www.pharmaerudition.org

ISSN: 2249-3875

International Journal of Pharmaceutical Erudition

Research for Present and Next Generation

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Research paper

FORMULATION OF FILM COATED ATORVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS

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Plasticizer (glycerin) at 150 mg concentration of total polymer weight gave excellent results in preliminary work. The formulated films of Zopiclone were evaluated for their physic-mechanical parameters like tensile strength, folding endurance, thickness, disintegration time and in vitro drug release. Estimation of drug content uniformity of Zopiclone films was performed and the results were satisfactory. This batch had satisfactory % elongation (87.34), moderate tensile strength (4.99 N/mm2), in vitro drug release after 3 minute was 97.11 which is comes under decided range (equal or more than 85%) and folding endurance more than 100 that was satisfactory for good handling during packaging and transportation point of view. Stability is major issue in FDFs so stability study in accelerated condition (40^0c and 75%RH) was performed for optimized batch F3. Results showed that FDFs were susceptible to high temperature (40^0C) and humidity (75%RH) due to presence of highly water soluble polymer and other excipients. To study the process parameters effect on final formulation behavior, drying time and drying temperature selected as a crucial parameters for solvent casting technique. Different drying temperature (30, 55 and 80^0C) and time period (10, 20 and 30 hrs) condition produced film with different tensile strength, % elongation, in vitro DT, drug released at 3 minute. Fast dissolving film of Zopiclone was successfully developed with good in vitro characteristics at laboratory scale. Hence, developed fast dissolving film formulation can be a new era of drug delivery in future.

Keywords - Zopiclone, Insomnia, HPMC 6cps, Maltodextrin

INTRODUCTION

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipient. According to the Indian Pharmacopoeia pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage forms, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and intended mode of administration. All medicaments are available in the Tablet form except where it is difficult to formulate or administer[4].

1.2.1 General properties of tablet dosage forms

- A tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
- Should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

1.2.2 Different types of tablets

Tablets are classified as follows

- According to the drug release rate from the tablet.
- According to the method of manufacturing.
- According to the route of administration or function.

I. According to the drug release rate from the tablet

a. Conventional tablets

The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as solution. It is the most common type and includes:

- Disintegrating tablet e.g. Acetaminophen tablet
- Chewable tablet e.g. Antacid tablet
- Sublingual tablet e.g. Vicks menthol tablet
- Buccal tablet e.g. Vitamin-C tablet
- Effervescent tablet e.g. Disprin tablet (Aspirin)

b. Controlled release tablets

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems solvent activated systems and chemically controlled systems. Diffusion controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so called programmed-release (tailored-release) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

AIM AND OBJECTIVE

Aim

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.

Objectives

- 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.

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[52]

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.

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

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

(c) 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}.

G) Drug identification

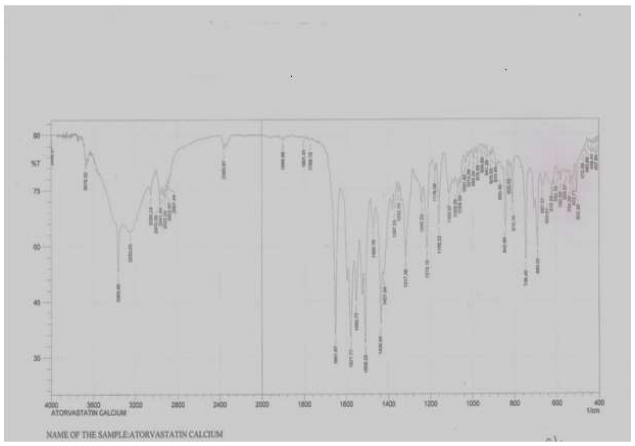

Fig.1 FTIR spectrum of atorvastatin calcium

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

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

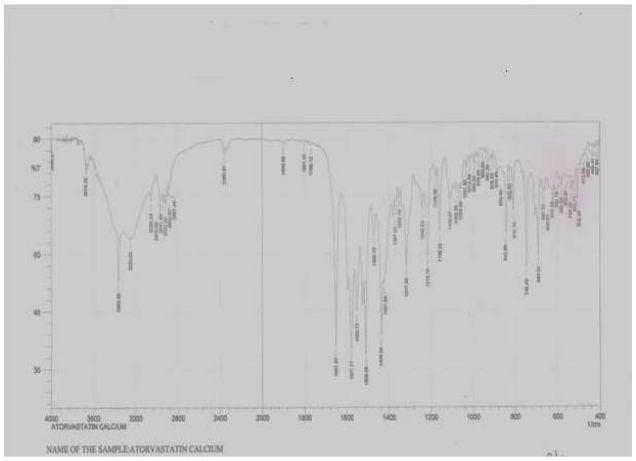

Fig.1: FTIR spectrum of atorvastatin calcium

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

(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

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. Assay values of the formulations were observed in the range of 98 to 102 %. Compatibility studies were performed and it was observed that all the ingredients used were compatible with the drug. Formulation (F9) was formulated by including 12mg of Croscarmellose sodium. The results showed disintegration was within limits and 100 % drug release was found in 30 min. So, formulation (F9) was taken as optimized formulation. Accelerated stability studies were performed for this batch. Assay and Dissolution studies were performed for the optimized formulation (F-9) at different time intervals. All the parameters were found to be satisfactory. Dissolution studies were performed and it was found that formulation F9 have shown best results and comparable with the innovator.

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ISSN 2249-3875

International Journal of Pharmaceutical Erudition