicalcium phosphate anhydrous to 845mg. To match the release profile of drug, the polymer concentration was still increased from 4.8% to 7.1% and HPMC 15 CPs in the ratio of 3.6%, 2.4% and 1.2% w/w respectively in formulation F7, F8 and F9 where the weight of tablets was adjusted with Dicalcium phosphate anhydrous to 845mg. It was found that release profile of F7, F8 and F9 was found to be satisfactory, where the release of drug in F7 and F8 at first and fourth hour was at lower side when compare with F9, which was meeting the proposed specification.

Among the three trials from F7 to F9, the trial F9 was found to be satisfactory, where the release of the drug at first, fourth and eighth hours was 30.1%, 69.6% and 89.6%, hence the reproducibility trials (F10 and F11) with the same formula of F9 was taken to confirm whether it meets the specification and it was found to be reproducible.

Layer-2 Atorvastatin Calcium

In the formulation F1, F2, F3 and F4 immediate release layer of Atorvastatin Calcium was prepared by wet-granulation method with calcium carbonate light, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide and quinoline yellow using purified water as granulating agent. The release profile of Atorvastatin Calcium was found to be lesser than the limits and hence the concentration of croscarmellose sodium was increased from 1.0% to 4.0% w/w in F1 to F4. The release profile of Atorvastatin Calcium for F1 to F4 was 36.5%, 43.8%, 55.1% and 60.7% respectively. In order to increase the release rate of Atorvastatin Calcium, solubility enhancer namely polysorbate-80 (tween-80) was added. The concentration of polysorbate-80 ranged from 0.5%, 1.0% and 1.5% w/w in F5, F6 and F7 respectively. The release of Atorvastatin Calcium for F5, F6 and F7 was 65.89%, 85.82% and 96.7% respectively.

From the above results it was found that polysorbate-80 used at concentration of 1.5% w/w in F7 was found to give better release profile for Atorvastatin Calcium (Table No.7).

Stability Studies

The trial F9 to F11 was charged for stability at 30^0C / 65 % RH and 40^0C/ 75 % RH and the one month accelerated condition results was found to be satisfactory (Table No.8).

Table No.1: Formulation of Metformin Hydrochloride sustained release layer

S.No	Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	Metformin HCl	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00
2	Dicalcium phosphate	95.00	90.00	85.00	75.00	70.00	65.00	25.00	35.00	45.00	45.00	45.00
3	HPMC K4M	20.00	20.00	20.00	40.00	40.00	40.00	60.00	60.00	60.00	60.00	60.00
4	HPMC 15cps	–	5.00	10.00	–	5.00	10.00	30.00	20.00	10.00	10.00	10.00
5	SCMC	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00
6	Povidone (K-30)	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
7	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	Colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
9	Talc	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
10	Magnesium state	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00
11	Average weight	845.00	845.00	845.00	845.00	845.00	845.00	845.00	845.00	845.00	845.00	845.00

Table No.2: Formulation of Atorvastatin Calcium immediate release layer

S.No	Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	Atorvastatin calcium	21.00	21.00	21.00	21.00	21.00	21.00	21.00	21.00	21.00	21.00	21.00
2	Calcium carbonate (light)	76.50	76.50	76.50	76.50	76.50	76.50	76.50	76.50	76.50	76.50	76.50
3	Lactose	56.50	56.50	56.50	56.50	56.50	56.50	56.50	56.50	56.50	56.50	56.50
4	MCC	82.75	79.45	76.90	74.35	82.07	71.79	70.525	70.525	70.525	70.525	70.525
5	Colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
6	Croscarmellose sodium	2.55	5.10	7.65	10.20	10.20	10.20	10.20	10.20	10.20	10.20	10.20
7	Qiunoline yellow lake	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500
8	Polysorbate 80	_	_	_	_	1.275	2.55	3.825	3.825	3.825	3.825	3.825
9	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Talc	1.275	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650
11	Magnesium stearate	1.275	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650	1.650
12	Sodium bicarbonate	7.650	7.650	7.650	7.650	7.650	7.650	7.650	7.650	7.650	7.650	7.650
13	Average weight	255.00	255.00	255.00	255.00	255.00	255.0	255.00	255.00	255.00	255.00	255.00

Table No.3: Film coating of Bilayer Tablet

S.No	Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	Transparent coat ic-U-6638	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
2	Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
3	Methylene chloride	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table No.4: Evaluation of Granules of Metformin HCl SR Layer 1 and Atorvastatin Calcium Layer 2

S.No	Formulation code	Bulk density (g/ml)		Tapped density (g/ml)		Carr's index (%)		Hausner's ratio		Angle of repose	
		layer 1	layer2	layer 1	layer2	layer 1	layer2	layer 1	layer2	layer 1	layer2
1	F-1	0.51	0.56	0.54	0.43	17.03	17.03	1.050	1.121	28.2	26.5
2	F-2	0.46	0.47	0.85	0.37	11.59	11.58	1.321	1.250	25.1	24.6
3	F-3	0.51	0.58	0.74	0.54	9.42	11.25	1.126	1.101	24.5	23.4
4	F-4	0.78	0.63	0.52	0.78	15.08	25.02	1.125	1.102	24.1	22.3
5	F-5	0.65	0.78	0.36	0.36	14.62	16.45	1.251	1.115	26.3	21.2
6	F-6	0.55	0.56	0.45	0.25	10.32	24.01	1.124	1.123	27.6	28.9
7	F-7	0.87	0.62	0.54	0.45	23.56	21.03	1.247	1.145	24.3	26.1
8	F-8	0.85	0.87	0.74	0.51	15.25	22.25	1.256	1.147	25.3	24.6
9	F-9	0.71	0.62	0.74	0.71	12.91	20.00	1.111	1.213	22.9	24.0
10	F-10	0.74	0.72	0.74	0.70	15.39	15.30	1.254	1.214	28.7	25.6
11	F-11	0.78	0.74	0.69	0.69	11.03	14.21	1.145	1.123	21.1	24.7

Table No.5: Evaluation of tablet of Metformin HCl SR Layer 1 and Atorvastatin Layer 2 (F1-F6)

S.No	Tests	F-1	F-2	F-3	F-4	F-5	F-6
1	Average weight	1099	1094	1098	1108	1106	1097
2	Thickness (mm)	5.81	5.82	5.81	5.8	5.85	5.9
3	Hardness (kg/cm^2)	11.5	12	10.5	10	9.5	10
4	Friability(%w/w)	0.11	0.14	0.12	0.11	0.16	0.15
5	Weight variation	1120	1122	1112	1118	1119	1117

Table No.6: Evaluation of tablet of Metformin HCl SR Layer 1 and Atorvastatin Layer 2 (F7-F11)

S.No	Tests	F-7	F-8	F-9	F-10	F-11
1	Average weight	1106	1104	1100	1100	1097
2	Thickness (mm)	5.84	5.89	5.96	5.85	5.86
3	Hardness (kg/cm^2)	10	10	11	10.5	10.5
4	Friability(%w/w)	0.18	0.12	0.15	0.15	0.14
5	Weight variation	1120	1118	1120	1118	1119

Table No.7: *In vitro* release study (F1-F11)

S.No	Time in mints/hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Immediate release layer												
1	45(min)	36.6	43.8	55.1	60.7	65.89	85.8	96.7	99.1	99.1	97.5	97.5
Sustained release layer												
2	1(hr)	50.2	53.4	56.7	41.5	43.6	46.8	22.3	24.1	30.1	31.8	34.7
3	4(hr)	87.7	85.8	87.7	77.6	78.2	81.2	56.2	59.4	69.6	69.8	72.5
4	8(hr)	102.9	103.8	105.7	99.4	101.2	102.0	80.8	82.6	89.6	89.4	89.6

Table No.8: Stability study of tablet properties of optimized formulations (F7 and F11)

S.No	Parameters	F9	F10	F11
		After one month	After one month	After one month
1	Appearance	Yellow/white, oval shaped film coated bilayer sustained release tablets	Yellow/white, oval shaped film coated bilayer sustained release tablets	Yellow/white, oval shaped film coated bilayer sustained release tablets
2	Hardness (kg/cm)	9.2 kg/cm^2	9.5 kg/cm^2	9.8 kg/cm^2
3	Thickness	6.9 mm	7.0 mm	7.1 mm
4	Assay Atorvastatin Metformin HCl	99.6 98.1	98.5 97.3	99.9 99.1

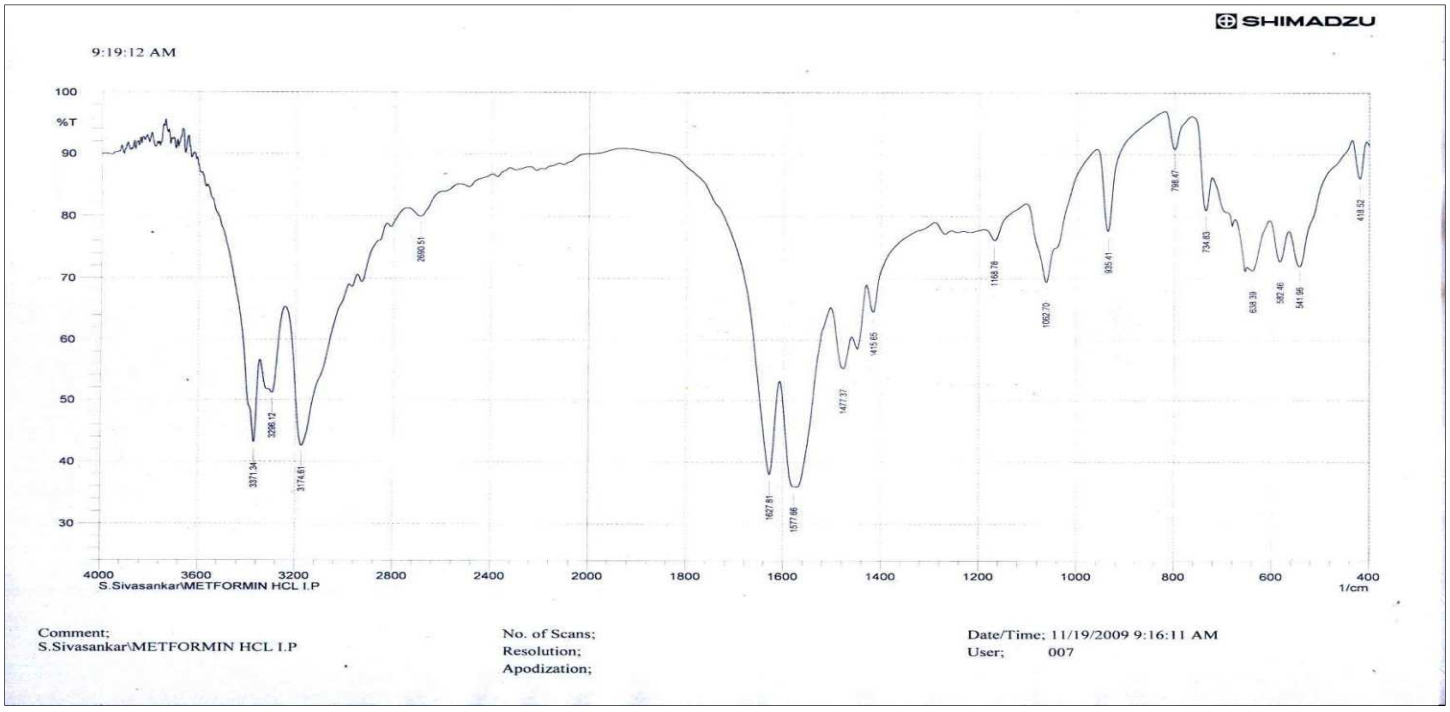

Figure No.1: FT-IR spectra of pure Metformin HCl

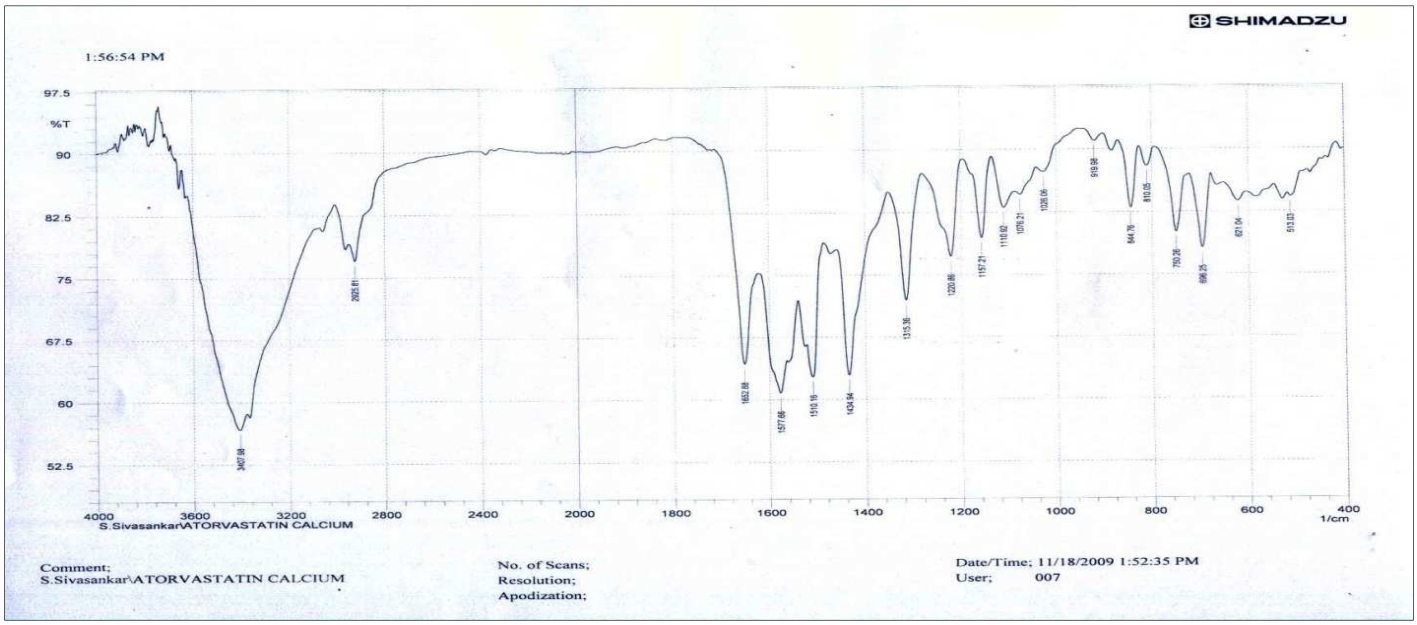

Figure No.2: FT-IR spectra of pure Atorvastatin Calcium

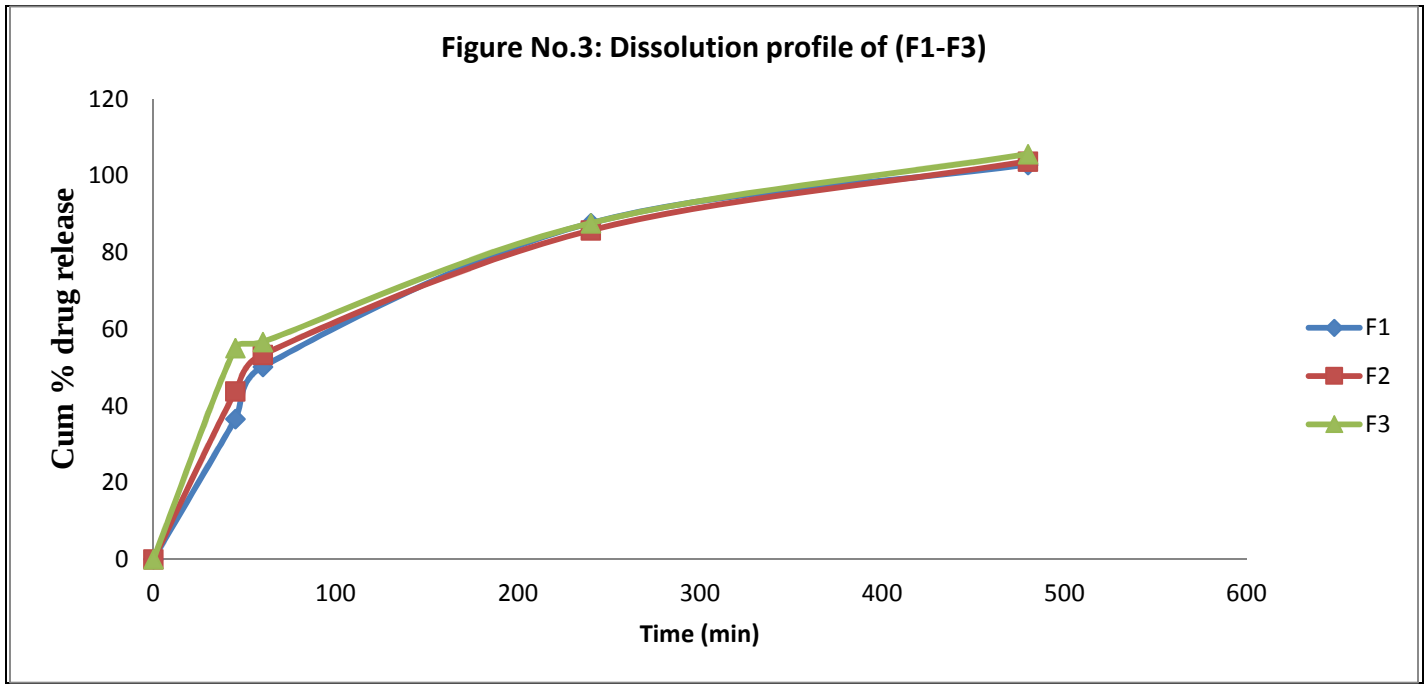

Figure No.3: Dissolution profile of (F1-F3)

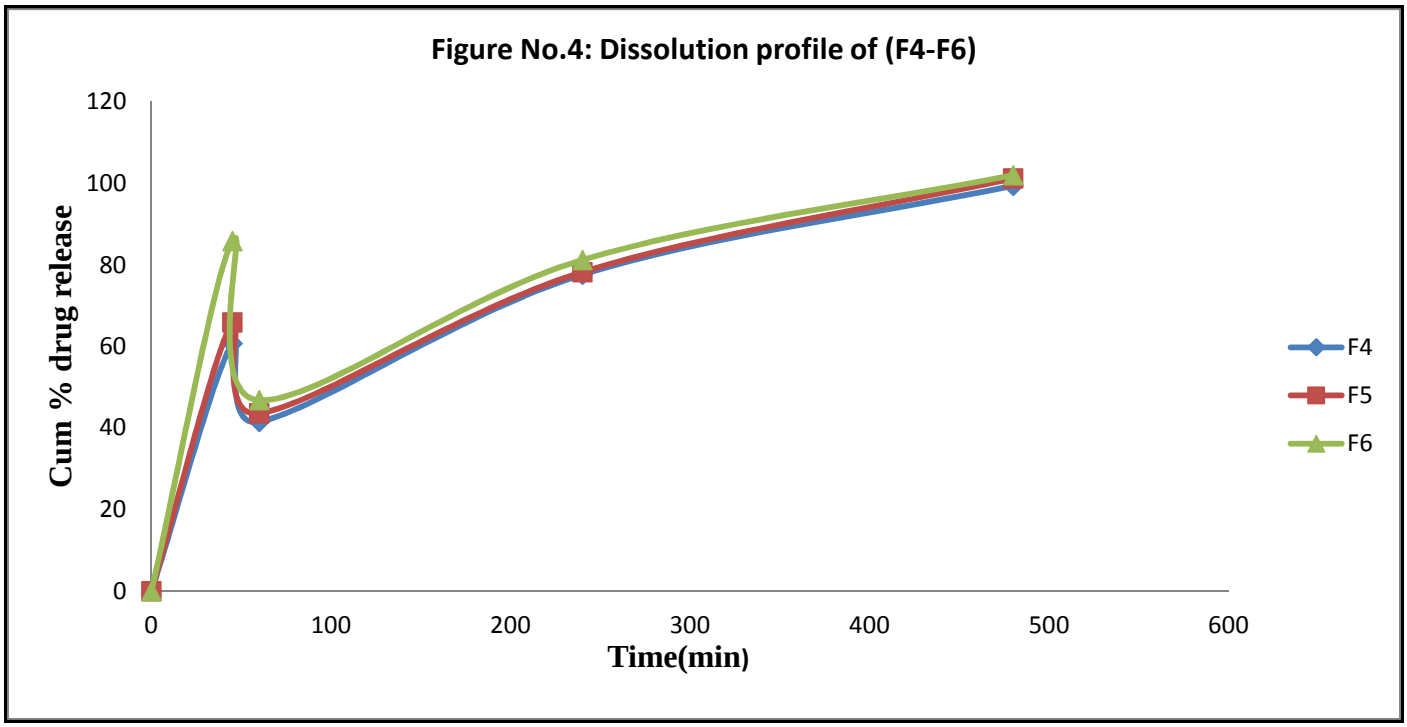

Figure No.4: Dissolution profile of (F4-F6)

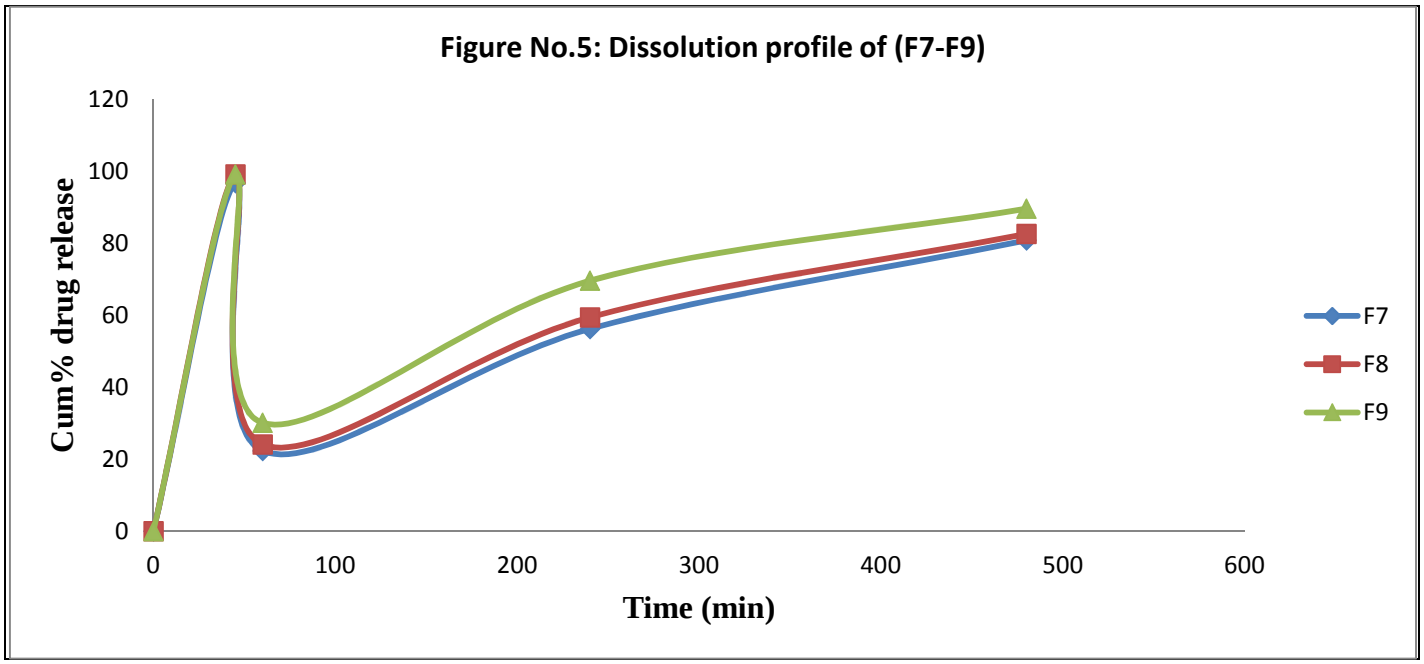

Figure No.5: Dissolution profile of (F7-F9)

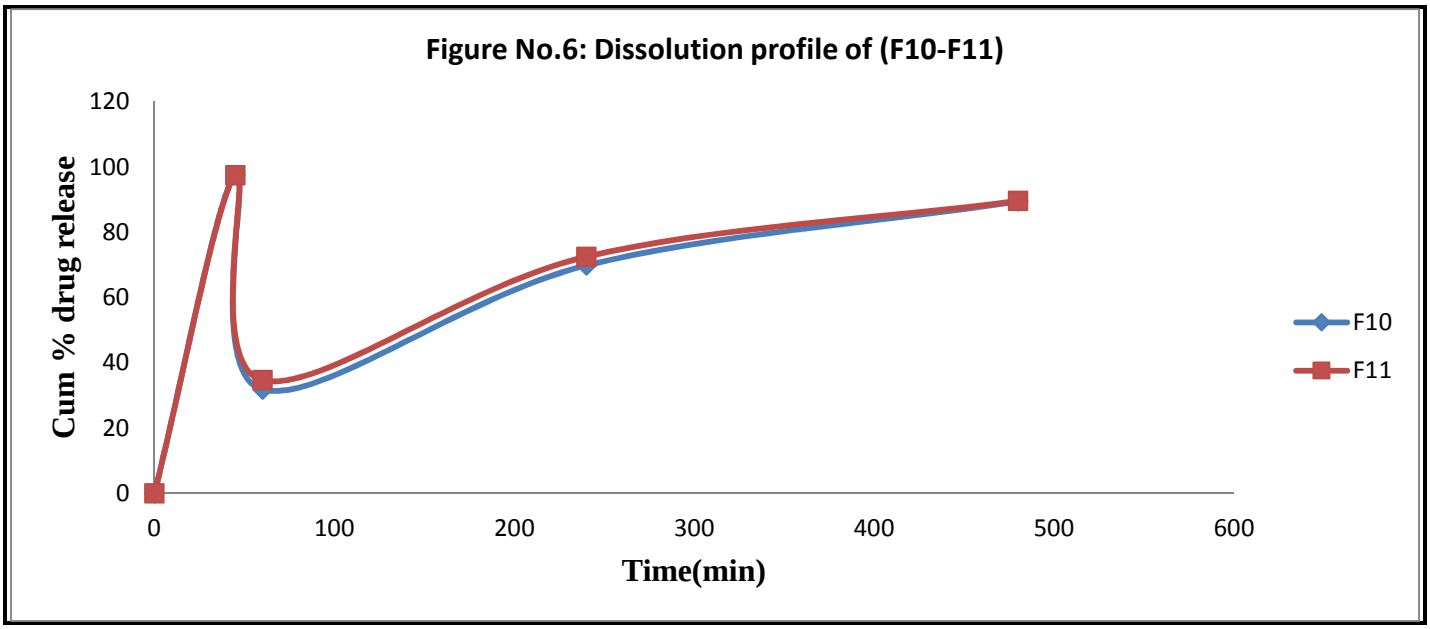

Figure No.6: Dissolution profile of (F10-F11)

CONCLUSION

Metformin is used in the management of diabetes mellitus. Atorvastatin reduces the blood cholesterol level in Diabetics mellitus patients. Combination of Atorvastatin with Metformin hydrochloride used in diabetic dyslipidemia will improve the patient compliance. The Metformin HCl Sustained release and Atorvastatin Calcium immediate release was evaluated for morphological characteristic, physical characteristic, chemical characteristic and stability. The results obtained were satisfactory and within specified limits. Accelerated drug excipient compatibility studies with the selected excipients showed good compatibility with Metformin HCl and Atorvastatin Calcium. Metformin HCl sustained release and Atorvastatin Calcium immediate release bilayer tablet were formulated by wet granulation method and the diluent, lubricant, glidant, binder and polymer concentration were optimized by various trials. The optimization trials showed good results in the bilayer tablet preparation. The Metformin HCl sustained release and Atorvastatin Calcium immediate release bilayer tablet prepared by the formulation F9 and optimized manufacturing processes showed good result in formulation of stable tablet dosage form. The dissolution profile values of Metformin HCl sustained release and Atorvastatin Calcium immediate release bilayer tablet was within specified limits. Formulation F9, F10 and F11 were kept in accelerated stability in 40°C / 75 % RH for 1 month. The product was analysed for assay, related substances, physical appearance and dissolution. Stability data showed that bilayer tablets are stable.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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