ISSN 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF BILAYER TABLET OF ATORVASTATIN AND PIOGLITAZONE FOR METABOLIC DISORDER

Syed Habeeb Ali*, R. Balaji Reddy

[1]Department of pharmaceutics, Deccan School of pharmacy, Darr-us-Salam, Aghapura, Hyderabad-500 001, Telangana, India.

Abstract:

The aim of the present study is to develop bilayered tablets of Atorvastatin and Pioglitazone which contains an immediate release layer and a sustained release layer of both the drugs for the effective treatment of metabolic disorder such as hyper lipidemia, type 2 diabetes milites and atherosclerosis. Croscarmellose sodium, and Crospovidone were used as super disintegrants along with Guggul gum in the immediate release layer (IR) and Ethyl Cellulose and Guar gum were used as release retardants for sustained release (SR). FTIR studies indicated there is no interaction between the drug, polymers, binders and other excipients. The pre compression parameters for IR &SR layer (F5) found as follow bulk density, (0.79 & 0.28), tapped density (0.88 & 0.29), Carr's index (10.81 & 18.56) and Hausner's ratio (1.15 & 1.12) and angle of repose (27.9) & (27.6) for the granules of both the layers which were within the limits of IP. The hardness (kg/cm^2) of optimized formulation was found to be (F5) 3.33±0.03, friability was found to be 0.02±0.070 (F5) and weight variation was found to be 99.98±0.08% (F5). All the evaluation parameters were found to be within the satisfactory limits (IP). The percentage drug release for the optimized formulation F5containing 5% of Crospovidone was 99.97% in 30 mins. The sustained release layer containing drug and Ethyl cellulose in the ratio of (1:2) (F5) released 99.68% of drug at the end of 10 hrs. Drug release followed Krosmeyer peppas. The percentage drug release from the bilayer tablets were 100.2% for immediate release layer at 30 mins and 100.05% for sustained release layer at the end of 10 hrs pH 6.8 phosphate buffer which depicts that the bilayered tablets of Atorvastatin and Pioglitazone will be useful in case of metabolic disorder such as Diabetes milites type 2 and Hyperlipidemia.

Keywords: Atorvastatin, Pioglitazone, Guggul gum, Bilayer tablet.

Corresponding Author:

R. Balaji Reddy

Department of pharmaceutics,
Deccan School of pharmacy,
Hyderabad-500 001, Telangana, India.

Please cite this article in press as Habeeb et al. ***Formulation and Evaluation of Bilayer Tablet of Atorvastatin and Pioglitazone for Metabolic Disorder****, Indo American J of Pharm Sci 2014:1(6).*

INTRODUCTION:

The term bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics [1,2]. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Metabolic disorder can develop when some organs, such as our liver or pancreas, become diseased or do not function normally. Diabetes, Hyperprotinemia and Hyperlipidemia are an example of metabolic disorder. Diabetes mellitus is a chronic disorder characterized by impaired metabolism of glucose. Diabetes mellitus is a group of disorders involving distinct pathogenic mechanisms with hyperglycemia as the common denominator. Regardless of the cause, the disease is associated with insulin deficiency, which may be total, partial or relative when viewed in respect of co-existing insulin resistance[3,4]. Some of the hypoglycemic agents are 1st generation sulfonylurea 2nd generation sulfonylurea, biguanides thiazolienediones etc.

Hyperlipidemia a broad term, also called hyperlipoproteinemia, is a common and degradation of plasma lipoproteins[5]. The term "dyslipidaemia" disorder in developed countries and is the major cause of coronary heart disease. It results from abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis the old term Hyperlipidemia. Hyperlipidemia means abnormally high now days is increasingly being used to describe abnormal changes in lipid profile, replacing levels of fats in the blood. These fats include cholesterol and triglycerides[6]. These are important for our bodies to function but when they are high, they can cause heart disease and stroke. Hyperlipidemia is manifested as hypercholesterolemia and/or hypertriglycerolemia. However, hypercholesterolemia is the most common Hyperlipidemia. Statins, Febrides, and cholesterol absorption inhibitors are the class of drugs for the treatment of Hyperlipidemia[7,8]. To formulate and evaluate the Bilayered tablets of Atorvastatin calcium & Pioglitazone HCl, carry out the drug - exciepiant compatibility studies by IR spectral analysis, pre-compressional parameters, post-compressional parameters for Bilayered tablets and *In-vitro* Dissolution studies

MATERIALS AND METHODS:

Atorvastatin and Pioglitazone gift sample from Dr. Reddy's Labs, Croscarmellose, Ethyl cellulose, Guar gum and Crospovidone from Reliance cellulose Products Limited., Hyderabad. Methanol and Potassium dihydrogen orthophosphate from S.D. Fine Chemicals, Mumbai, India. All chemicals are analytical grade.

PREPARATION OF BILAYER TABLET: In this present investigation, bilayered tablet of Atorvastatin and Pioglitazone was prepared by direct compression method.

Formulation of immediate release layer of Atorvastatin and Pioglitazone

By direct compression method:

Direct compression: Accurately weighed amounts of drug, super disintegrants, binder and diluents were mixed geometrically in a mortar. This mixture was passed through No.40 sieve. The powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets on a 9 station rotary tabletting machine using 6 mm round, flat-faced dies.

Formulation for extended release layer of Pioglitazone:

By direct compression method:

Direct compression: Accurately weighed amounts of drug, Ethyl Cellulose, binder Guar Gum and diluents were mixed geometrically in a mortar. This mixture was passed through No.40 sieve. Powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets on a 9 station rotary tabletting machine using 6 mm round, flat-faced dies.

Composition of immediate release layer

Table 1:Formulations table for Pioglitazone and Atorvastatin immediate release layer

S.No	Ingredient	F1	F2	F3	F4	F5
1	Atorvastatin	10	10	10	10	10
2	Pioglitazone	5	5	5	5	5
3	Crospovidone	2	2.5	3	0	5
4	Croscarmellose 2-5%	3	2.5	2	5	0
5	Guggul	2	2	2	2	2
6	Mg. stearate	3	3	3	3	3
7	Talc	2	2	2	2	2
8	Lactose	60	60	60	60	60
9	Total wt	87	87	87	87	87

Composition of extended release layer:

Table 2: Formulation table for Pioglitazone extended release layer

s.no	Ingredient	F1	F2	F3	F4	F5
1	Pioglitazone	5	5	5	5	5
2	Ethyl cellulose	3	2	3	2	3
3	Guar gum	2	2	2	3	3
4	Mg.stearate	2	3	2	2	1
5	Talc	1	1	1	1	1
6	Total wt	13	13	13	13	13

Table: 3 Formulation of Bilayer Tablet of Pioglitazone &Atorvastatin

S.No	Ingredient	F1	F2	F3	F4	F5
1	Atorvastatin	10	10	10	10	10
2	Pioglitazone	5	5	5	5	5
3	Crospovidone	2	2.5	3	0	5
4	Croscarmellose 2-5%	3	2.5	2	5	0
5	Guggul	2	2	2	2	2
6	Mg. stearate	3	3	3	3	3
7	Talc	2	2	2	2	2
8	Lactose	60	60	60	60	60
9	Pioglitazone	5	5	5	5	5
10	Ethyl cellulose	3	2	3	2	3
11	Guar gum	2	2	2	3	3
12	Mg.stearate	2	3	2	2	1
13	Talc	1	1	1	1	1
14	Total wt of bilayer tablet	100	100	100	100	100

PREFORMULATION STUDIES:

Preformulation may be described as a stage of development during which physicochemical and biopharmaceutical properties of a drug substance are characterized. Characterization of the drug is a very important step at Preformulation phase of product development followed by studying properties of exciepiants and their compatibility.

Micromeritic properties

Angle of repose:

$\theta = \tan^{-1}(h/r) = \tan^{-1}$ (height of pile/0.5base)

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

Bulk density:

Bulk density = Weight of powder / Bulk volume

Limits:

It has been stated that, bulk density values having less than 1.2 g/cm3 indicates good packing and values greater than 1.5 g/cm3 indicates poor packing.

Tapped density:

Tapped density = Weight of powder / Tapped volume

Compressibility index (Carr's index):

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

Hausner's ratio:

Hausner's Ratio = Tapped density /Bulk density

DRUG-EXCIPIENTS COMPATIBILITY STUDIES BY FTIR: Careful selection of drugs and exciepiants is done by infra-red spectroscopy

FTIR Studies: FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

FTIR analysis of Pioglitazone: Fourier Transform Infra Red (FTIR) analysis of pioglitazone was obtained using KBr pellet technique and the peaks mentioned in standards were compared with those obtained. The peaks were found to be at 1705 refers to -C=O stretching vibration from ketone group, at

3223 cm-1 refers to the O-H group and at 1350 cm-1 O-H bending. This confirms the purity of PIO sample.

FTIR analysis for Atorvastatin: An FTIR spectrum of Atorvastatin was obtained in the range of 400-4000 cm-1 using KBr pellet technique and the peaks mentioned in standards were compared with those obtained. This confirms the purity of Atorvastatin sample. The studies of Fourier Transform – Infra Red spectra showed NH group peak at 3255cm^{-1},C=O of alkyl group peak at 1674cm^{-1} and SO stretching peak at 1035cm^{-1}.C-C stretching at 1111 cm^{-1}

Evaluation of bilayer tablets of Atorvastatin and Pioglitazone

Hardness test: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm2.

Friability test: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W) final. The % friability was then calculated by

%F = initial weight-final weight/initial weight x 100

Where,

%F= Friability in percent

% friability of tablets <1% were considered acceptable.

Weight variation test: Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of tablet by U.S. Pharmacopoeia.

Drug content uniformity: Tablet containing drug is dissolved in 100 ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1 ml of filtrate was taken in 50 ml of volumetric flask and diluted up to mark with 0.1N HCl and analyzed spectrophotometrically at 282nm.

By using disintegration apparatus, tablets were tested for disintegration time at 37± 0.5^0C taking distilled water as medium.

In-vitro dissolution study for immediate & sustained release layer

In-vitro release studies were carried out USP II paddle type dissolution test apparatus. 900 ml of Phosphate buffer 6.8 was filled in dissolution vessel and the temperature of the medium were set at 37° C ± 0.1°C.The speed was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time intervals for 8 hrs and same volume of fresh medium was replaced. The samples were analyzed for drug content against Phosphate buffer 6.8 as a blank at λmax 229nm using spectrophotometer.

Kinetic Analysis of Dissolution Data:

To analyse the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannouet al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2}$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data :

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

RESULTS AND DISCUSSIONS:

The drug compatibility study shows that both the drugs are compatible with each other as FTIR report shows(figures 1-3) the wavelength cm^{-1} values of functional groups are of ATV and PIO are not blocked due to chemical interaction, when compare to FTIR standard spectrum of Atorvastatin and Pioglitazone as in Indian Pharmacopoeia. The Preformulation studies such as angle of repose, bulk density, tapped density, etc. were done and the mean +- SD values of angle of repose was obtained as 28.53±0.77 and values for bulk density and

tapped density are obtained as 0.487 and 0.539 respectively the results were shown in tables 4&5. The post formulation parameters shows tablet weight variation, hardness, friability and disintegrating time found that IR layer was 99.20-100.87, 0.083-0.36, 0.02-0.12 disintegrated in 20 seconds respectively and controlled released layer was taken 12 hrs time for disintegration The percentage release of ATV was released upto 100% by 30 minutes. After words the % release was maintained above 90%C upto 480 minutes. The release profile of PIO is represent in release pattern it will be clear that it took 150 minutes for 100% release of PIO, the study was conducted upto 480 minutes results were shown in table 7 figure 4. The release pattern best fitted with krosmeyer peppas model as release kinetic scale shows 0.997 release kinetics of drug. The correlation coefficient value was found to be maximum in case of krosmeyer peppas model for both drugs shown in table 8 and figure 5.

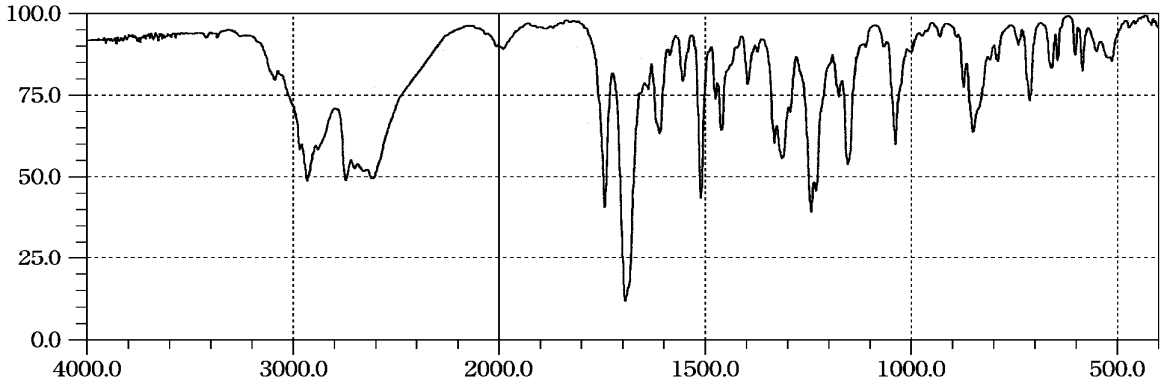

Fig: 1 Standard spectra of Atorvastatin pure drug

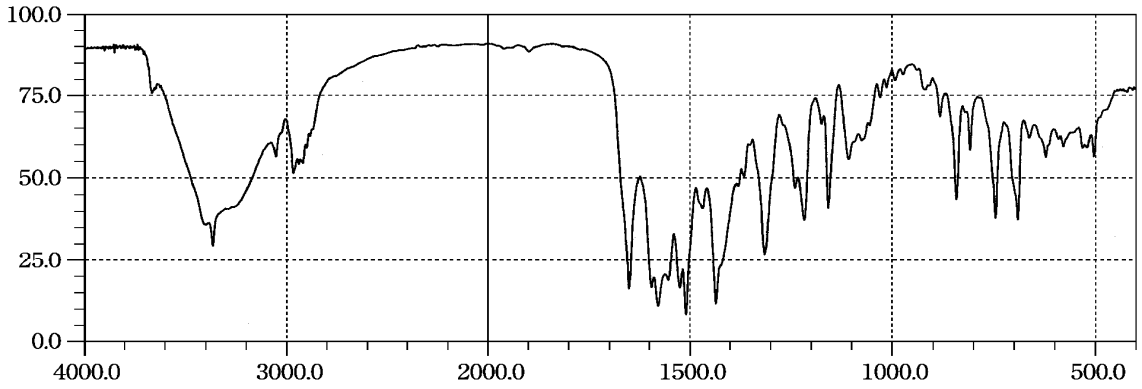

Fig: 2 Standard spectra of Pioglitazone pure drug

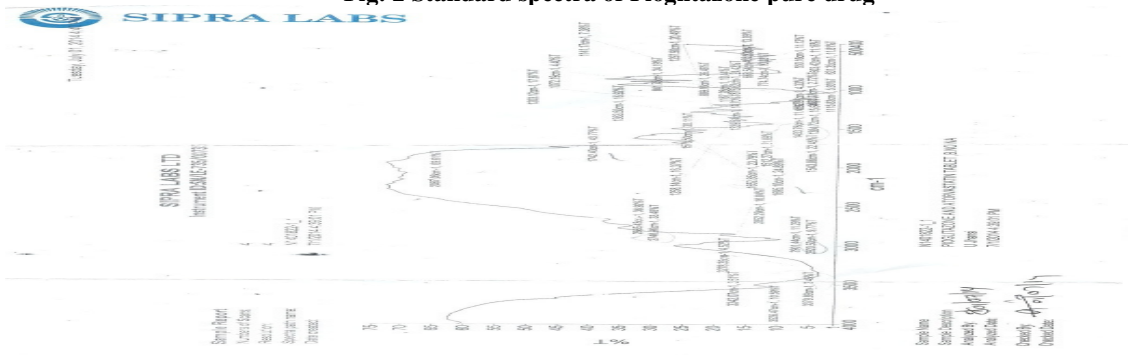

Fig: 3 FTIR spectroscopy of formulated bilayered tablet of atorvastatin and pioglitazone

Table 4: Preformulation studies for immediate release layer of Atorvastatin

Formulation	Angle of repose(□)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	26.2	0.472	0.546	15.36	1.13	Good
F2	25.6	0.789	0.881	11.23	1.14	Good
F3	22.0	0.676	0.777	11.32	1.12	Good
F4	25.7	0.762	0.855	13.33	1.12	Good
F5	27.9	0.798	0.888	10.81	1.15	Good

Table 5: Preformulation studies for sustained release layer of Pioglitazone

S.No	Angle of repose(□)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	22.0	0.31	0.401	19.87	1.24	Fair
F2	24.6	0.34	0.389	19.39	1.23	Fair
F3	25.9	0.39	0.463	15.12	1.17	Good
F4	23.8	0.45	0.51	14.60	1.15	Good
F5	27.6	0.28	0.29	18.56	1.12	Good

Table 6: Evaluation tests for various formulation of bilayer tablet of Pioglitazone &Atorvastatin

Formulation Code	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)
F1	99.20	0.114018	0.12	6.5
F2	99.89	0.167332	0.09	7.2
F3	98.68	0.167332	0.11	9.1
F4	100.87	0.363318	0.06	8.4
F5	99.98	0.083666	0.02	12.1

Table 7: Comparative in Vitro Dissolution Study of Bilayer Tablet of Atorvastatin and Pioglitazone

s.no.	Time (mins)	Cumulative %Drug Release				
		F1	F2	F3	F4	F5
1.	0	0.00	0.00	0.00	0.00	0.00
2.	15	49.32	52.43	60.21	79.32	86.30
3.	30	58.48	61.49	71.37	90.67	100.44
4.	60	61.56	64.58	78.14	86.34	90.52
5.	90	63.78	66.63	69.87	84.65	98.46
6	120	66.39	67.46	73.65	89.22	95.48
7.	150	65.31	70.95	75.82	79.1	93.99
8.	180	69.13	73.23	77.65	76.98	91.51
9.	240	71.21	78.86	68.1	81.54	100.94
10.	300	72.54	72.48	74.32	77.32	93.00
11.	360	68.46	71.39	76.56	88.23	95.72
12.	420	66.1	76.83	81	72.23	94.49
13.	480	64.75	70.3	79.2	79.15	88.28

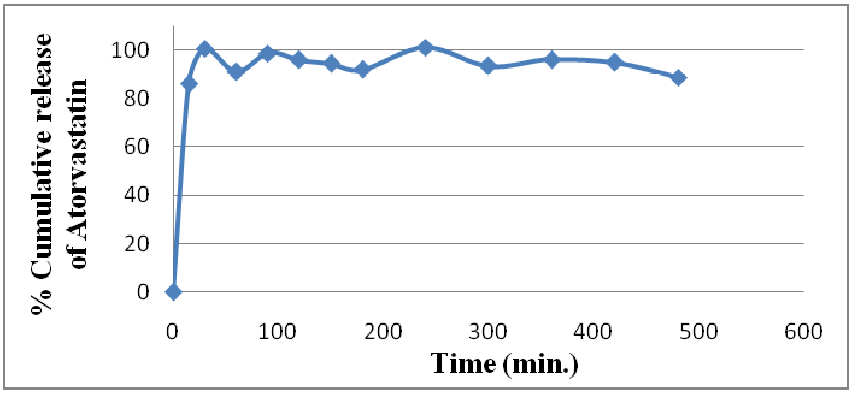

Fig 4: % Cumulative Release for Optimized Formulation - 5 of Bilayer Tablet of Atorvastatin And Pioglitazone

Table 8: Release kinetics of bilayer tablet of ATV & PIO

DRUG	Zero Order Plot	First Order Plot	Higuchi Matrix	Korsmeyer- Peppas		Best Fit Model
	R^2	R^2	R^2		R^2	
AT V	0.853	0.774	0.975		0.996	**Korsmeyer-Peppas**
PI O	**0.864**	**0.778**	**0.979**		**0.997**	**Korsmeyer-Peppas**

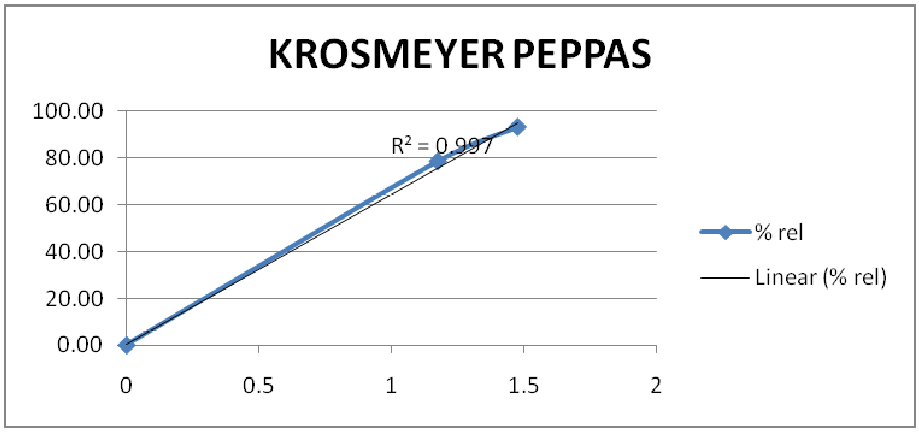

Fig: 5 **Krosmeyer Peppas Model Release Kinetics Of Bilayer Tablet Of Atorvatatin And Pioglitazone**

CONCLUSION:

From the obtained results it can be concluded that: IR identification results of drugs indicate the purity of drug. IR spectra of pure drug and with the excipients are identical and do not show any incompatibility, thus the excipients are compatible with the drug. Lower values of angle of repose below 30 indicate good flow properties of powder blends. Friability and hardness were within the pharmacopoeial limits thus showing good mechanical strength of tablets. Formulation F5 showed drug release for atorvastatin layer faster release which containing 1% croscarmellose sodium and 4% crospovidone used in the allowable range and for pioglitazone layer showed maximum delayed release which containing 2% Ethyl cellulose and 4% guar gum. Curve fitting analysis showed the drug release data of bilayer tablet of atorvastatin and Pioglitazone I best fitted to Krosmeyer Peppas model

ACKNOWLEDGEMENT:

The authors would like to thank Mr. R. Balaji Reddy and Rajender Daas for instructive and careful review of this manuscript.

REFERENCES:

1. Kadhe G, Arasan RE. Advances in drug delivery of oral hypoglycemic Agent. Current science, 2002; 83(12):1539-43.

2. Patel M, Sockan GN, Kavitha, Tamizh M. Challenges In The Formulation of Bilayered Tablets: A Review International Journal of Pharma Research and Development. 2010; 2(10):30-42.

3. Rudnic EM, Lausier JM, Chilamkurti RN, Rhodes CT. Studies of the utility of cross linked polyvinylpolypyrrolidine as a tablet disintegrant. Drug Dev Ind Pharm 1980; 6: 291–309.

4. Lebov Citz HE, Leslie RD, Robbins DC. Diabetes: Clinical Science in Practice. New York: Cambridge University Press; 1995:450-64.

5. Eurich DT, McAlister FA, Blackburn DF. Benefits and Harms of Antidiabetic Agents in Patients with Diabetes and Heart Failure: Systematic Review. BMJ. 2007; 335 (7618): 497. DOI.10.1136/bmj.39314.620174.80. PMID 17761999,
2007.

6. Lars P. Bechmann, Rebekka A. Hannivoort, Guido Gerken, Gökhan S. Hotamisligil,Michael Trauner, Ali Canbay2010;5:215-226.

7. Maggi Banning Medication taking behavior and hypertension: a literature review

8.Gunarathne A, Patel JV, Potluri R, Gill PS, Hughes EA, Lip GYH. Secular trends in the cardiovascular risk profile and mortality of stroke admissions in an inner city, multiethnic population in the United Kingdom (1997-2005).Journal of human hypertension. 22: 18-23, 2008.