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Research Article

To Develop Sustained Release Mucoadhesive Tablets of Atorvastatin by Using Hydrophilic Polymers

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Abstract

Atorvastatin is a choice of drug for anti-hyper lipidemic the concept of formulating and evaluating matrix tablets that it offers a suitable and practical approach in serving desired objective of prolonged action for anti-hyper lipidemic activity exhibiting good absorption of the drug of the different batches of formulations were prepared increasing the concentrations of HPMC K 15 M, Gum Karaya and Guar gum. A controlled release Gastro retentive blend formulated were evaluated for Bulk density, tapped density, Angle of repose, Compressibility index, carr's index and in-vitro drug release studies.

Keywords: Compressibility index, in-vitro drug release, carr's index, anti-hyper lipidemic

Article Info

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CONTENTS

1. Introduction

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached.

Mucoadhesive (bioadhesive) systems:

Several approaches have been immerged to prolong the residence time of the dosage forms at the absorption site and one of these is the development of oral controlled release bioadhesive system. In the early 1980's, *Professor Joseph R. Robinson* at the University of Wisconsin

pioneered the concept of bioadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Various gastrointestinal mucoadhesive dosage forms, such as discs, microspheres, and tablets, have been prepared and reported by several research groups.

Drug Profile:

Name: Atorvastatin

Description: Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below.

Structure:

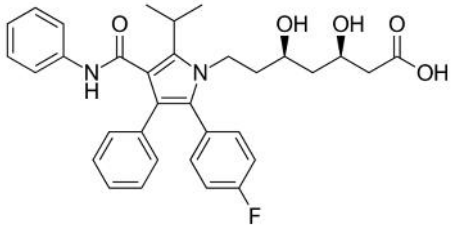

Fig.1

Synonyms: Lipitor, Atorva

Chemical Formula: $C_{33}H_{35}FN_2O_5$

Dosage: 10 to 80 mg

IUPAC Name: (3*R*,5*R*)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

Mechanism of action: As with other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase.Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases *de* novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol.

2. Methodology

Determination of UV Absorption maxima:

Atorvastatin solution was prepared in phosphate buffer 6.8 and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 244 nm. The procedure was repeated with pH 6.8 phosphate buffer.

Formulation of Atorvastatin Controlled release Tablet by Direct- Compression:

Composition of preliminary trials for Atorvastatin Controlled release Tablet by direct compression is shown in table given below. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 12mm flat punch, B tooling. Each tablet contains 110mg of Atorvastatin calcium and other pharmaceutical ingredients.

Evaluation parameters:

Precompression parameters:

- Bulk Density (D_b)
- Tapped Density (D_t)
- 3.Angle of Repose (Θ)
- Carr's index (or) % compressibility
- Hausner ratio

Post compression parameters:

- Weight variation
- Hardness
- Thickness
- Friability (F)
- In-Vitro drug release
- Assay

Table.1 List of Materials

Materials	Source
Atorvastatin	Gift sample from SDL laboratories
Gum karaya	SD Fine Chemicals, Hyderabad
Xanthan gum	SD Fine Chemicals, Hyderabad
Guar gum	SD Fine Chemicals, Hyderabad
Magnesium stearate	SD Fine Chemicals, Hyderabad
Talc	SD Fine Chemicals, Hyderabad
Microcrystalline Cellulose pH 102	Merk chemicals, Mumbai

Table.2 List of Equipments

Equipments	Model/Company
Electronic balance	Wensar
Tablet compression machine	Karnavati , Rimek Mini Press II
Tablet hardness tester	Monsanto hardness tester
Dissolution test apparatus	Lab India Dissolution Apparatus Ds 8000(USP)
Friability test apparatus	Lab India Friability Apparatus FT 1020 (USP)

UV-Visible Spectrophotometer	Lab India
Hot air oven	VJ Instruments
pH meter	Lab India pH apparatus

Table.3 Different Formulations of Atorvastatin Gastro retentive tablets

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Atorvastatin	20	20	20	20	20	20	20	20	20	20	20	20
Gum karaya	10	20	30	40	-	-	-	-	-	-	-	-
Hydroxy propyl methyl cellulose 15 cps	-	-	-	-	10	20	30	40	-	-	-	-
Guar gum	-	-	-	-	-	-	-	-	10	20	30	40
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Microcrystalline Cellulose pH 102	74	64	54	44	74	64	54	44	74	64	54	44
Total	110	110	110	110	110	110	110	110	110	110	110	110

3. Results and Discussion

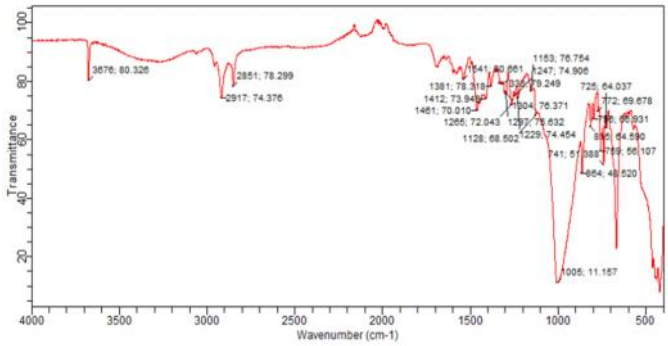

Figure 2. FTIR Studies

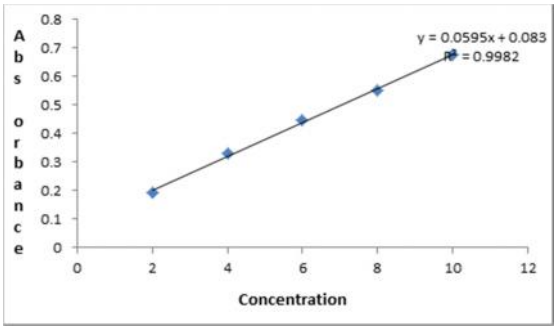

Figure 3. Standard graph of Atorvastatin in pH 6.8 Phosphate buffer

Table.4 Concentration and absorbance obtained for calibration curve of Atorvastatin in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 244nm)
1	2	0.196
2	4	0.326
3	6	0.438
4	8	0.446
5	10	0.665
Correlation Coefficient = 0.9982 y = 0.0595x + 0.083		

It was found that the estimation of Atorvastatin by UV spectrophotometric method at λ_{max}244 nm in pH 6.8 Phosphate buffer. Had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.0595x + 0.083.

Table.5 Evaluation Parameters for Gastro retentive tablets of Atorvastatin:

Table.5 : Pre-compression parameters					
Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle of Repose(Θ)
F_1	0.46	0.57	18.14	1.22	27.91
F_2	0.48	0.55	14.54	1.15	28.23
F_3	0.50	0.58	13.82	1.16	29.34

F_4	0.45	0.59	16.36	1.17	26.71
F_5	0.50	0.58	13.71	1.16	29.34
F_6	0.49	0.53	14.50	1.17	28.23
F_7	0.50	0.59	13.76	1.14	29.34
F_8	0.42	0.50	18	1.29	26.78
F_9	0.45	0.50	18	1.21	26.78
F10	0.46	0.51	18.21	1.20	26.68
F11	0.48	0.56	18.12	1.21	26.70
F12	0.41	0.54	18.11	1.22	26.71

Table.6. Post compression Parameters

Formulations	Weight variation (mg)	Hardness(kg/cm^2)	Thickness (mm)	Friability(%)	Assay(%)
F_1	104	4.8	1.5	0.42	97.23
F_2	104	4.3	1.6	0.39	98.55
F_3	100	4.4	1.5	0.49	98.16
F_4	105	4.2	1.4	0.45	99.34
F_5	102	4.6	1.6	0.49	98.16
F_6	98	4.3	1.5	0.32	98.55
F_7	100	4.4	1.4	0.49	98.16
F_8	104	4.5	1.5	0.34	99.25
F_9	106	4.4	1.5	0.34	99.25
F10	101	4.4	1.5	0.43	98.6
F11	102	4.3	1.5	0.54	98.7
F12	104	4.5	1.5	0.43	98.5

Table.7 : In-vitro dissolution data of different formulations

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.5	20.1	16.4	11.4	15.4	10.4	9.4	8.5	49.5	38.2	26.4	18.9
1	46.7	39.4	26.7	18.6	29.4	16.5	15.6	14.5	78.8	41.9	38.2	28.3
2	76.5	55.3	34.6	29.5	38.5	28.6	21.4	18.4	96.9	62.4	43.4	36.4
3	98.4	75.3	42.4	39.5	55.4	39.5	36.7	23.4	96.1	78.2	59.3	49.5
4		87.3	55.4	49.6	68.4	48.5	42.4	28.2		81.4	76.3	69.3
5		99.4	67.4	57.4	87.1	59.4	49.6	34.8		96.8	88.4	78.1
6			85.4	69.3	98.3	69.2	55.3	40.2			95.4	89.7
7			91.5	78.5		74.5	60.3	44.8			98.5	97.5
8			98.91	82.3		82.3	72.8	50.4				

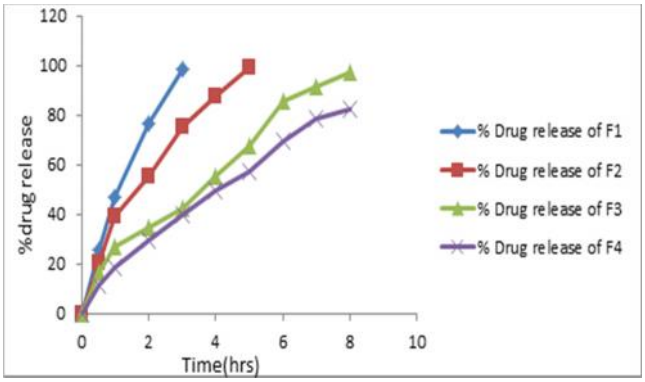

Figure 4. Dissolution profile of formulations prepared with GUM KARAYA polymer

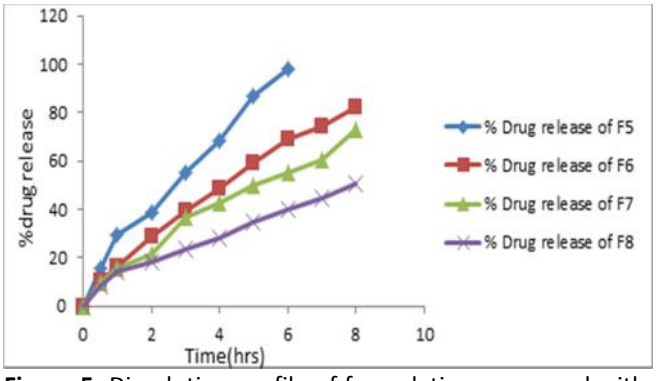

Figure 5. Dissolution profile of formulations prepared with HPMC polymer

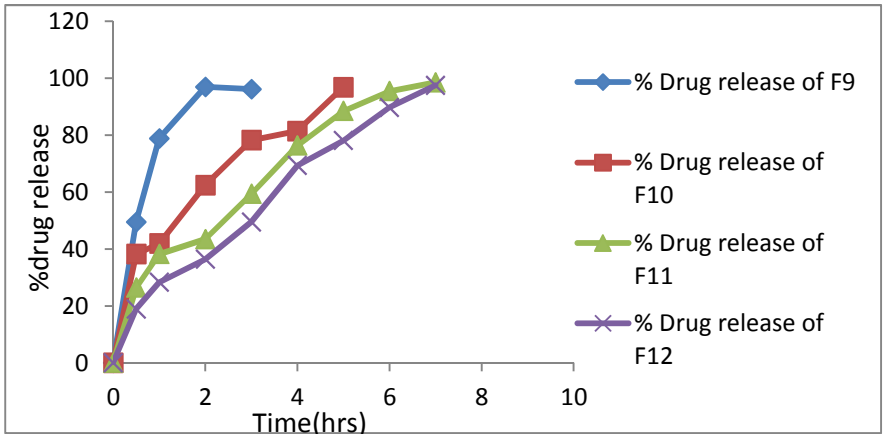

Figure 6. Dissolution profile of formulations prepared with Guar gum as polymer

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

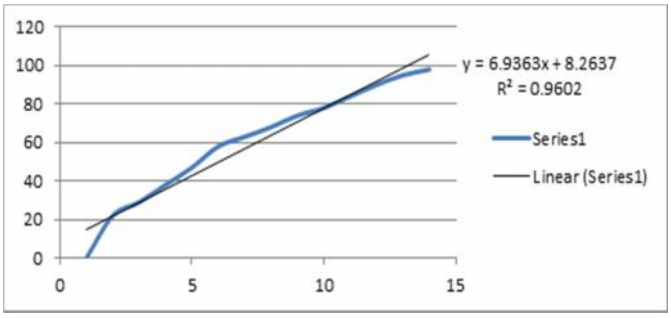

Figure 7. Zero order kinetics graph

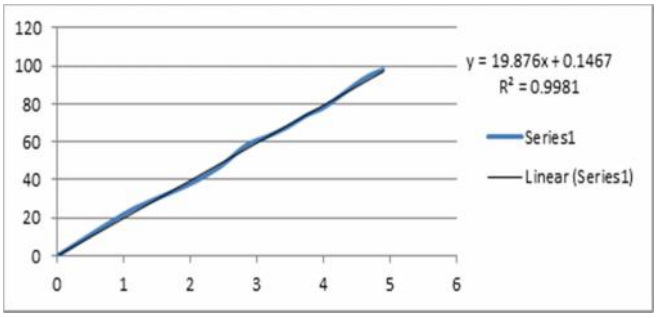

Figure 8. Higuchi release kinetics graph

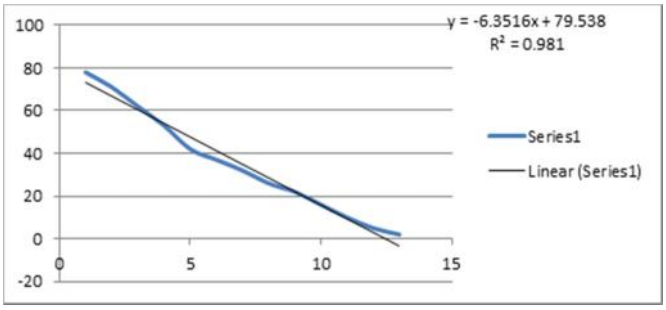

Figure 8. First order kinetics graph

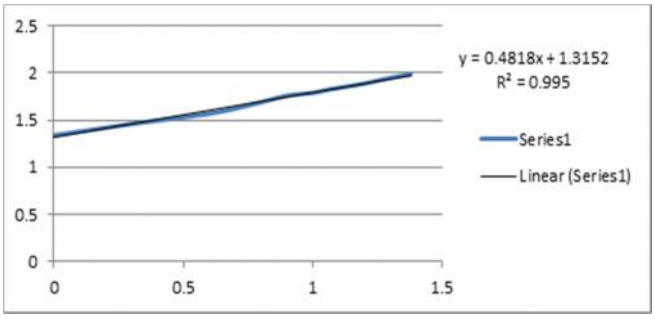

Figure 9. Kosmeyer- peppas graph

Discussion:

The λ max of Atorvastatin in pH 6.8 phosphate buffer was scanned and found to have the maximum absorbance at 244 nm. Standard graph of Atorvastatin was plotted. The Bulk density and tapped density of the blend were found to be 0.41 to 0.475 and 0.44 to 0.591 respectively. The angle of repose values obtained for the blend ranged from 20.48 to 27.4 this indicates good flow property of the powder blend. The compressibility index values for the blend ranged from 11.36 to 21.8 this indicates the powder blends have good flow property. The cars index values for the blend ranged from 1.12 to 1.25 this indicates the powder blends have good flow property. *In vitro* drug release profiles for all formulations were carried out by using pH 6.8 phosphate buffers as dissolution medium for about 8 hrs. From the above results it was found that the release of drug from F3 formulation with gum karaya gave the better release than other formulations. The morphological characters of Metformin HCl liposomes for F 1 – F 4 didn't show any characteristic changes after it was stored at 4ºC and 25ºC±2ºC for a period of one month. F 5 and F 6 formulations were showed slightly reduced in the size after it was stored at 25ºC±2ºC for a period of one month but there was no changes for the same formulation when it was stored at 4ºC. Microscopic images of all the formulations (F 1 – F 6) of Metformin HCl liposomes were compared with before and after stability studies. The results show there no significant changes. After one

month, Metformin HCl liposomes formulations F 1 to F 6 were showed difference in in vitro drug release profile. Dissolution rate was decreased in all Metformin HCl liposomes formulations at both storage conditions like 4°C and 25ºC±2ºC. The results of in vitro drug release of all the formulations at both storage conditions were compared with before and after stability studies.

4. Conclusion

Atorvastatin is a choice of drug for anti-hyper lipidemic the concept of formulating and evaluating matrix tablets that it offers a suitable and practical approach in serving desired objective of prolonged action for anti-hyper lipidemic activity exhibiting good absorption of the drug of the different batches of formulations were prepared increasing the concentrations of HPMC K 15 M, Gum Karaya and Guar gum. A controlled release Gastro retentive blend formulated were evaluated for Bulk density, tapped density, Angle of repose, Compressibility index, carr's index and invitro drug release studies. Among the thirteen formulations of Atorvastatin formulation F3 with the highest concentration Gum karaya showed the best results when compared to the others. The F3 8 hours was found to be 98.91 % the best formulation. As the viscosity of the polymers increased and the concentration of polymers increased there was a decrease in the drug release and control in the release pattern which IR-spectroscopic studies indicated that there is no drug–excipient interactions.

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