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Research paper

DEVELOPMENT AND EVALUATION OF FILM COATED ATORVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS

Gupta D, Kishor A, Wadhwani S, Bhadauria RS,

Department of Pharmaceutics,
Srinathji Institute of Pharmacy,Nathdwara (Rajasthan)

Compatibility studies were carried out and found that drus and excipients are compatible with each other. Formulation (F9) containing 12mg of croscarmellose sodium was found to have closeness to the innovator product from similarity and difference factor which was found to be 84.29 and 0.81 respectively. Also dissolution data of all formulations reveals that as concentration of superdisintegrants increases the percentage drug release was found to be increased. Formulation (F9) containing high percentage of Croscarmellose sodium shows that the disintegration was within limits and 100% drug release was found in 30 min. So, formulation (F9) was taken as optimized formulation. For the formulation F9, there was no significant change in physical appearance, hardness, friability, disintegration time, assay and dissolution even after three months of stability study.

KEYWORDS- Croscarmellose sodium, excipients, anti-hypercholesterolemic agent

INTRODUCTION

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century.

Oral solid dosage forms

The conventional oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates and formulation. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods, and generally improve shelf life of the product. In fact the development of a pharmaceutical product for oral drug delivery, irrespective of its physical form (solid, semisolid, or liquid dosage form) involves varying contents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal physiology[1].

Oral solid dosage forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled release and sustained release drug delivery system have been developed. Although these new systems are in fast progression, for many drugs and therapeutic indications, conventional oral solid immediate release drug delivery systems provided satisfactory clinical performance with an appropriate balance of efficacy and safety.

The major drawbacks in developing a controlled release

and sustained release drug delivery systems decreased systemic availability when compared with immediate release conventional dosage forms due to incomplete release[2].

AIM AND OBJECTIVE

Atorvastatin calcium is an anti-hypercholesterolemic agent and a synthetic lipid lowering agent, used to treatdyslipidaemiaandeffective in both the primary and secondary prevention of coronary heart diseases. Atorvastatin calcium is absorbed rapidly after oral administration with maximum plasma concentration achieved in 1 to 2hrs. Half-life is about 14hrs, but half-life of HMG-CoA inhibitor activity is 20-30 hours due to longer-lived active metabolites.

So, the aim of present study is to design a robust and stable formulation of film coated atorvastatin calcium immediate release tablets and comparison with Lipitor.

In the present study the main objective is directed towards development and evaluation of film coated atorvastatin calcium immediate release tablets to achieve faster dissolution to match the innovator product.

It involves preformulation studies specifically compatibility studies for possible drug-excipient interactions using Fourier Transform Infrared Spectrophotometer.

- Evaluation of pre compression parameters.
- Design and development of various formulations with different superdisintegrants.
- Evaluation of post compression parameters of the formulated tablets.
- To carry out *in-vitro* drug release studies.
- To carryout accelerated stability studies as per ICH guidelines.

- **PLAN OF WORK**

The scheme of proposed work is as follows:

A. Preformulation studies

1) Analysis of drug

a) Description
b) Solubility
c) Loss on drying
d) Melting point
e) Water content
f) Specific optical rotation
g) Drug identification
h) Identification of λmax
i) Calibration curve

2) Compatibility studies

3) Evaluation of tablet blend

B. Preparation of immediate release tablets

C. Evaluation parameters for tablets

1) Thickness
2) Weight variation
3) Hardness
4) Friability
5) Disintegration time
6) Assay
7) In-vitro dissolution

D. Comparison with marketed formulation

1) Data treatment

E. Accelerated stability studies

METHODOLOGY

Preformulation studies

Preformulation involves the application of biopharmaceutical principles and physicochemical parameters of drug substance were characterized with the goal of designing optimum drug delivery system. It is important part in drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in further stages of development. Characterization of drug is very important step at

preformulation phase of product development followed by studying the properties of excipients and their compatibility.

(1) Analysis of drug

(a) Description

- Color
- Taste
- odor

(b) Solubility

(c) Loss on drying

(d) Melting point

(e) Water content

(f) Specific optical rotation

(g) Drug identification

(h) Identification of λmax

(2) Drug-excipient compatibility studies

(3) Evaluation of blend

(a) Angle of repose

(b) Bulk density

(c) Tapped density

(d) Carr's index

Organoleptic properties

(a) Description

- Color
- A small amount of Atorvastatin calcium powder were taken on a butter paper and viewed in illuminated place. It appears as white powder.
- Taste and odor

Very less quantity of Atorvastatin calcium was used to get taste with the help of tongue as well as smelled to get odor. Taste was found to be bitter and characteristic odor.

(b) Solubility of drug

The solubility of the drug sample was carried out in different solvents (aqueous and organic) according to the United States Pharmacopoeia. The results are then compared with those given in the United States Pharmacopoeia. Solubility can be determined by placing the drug in a vial along with the solvent. The tightly closed vial is then agitated at constant temperature and the amount of drug in solution is determined periodically by assay of filtrate sample of the supernatant. Solubility of drug substance was performed in purified water, 0.1N HCl, Acetate buffer pH 4.5 and phosphate buffer pH 6.8. 50 mg of atorvastatin calcium was weighed and solubility of this sample was checked in water, methanol and phosphate buffer. The drug was found to be soluble in methanol. The approximate solubilities of substances are indicated by descriptive terms in the accompanying table 1.

Table 1: Approximate solubilities of substances

Descriptive term	Part of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	Greater than or equal to 10000

Loss on drying

One gram of granules were weighed and kept for checking the loss on drying on moisture sensitive

balance at 105˚C for 3 min. Percentage loss of moisture content is determined.

(d) Melting point

Small quantity of power was heated until it gets melt. Melting point for atorvastatin calcium should be in the range of 157-161˚C.

(e) Water content

Methanol was transferred to the titration vessel and titrated with Karl fisher reagent to the electrometric end point to consume any more moisture content that may be present. 300-500 mg of drug was transferred to the titration vessel and titrated with the Karl fisher reagent to the electrometric end point. Water content present in the sample was calculated by the formulae

Calculation

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where, S = volume in ml of reagent consumed in the second titration

F = water equivalent factor of KF reagent

W = weight of sample taken in mg

(f) Specific optical rotation

It is determined in a 1 percent w/v solution of dimethylsulphoxide.

Limits for specific optical rotation: -6 to -12˚.

(g) Drug identification by FTIR

FTIR spectroscopic studies were conducted for pure drug. FTIR spectrometry is the most powerful technique to identify functional groups of the drug. In the present study potassium bromide disc (pellet) method was employed.Solid sample is milled with potassium bromide (KBr) to form a very fine powder. This powder is then compressed into a thin pellet under hydraulic press which can be analyzed. KBr is also transparent in the IR, the FTIR spectra was recorded between 400 cm^{-1} and 4000 cm^{-1}.

(h) Identification of λmax of atorvastatin calcium

About 50 mg of drug was weighed and was dissolved in 50 ml ofmethanol(1 mg/ml). 10 ml of this solution was withdrawn and volume was made upto 100 ml. Appropriate dilutions were made with methanol to give concentration of 10 µg/ml, scanned in UV range from 200-400 nm, which could be utilized for analysis and spectrum was recorded.

(I) Calibration curve

Preparation of standard stock solution

50 mg of pure Atorvastatin calcium was accurately weighed and transferred to 50ml of volumetric flask. Drug was dissolved in phosphate buffer P^H 6.8 and volume was made up to 50ml. The concentration of drug was 1mg/ml. 2.5ml of this solution was taken in a 25ml volumetric flask and volume was made up to the mark with buffer. Thus Atorvastatin calcium of strength 100 µg /ml was obtained.

Procedure for plotting calibration curve of pure drug

From the standard stock solution 0.5ml ,1ml ,1.5ml, 2ml, 2.5ml dilutions were made in 10ml volumetric flask and volume was made upto the mark with phosphate buffer P^H 6.8 to obtain concentration in range of 5-25 µg/ml. The spectra were recorded, absorbance were measured at 246nm and calibration curve was plotted

Estimation of Atorvastatin Calcium

UV Spectrophotometric method was used in the present study for the estimation of Atorvastatin Calcium

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RESULT AND DISCUSSION

Preformulation studies

Table 2: Analysis of drug

S. No	Test	Specifications	Result
a.	Description	White to off white coloured crystalline powder	White powder
b.	Solubility	Freely soluble in methanol, slightly soluble in ethanol, very slightly soluble in water and acetonitrile and insoluble in aqueous solutions of pH 4 and below	Complies
c.	Loss on drying	Not more than0. 5 %	0.37 %
d.	Melting point	157-161 ˚C	160.2 ˚C
e.	Water content by KF	3.0-7.0 %	3.05 %
f.	Specific optical rotation	-6.0 and -12.0˚	-7.27˚
g.	Drug identification	Performed by FTIR	Functional groups identified
h.	Identification of λmax	Based on highest peak	Found at 246 nm

(G) Drug identification

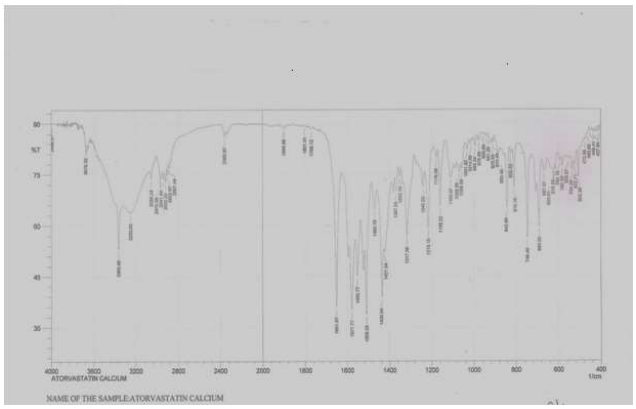

Fig.1: FTIR spectrum of atorvastatin calcium

Table 3: Different functional group regions of FTIR spectrum

Functional group	Type of Vibration	Wave No.
Amine (-N-H)	Stretching	3366.14
Aromatic (-C-H)	Stretching	2965.98
Carbonyl (C=O)	Stretching	1651.73
Aromatic (C=C)	Stretching	1576.52
Carboxylate	Stretching	1512.88
Aromatic (C-H)	Bending	1315.21

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(H) Calibration curve

Table 4: Standard curve of Atorvastatin calcium in phosphate buffer pH 6.8

S.No	Conc. (µg/mL)	Absorbance at 246 nm
1	5	0.23976
2	10	0.48377
3	15	0.71987
4	20	0.95515
5	25	1.22341

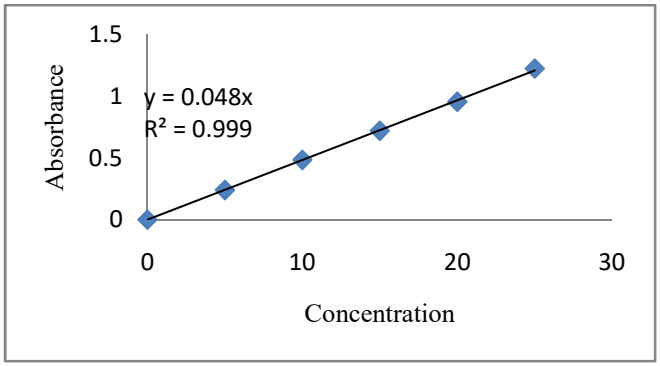

Fig.2 Standard curve of Drug

Drug Excipient Compatibility studies

Table 5 : Results of drug-excipient compatibility studies

S.No	API and excipients	Initial	40° ± 2C, 75 ± 5 % RH		
			7 days	14 days	30 days
1	Atorvastatin calcium + lactose monohydrate	White or off-white powder	No change	No change	No change
2	Atorvastatin calcium + MCC		No change	No change	No change
3	Atorvastatin calcium + calcium carbonate		No change	No change	No change
4	Atorvastatin calcium + HPC		No change	No change	No change
5	Atorvastatin calcium + croscarmellose sodium		No change	No change	No change
6	Atorvastatin calcium + polysorbate 80		No change	No change	No change
7	Atorvastatin calcium + sodium starch glycolate		No change	No change	No change
8	Atorvastatin calcium + crospovidone		No change	No change	No change
9	Atorvastatin calcium + opadry white		No change	No change	No change
10	Final tablet blend		No change	No change	No change

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Chemical compatibility studies

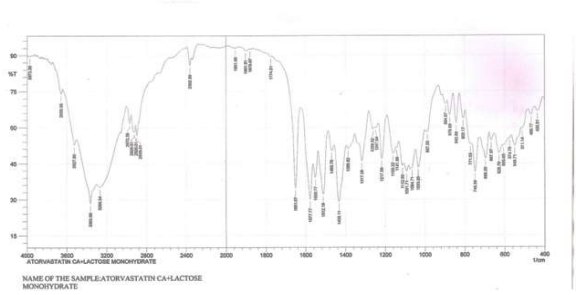

Fig.3 FTIR spectrum of atorvastatin calcium + lactosemonohydrate

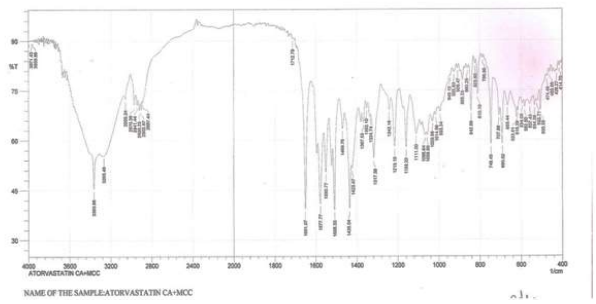

Fig.4 FTIR spectrum of atorvastatin calcium + microcrystalline cellulose

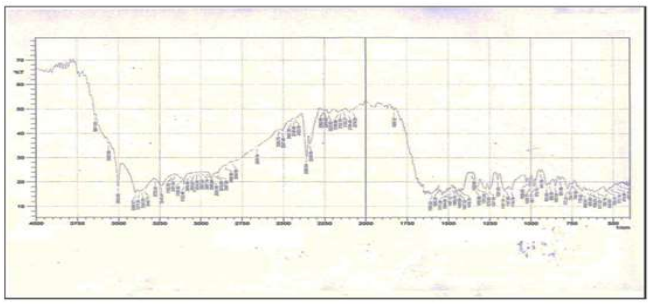

Fig.5 FTIR spectrum of atorvastatin calcium + opadry white

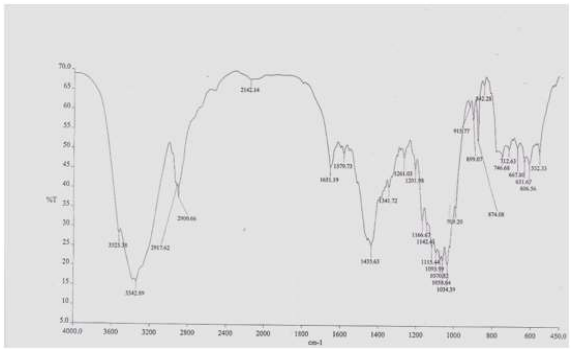

Fig.6 FTIR spectrum of optimized formulation

Evaluation of tablet blend

Table 6P: Evaluation of pre compression parameters

S. No	Batch No.	angle of repose(°)	bulk density g/mL	Tapped density (g/mL)	C.I
1	F1	28.23	0.495 ± 0.01	0.562 ± 0.05	11.92 ± 0.08
2	F2	25.51	0.389 ± 0.02	0.445 ± 0.03	12.58 ± 0.03
3	F3	27.12	0.390 ± 0.02	0.450 ± 0.04	13.34 ± 0.04
4	F4	26.34	0.410 ± 0.05	0.465 ± 0.06	11.85 ± 001
5	F5	32.13	0.495 ± 0.09	0.587 ± 0.11	15.27 ± 0.06
6	F6	*29.23*	*0.389 ± 0.11*	0.440 ± 0.08	11.59 ± 0.07
7	F7	*26.48*	*0.391 ± 0.07*	*0.462 ± 0.12*	14.22 ± 0.03
8	F8	*26.81*	*0.373 ± 0.10*	0.430 ± 0.01	13.26 ± 0.01
9	F9	*25.13*	*0.394 ± 0.10*	0.450 ± 0.03	12.45 ± 0.02

Mean ± S.D, n=6C.I- Compressibility index

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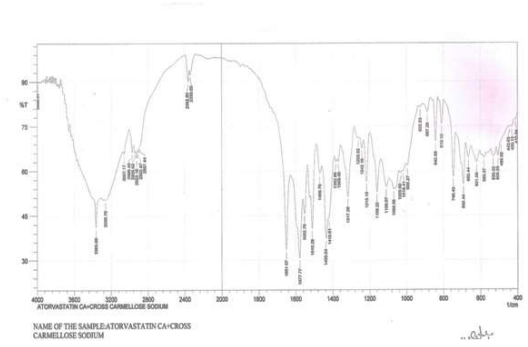

Fig.7 FTIR spectrum of atorvastatin calcium + Cross Carmellose sodium

SUMMARY AND CONCLUSION

The present study was mainly based upon the "Development and Evaluation of Atorvastatin calcium immediate release tablets 20 mg" (Antihypercholesterolemic and antihyperlipidemic) by Wet Granulation Technique. Various formulations of Atorvastatin calcium tablets were prepared by using different proportion & combination of Excipients. Tablet blends were prepared and micromeritic studies were carried out for those blends.Precompressional parameters such as angle of repose, bulk density, tapped density, compressibility index for physical mixtures of immediate release layer formulations (F1- F9) were evaluated and results were reported. From the results obtained by HPLC, the calibration curve was constructed having regression value of 0.999.

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