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Development of film coated Atrovastatin calcium tablet using Opadry-OY

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Abstract

Purpose: The aim of this study was to develop and evaluate the stability of film coated Atorvastatin Calcium (AtC) tablets using Opadry-OY-B-28920.Method:AtC uncoated tablets were developed and manufactured through the Wet Granulation process. Opadry-OY-B-28920 white aqueous coating dispersion was used as film coating material. Results: The film coated tablets were completely disintegrated within 10 minutes in water media, it was also completely dissolved (more than 85% of the drug was released) within 30 minutes in pH 6.8buffersolutions.The film coated tablets were studied under both long term and accelerated stability study and the results showed no significant variation in physical characteristics, color, hardness, no obvious defects or signs of peeling or chipping. These results reflect that the film coated system Opadry-OY-B-28920 can be successfully used in order to produce AtC film coated tablet that is protected from environmental conditions such as light and humidity. Conclusion: These findings suggest that aqueous film coating with Opadry-OY-B-28920 system is an easy and economical approach for preparing stable film coated AtC tablet of immediate release.

Keywords: Atorvastatin calcium, tablets, film coating, aqueous dispersion system, opadry.

Introduction

The objective of this study is to design and develop a solid dosage form in a large scale manufacturing settings which will achieve predictable therapeutic response, and reproducible product quality. Realizing these objective is usually difficult and become challenging when the active ingredient is sensitive to environmental conditions. Film coating is the more contemporary and thus commonly used process for coating oral solid dosage forms[1] which will confer specific benefits that broadly range from: (i) improving the aesthetic qualities of the dosage form, (ii) masking unpleasant odor or taste and (iii) improving product stability. Usually film coating is obtained by spraying a thin layer of a mixture of film forming polymer/s, plasticizer/s and pigments on the surface of a solid dosage form. Selection a suitable mixture of these components is usually a difficult task and may result in unsatisfactory results in term of appearance, stability. Many industries of raw materials have developed a ready for use film coating blends, which are ready for use. These polymer blend formulations provide the user with the ability to impart many beneficial features to a solid oral dosage formulation. The most commonly used film coating polymers today include the cellulose derivatives[2]. Recently, these polymers were considered as the most preferred materials for producing film coating formulations in terms of performance and global acceptability[3, 4]. The aqueous based coating systems are preferred when compared with the organic solvent based systems as the organic solvents based coating systems have many drawbacks including pollution, explosion hazards, solvent toxicity and risks for operators[5, 6]. Opadry Yellow 20A82938 is an immediate release, pearlescent, film coating system which was to protect drug from the effect of moisture and light for an extended period of time without interfering with the immediate release profile of the drug[7, 8].It consists of a combination of polymers (based on hydroxypropylmethyl cellulose), plasticizers and pigments. The dry powder blend can be easily prepared by simply mixing with water, the resulting mixture meets compendial requirements of the USP/EP/JPE for pharmaceutical applications[9]. Opadry film coating system will provide an excellent strength, elasticity adhesion characteristics film which strengthen friable cores and improve drug stability. Coatings prepared from such dispersions are resistant to moisture, light and oxidative conditions of the environment but readily dissolve at acidic pH. AtC is one of the most used lipid lowering agents. However it is a photosensitive and highly susceptible to degradation under acidic conditions[10]. Moreover it is available in

several polymorphic forms that may have different pharmacokinetic behaviors. Changing from polymorphic form to another may arise during the manufacturing process or the storage of atorvastatin tablets[11]. Accordingly, the used film coat should eliminate these inconveniences. Therefore, this study aims to develop film coated atorvastatin tablets using Opadry-OY-B-28920 as coating material and to evaluate its stability under both long and accelerated stress conditions, the quality of the obtained coated tablets including the physical appearance, hardness, weight variation and drug content of AtC tablets were evaluated according to the USP 33.

Material& method

Materials:

Atorvastatin calcium (Arch Pharmalabs Limited), microcrystalline cellulose (FMC Corp, Ireland), Aerosil (Evonik, Germany), Lactose Monohydrate (DMV-Fonterra, Holand), Calcium carbonate and magnesium stearate (Magnesia, Germany), Tween 80 (klop Ag Switerland) , Hydroxypropyl cellulose (SamaImpex LTD). Sodium hydroxide (Merck, KgaA, and Darmstadt, Germany) dibasic sodium phosphate (Merck, KgaA, Darmstadt, Germany), Opadray white material was provided by Colorcon GmbH (Germany), Glacial acetic acid (Merck, KgaA, Darmstadt, Germany). Aluminum foil (INEOS)) and PVC (Klocknerpentaplast) and all the other chemicals used were of analytical grade and obtained from commercial sources.

Instruments:

The analysis and quantification of AtC in the sample was performed by Merck Hitachi HPLC system; (Interface module D-7000, Autosampler L-7200, Pump L-7100, Detector L-7450) was used. Li Crospher 100 RP-18, 5 μm, 250×4mm was used as stationary phase to achieve separation. An electronic balance (Precisa 205 ASCS) , Thickness and diameter were measured by Vernier caliper (TA-100 Erweka friabilator) , The tablet hardness was tested by hardness tester (Pharma test PTB311E), ZT-221mode disintegrator tester (Erweka, Husenstamn, Germany) was used to test disintegration. A dissolution apparatus (Erweka DT 70, Husenstamn, Germany) was used for drug release testing. The tablet coating was performed in a coating pan (Erweka GmbH., type UG, Frankfurt, Germany) using external spray gun and a dryer (Ceccato air compressor S.p.A, mod:8566 Mfg by CDA Engineering sdnBhd-Malysia). The tablets were packed using packing machine (Ulhmann-200, Germany). For accelerated stability study a stability chamber (Binder GmbH Bergster, Tullingen, Germany) was used. A Modulated Dynamical Scanning Calorimetry (MDSC Q200) made by TA instruments was used

Methods

Preparation of uncoated Atorvastatin (80 mg) tablets

AtC uncoated granules were prepared by Pharmacare PLC. All the ingredients were properly weighed and sieved through 24 mesh. The granules were composed of microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, aerosol, calcium carbonate and magnesium stearate. The granules were prepared by wet granulation method, then dried and lubricated by magnesium stearate. The obtained flowable granules were compressed using Manesty tableting machine. The average weight of the final uncoated tablets was about 1200 mg. After compression, in process control of AtC tablets were evaluated according to the USP 33 tests [17]; dissolution test using 900ml of pH 6.8 phosphate buffer maintained at 37°C and with the paddle II operating at 75 rpm was carried out according to FDA requirements. [18].

Film coating of Atorvastatin calcium (80 mg) tablet

Preparation of Opadry Yellow 20A82938 dispersion for film coating

Opadry Yellow 20A82938 (150gm) was mixed with 1000 ml distilled water using a mixing pan for about 20 - 25 minutes. The aqueous dispersion was passed though a 250 micron sieve before starting the coating process and was continuously stirred during the coating process.

Coating methodology

Tablet coating parameters are shown in (Table1), It was performed in a coating pan of 5 kg capacity using a spraying gun. The core tablets (4.0 kg) were placed into the coating pan and were pre-heated to about 40°C by a dryer of a high pressure air spray guns. Warm air was then introduced into the coating pan (temperature 55–60 °C) during the entire coating process. The spray gun was filled with Opadry-OY-B-28920 white aqueous dispersion and operated at a suitable flow rate. The motion of the pan was adjusted and the seal coating dispersion was sprayed onto the falling cores using a suitable air pressure (1.7 bars). The air heater was switched off and tablets blow dried for 20-25 minutes in the coating pan.

The core tablets gained an extra 3% of its original weight after coating (Table 2). The coated tablets were then blistered in an aluminum-aluminum strips using (Ulhmann-200, Germany) packing machine.

Evaluation of Atrovastatin Calcium (50mg) Coated Tablet

Mechanical strength

The hardness of the coated tablets was tested by randomly selecting 20 tablets from each three study batches at different time intervals of the study.

Disintegration test of film coated tablets

The disintegration test of film coated Atc 80mg tablets was performed according to USP 33[17]. Six coated tablets of atorvastatin were placed in pH 6.8 buffer solutions in a USP basket rack assembly (Erweka ZT-2, Husenstamn, Germany) and the time of complete disintegration was reported.

Assay for film coated tablets

The percentage assay of atorvastatin coated tablet was performed according to the USP 33 assay method using a reverse phase HPLC atλ 238nm [17].

Dissolution Test of Film Coated Tablets

The dissolution test for film coated tablets was performed using a phosphate buffer of pH 6.8 media according to FDA requirements[18]. Atorvastatin release was measured in a USP dissolution apparatus II, the operating temperature was 37± 0.5 ºC. The paddle stirring rate was 75 rpm. The dissolution of six tablets was determined after 30 minutes run; an aliquot of the fluid was drawn and assayed by HPLC at absorption λ of 238 nm.

Stability study of coated tablets

A selected samples of the film coated tablets in a blister of aluminum foil and PVC were subjected to both long term and accelerated stability study in accordance with the ICH guidelines[19]. The long term stability study samples kept at room temperature (25±2^{o}C) and 65±5% relative humidity conditions. The samples were collected for testing at a time interval of 0, 3, 6, 9 and 12 months. The accelerated stability study were kept at 40 °C ± 2 °C and relative humidity 75% ± 5% and were tested at time interval of 0, 3 and 6 months. Samples in both studies were tested for their appearance, disintegration, dissolution, hardness and assay using the above described procedures to evaluate the stability of the coated tablets.

Differential Scanning Calorimetry

The test was done to check the compatibility of the coating with the drug formulation; the test was performed by monitoring the thermal transition of the AtC and the opadry. The sample was heated from 25 ºC to 200 ºC at ramping rate of 10 ºC/min with a nitrogen flow rate of 60 mL/min.

Result and discussion

The aim of this study was to develop film coating of atrovastatine calcium 80 mg tablet by using Opadry-OY-B-28920 white coating aqueous dispersion without a sub-coating step. Opadry-OY-B-28920 white dispersions method consists of a simple addition of the formulated polymer with water. This process is efficient and requires little effort and time. The sieving of the dispersion was performed to ensure that there is no dispersed particles that could cause gun blockages or adversely affect the smoothness of the tablet film coating. The continuous stirring of the dispersion during the coating process was done to avoid sedimentation and coalescence of particles.

The uncoated tablets were processed under strictly good condition in order to achieve best coating results. The granules were appropriately lubricated to allow good flowability in order to reduce tablet weight variation. The compressed granules produced tablets free from defects such as capping and lamination. The hardness (good breaking force higher than 7.0 Kps), friability (a maximum loss of mass not greater than 1%) physical appearance, weight variation and drug content evaluation of the uncoated tablets were found to be satisfactory. Generally tablets processed for the coating process must withstand the mechanical stresses and must have low potential for erosion or edge chipping.

The produced coated tablets had no visible defects such as orange peel effect, chipping, tacking or any other physical flaws. Compared to the traditional aqueous film coating systems which consist of multiple component steps before coating; our coating system was dispersed in the minimum amount of time, and produced acceptable weight gains.

Our tablet coating was carried out in conventional coating pan using spray coating technique. The temperature of coating pan and spray rate of coating solution were maintained properly as temperature in relation to the spraying rates in some studies[12, 13] showed that at low rates; the temperature of the coating pan did not affect the roughness of the coated tablets while at higher spray rates, higher temperature gave smoother films.

All other variables including the inlet airflow, pan speed, inlet air temperature, coating time, atomization pressure, and fan pressure were fully controlled as they significantly affect coating uniformity [14, 15]. Studies showed using high inlet-air temperature and low spray rate will slow the drug release from the coated tablets, while increasing the temperature in order to remove water and solvent from the product will affects the properties of final products[16].

Our film coating process avoided the sub-coating step which sometimes is used in order to strengthen friable cores before the application of the coat orto prevent interaction between the drug substance and the coating formulation ingredients. In our study sub-coating was avoided to save process time, complexity, cost and environmental pollution due to the use of organic solvents.

Moreover, thermal analysis was conducted to evaluate the compatibility between AtC and the used opadry. In this study three runs were done separately for the opadryl coating only, and then a mixture of the opadryl coating material with AtC was performed to

Table 1: Parameters of enteric coating process

Factor	Conditions
Equipment	Erweka Coating Pan
Substrate	1200mg AtC Tablets
Pan Charge	4 Kg
Inlet Temperature	55-60 °C
Bed Temperature	35-40 °C
Diameter of spray tip	1.2 mm
Distance Between spray gun and tablet bed	15 cm

Table 2: Parameters of film coating formulation

Parameter	Amount (% w/w)
Theoretical weight gain	3
Dispersion solid content	15.0
Deionized water	72.5

Table 3: Long term stability study of film coated Atorvastatin calcium 80 mg/tablet

Tests	Time (months)					Limit
	0	3	6	9	12	
%Assay	102.5±0.3	102.3±0.1	101.7±0.1	101.9±0.5	102.2±0.2	90.0% - 110.0%
%Dissolution						Min. 80
Average	100.5±2.0	100.6±3.1	100.8±1.9	101.2±1.1	100.1±2.3	Min. 85
Min. (individual)	97.3±2.2	98.2±2.3	98.2±1.2	99.3±1.6	97.4±2.1	
Disintegration	Complete	Complete	Complete	Complete	Complete	Complete
Appearance test	Complies	Complies	Complies	Complies	Complies	White tablets
Hardness (Kb)	8.5±1.1	8.2±0.8	8.0±1.0	7.9±2.3	8.4± 1.2	Min. 6

Table 4: Accelerated Stability Study of film coated Atorvastatin calcium 80 mg/tablet

Tests	Time (months)			Limit
	0	3	6	
%Assay	102.5±0.3	102.6±0.3	101.1±0.5	90.0% - 110.0%
%Dissolution				Min. 80
Min. average	100.5±2.0	101.3+ 1.5	100.9+ 1.2	Min. 85
Min. (Individual)	97.3±2.2	96.8+ 1.9	98.2+ 1.4	
Disintegration	Complete	Complete	Complete	Complete
Appearance test	Complies	Complies	Complies	White tablets
Hardness (Kb)	8.5±1.1	8.8± 0.8	9.1± 0.5	Min. 6

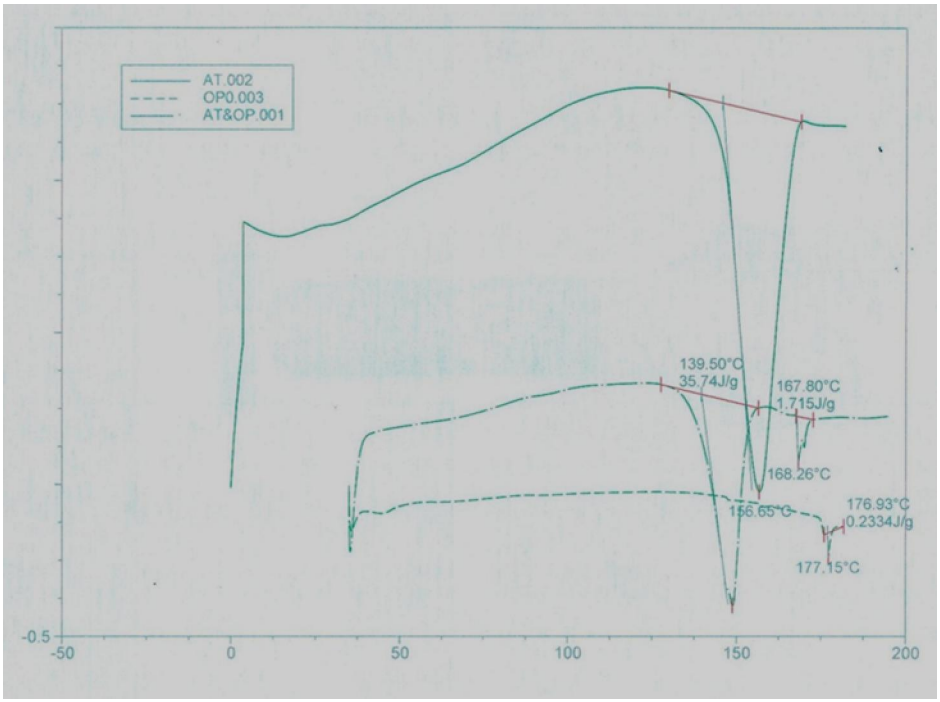

Figure 2: DSC thermogram of atorvastatin Calcium and Opadray

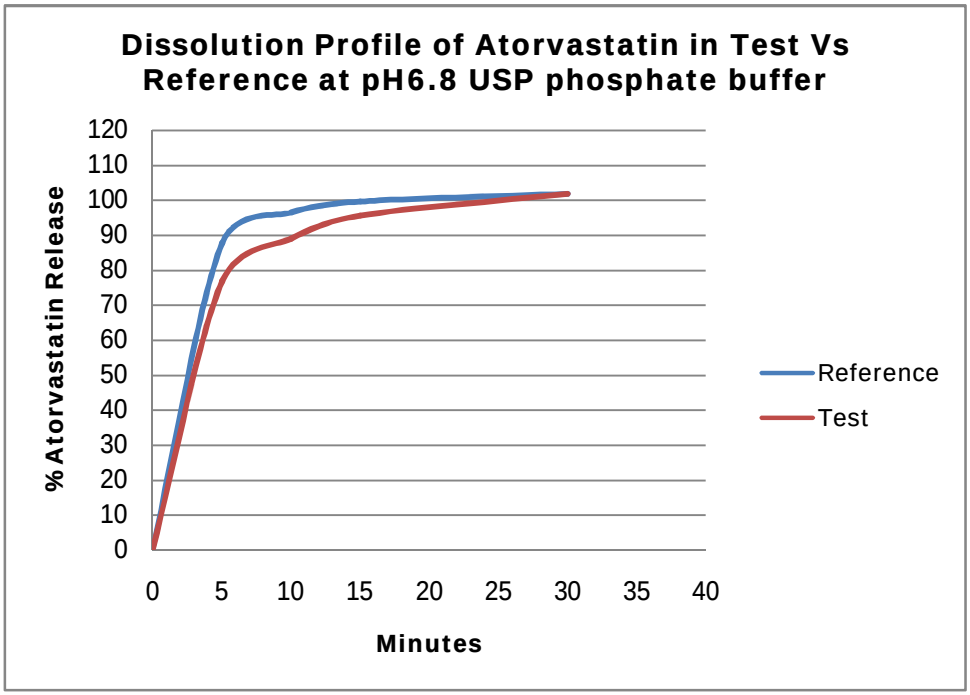

Figure 3: In-vitro dissolution profile of Atorvastatin calcium 80 mg / tablet.

check for its compatibility. Thermograms of pure AtC showed sharp endothermic peak at 156.65 ℃ while opadry sample showed a clear endothermic peak at 177.15 ℃. The same peaks were observed in the thermogram of the mixture of both AtC and opadry without any overlapping as reported in Figure 2,this clearly indicated there is no drug opadry interaction.

The long term and accelerated stability study results clearly demonstrated that the formulated coated tablets were robust and all the tested parameters were constant within the studied stability period as reported in Table 3&4. The result in the tables clearly show that both the long term and accelerated study showed no significant variation in physical characteristics, color, hardness, no obvious defects or signs of peeling or chipping and the coated tablets showed complete disintegration and dissolution within sufficient time.

In vitro drug release studies which are considered the best tool for assessing in vivo drug behavior were carried out and both the percent dissolution and assay were within the acceptable limits as shown in Figure 3.The figure shows no significant difference between the Atc film coated tablets and the reference and all were completely dissolved within 30 minutes

Three different batches of coated atorvastatin calcium were prepared and tested parameters of the three batches showed no significant differences for each set of these batches, indicating that this manufacturing process is reliable and reproducible.

Conclusion

AtC film coated tablets were developed using Opadry-OY-B-28920 system. Aqueous film coating was successfully conducted under lab-scale facilities. Opadry-OY-B-28920 system provided acceptable film performance. The produced coated tablets were stable within 12 months when stored at room temperature. Moreover, AtC was stable when stored for 6 months at 40 °c ± 2 °C and relative humidity 75% ± 5%. Three batches were produced and tested under the same conditions. All batches showed the same results which means that this formulation is reliable and reproducible. Therefore, these findings suggest that aqueous film coating with Opadry-OY-B-28920 system is an easy and economical approach for preparing stable atorvastatin calcium tablets.

Conflict of Interests: The author declare no conflict of interests

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