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Research Article

EFFECT OF FORMULATION AND PROCESS VARIABLES ON DEGRADATION PRODUCTS OF LOVASTATIN IN TABLET DOSAGE FORM

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ABSTRACT

Objective: Quantification of degradation products in drug substances and products is the most challenging tasks in pharmaceutical industries nowadays. Systematic study on the degradation products of lovastatin in compressed tablets has not been reported in the literature. The objective of the present study is to investigate the effect of excipients and method of manufacturing on the degradation products of lovastatin in compressed tablets manufactured by three different methods. The study also aims to evaluate the impact of aging and packaging material on the degradation products.

Methods: Tablets of lovastatin were prepared by wet granulation, dry granulation and direct compression methods with different excipients. The tablets were assayed by a validated HPLC method for lovastatin and its major degradation products initially and after 12 months period while storing at 25±°C in glass bottles, Polyvinyl chloride/Aluminum foil blisters and Alu/Alu blisters.

Results: Results have shown that excipients and method of manufacturing influence the amounts of major degradation products hydroxyacid lovastatin (HAL) and dehydrolovastatin (DHL) which were found in amounts of 0.67% and 0.45% in tablets compressed via wet-granulation, 0.42% and 0.19% in tablet compressed via dry-granulation and 0.30% and 0.20% in tablets compressed via direct compression method respectively. The tablets showed maximum stability in Alu/Alu packing followed by packing in glass bottles and PVC/Al. foil blisters, respectively.

Conclusion: This study concluded that lovastatin obtained from different sources have different degradation products showing that they are originated from the manufacturing stage of the API. The varying contents of the degradation products in tablets manufactured by different methods initially and with time indicate that the manufacturing process and excipients also have important role in generation of degradation products. Furthermore, packaging material significantly affect the stability of the tablets during storage. Therefore, all these conditions and factors must be considered and controlled during formulation, manufacturing, and storage of the compound and its formulated products.

Keywords: Lovastatin, Degradation products, Hydroxy acid lovastatin and dehydro lovastatin.

INTRODUCTION

Lovastatin is (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate) is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor and is widely used in the treatment of hypercholesterolemia [1]. It is commonly available in tablet dosage form. These tablets may have varying level of impurities that may be critical to the quality, safety and efficacy of the drug product. The impurities may be originated from the drug substance [2]. Some impurities may also be introduced into the drug product from the excipients used for formulating the drug product or through the formulation process or by contact with the packaging material [3-6]. Degradation of a drug product during shelf-life may also give rise to various impurities that are commonly known as degradation products [2]. The role of these impurities is so significant that their control and monitoring is necessary under various regulations and guidance documents [7-11]. Thorough search of the literature shows that no systematic work has been published for lovastatin on these aspects. These facts motivated the present work which is an attempt to assess the effect of excipients and manufacturing process variables on the common degradation products of lovastatin in compressed tablets. Attempts have also been made to explore the effect of aging and packaging material. The European pharmacopoeia 2005 method for related substances of lovastatin [12] is used in this study for estimation of the parent compound and its degradation products.

Time (min)	Mobile phase A (acetonitrile R) % v/v	Mobile phase B (0.1% solution of phosphoric acid R) % v/v
0-5	60	40
5-7	60→65	40→35
7-13	65→90	35→10
13-15	90	10
15-17	90→60	10→40
17-20	60	40

METHODS

Reference standards of lovastatin, hydroxy acid lovastatin (HAL) and dehydro lovastatin (DHL) were donated by M/S. MSD Pakistan. Lovastatin raw material was purchased from M/S. Wuhan chemical China. M/S. Ningbo Chemical China and M/S. Exconcord Pototech, India. All the reagents used were of analytical grade, and the solvents were of spectroscopic grade. A fresh Milli-Q system (Millipore, USA) purified water was used throughout the analytical work.

High-performance liquid chromatography (HPLC) apparatus and conditions

The HPLC analysis was carried out on a Shimadzu class-20 (Kyoto, Japan) system that consisted of an LC-20AT pump, an SPD-20A ultraviolet-visible detector with a mixer for gradient elution and an inbuilt CBM-20A lite communication bus module. Data collection and integration were achieved using Shimadzu LC solution computer software version 1.2 (Kyoto, Japan). All separations were achieved using stainless steel column (250 mm × 4.6 mm) packed with 5 µ

Table 1: Percentage composition of tablets manufactured by the three different methods

Percentage (w/w) composition of tablets manufactured by wet-granulation method	Percentage (w/w) composition of tablets manufactured by dry-granulation method	Percentage (w/w) composition of tablets manufactured by direct compression method
Lovastatin - 10	Lovastatin - 10	Lovastatin - 10
PVP-K-30-2.5	Lactose - 65	Microcrystalline cellulose - 200-61
Isopropyl alcohol - 16	Maize starch - 10	Microcrystalline cellulose - 102-15.2
Lactose - 75	Sodium starch glycolate - 2.4	Sodium starch glycolate - 3
Sodium starch glycolate - 2	Magnesium stearate - 0.8	Magnesium stearate - 0.8
Magnesium stearate - 0.8		

PVP-K-30: Polyvinylpyrrolidone K 30

Table 2: Assay of lovastatin, HAL and DHL in lovastatin samples obtained from different sources

Source	Fresh samples analysis			Analysis after 1 year		
	% Lovastatin	% HAL	% DHL	% Lovastatin	% HAL	% DHL
Wuhan China	100±0.39	0.34±0.06	0.2±0.03	99.8±0.21	0.6±0.14	0.2±0.05
Ningbo China	99.77±0.48	0.42±0.12	-	99.6±0.39	0.4±0.11	-
Exconcord Biotech, India	100.2±0.55	0.27±0.05	-	99.45±0.23	0.59±0.23	0.13±0.06

*Each value is mean of five observation±SD, SD: Standard deviation, HAL: Hydroxy acid lovastatin, DHL: Dehydro lovastatin

octylsilyl silica gel particles while keeping the flow rate of 1.5 ml/min and detection at 238 nm. The chromatograph was programmed as follows:

HPLC analysis

Reference solutions of different concentrations (5-75 µg/ml) of lovastatin, HAL and DHL, were prepared in acetonitrile and calibration curves were constructed. Test solutions were prepared in acetonitrile and/or further diluted with the same solvent to make the final concentration of 50 µg/ml. The solutions were filtered through 0.45 µ filter paper and then injected to the liquid chromatograph for analysis. The concentration of lovastatin, HAL and DHL was estimated from their calibration curves.

Preparation of tablet formulations

The commonly used methods of tablet manufacturing, i.e. wet-granulation, dry-granulation and direct compression were used in this study. The % age composition of tablets manufactured by the three different methods is given in Table 1.

Data analysis

All the data were expressed as the mean of five replicate determinations (n=5). Computer based statistical package for social sciences (SPSS version 10, LEAD Technologies Inc., USA) has been used for descriptive statistics. Data were compared using Student's *t*-test. The statistical significance was defined as $p<0.05$.

RESULTS AND DISCUSSION

Assay of lovastatin and its major degradation products in active pharmaceutical ingredient

Lovastatin and its major degradation products studied in this investigation were identified by comparison of their t_R values with those of the reference standards. A typical chromatogram showing lovastatin and its major degradation products, HAL and DHL is shown in Fig. 1. The assay data on lovastatin and its major degradation products in the lovastatin samples obtained from different sources is given in Table 2. HAL was found to be the common impurity ranges from 0.27 to 0.43% in fresh samples while 0.4-0.6% in the samples after 1-year period stored at 25±2°C in tightly closed containers. The results show varying amounts of these two degradation products in samples of drug substance obtained from different sources possibly because of varying level of purification, synthetic routes and purity of chemicals used in basic manufacturing. The amounts of impurities also increase with aging and may become critical with time [2].

Table 3: Assay of lovastatin, HAL and DHL in compressed tablets manufactured by different methods at zero time

Tablets manufacturing method	% Lovastatin	% HAL	% DHL
Wet-granulation	99.4±0.31	0.67±0.2	0.45±0.09
Dry-granulation	99.78±0.23	0.42±0.13	0.19±0.07
Direct compression	99.8±0.26	0.3±0.06	0.2±0.02

*Each value is mean of five observation±SD. SD: Standard deviation, HAL: Hydroxy acid lovastatin, DHL: Dehydro lovastatin

Assay of lovastatin and its major degradation products in compressed tablets

To evaluate the effect of drug-excipient interaction, manufacturing process and packaging material, tablets were manufactured by three different methods i.e. direct compression, dry granulation and wet granulation, each involving different excipients however similar source (Wuhan Industries) API (Table 1). The tablets were assayed for lovastatin and its major degradation products initially and after 12 months period while storing at 25±2°C in glass bottles, polyvinyl chloride (PVC)/aluminum (Alu) foil blisters and Alu/Alu blisters. The assay data of compressed tablets at zero time and after 12 months is presented in Table 3. The data indicate that tablets manufactured by different methods show varying level of degradation at zero time showing the impact of manufacturing process. Tablets manufactured by wet-granulation method show more degradation followed by dry-granulation method and direct compression method respectively. More degradation in tablets manufactured by wet-granulation method may be due to the wet-environment provided by the solvent used for wet massing and more heating and crushing processes involved as compared to dry granulation and direct compression methods [13]. This factor was established by comparing the degradation profile of mixed powder for wet-granulated tablets to the degradation profile of the wet-granulated tablets and before and after packing in PVC/Alu foil blisters. The amount of the degradation products increased slightly after tableting (0.85% HAL and 0.39% DHL) and after packing in blisters (0.31% HAL and 0.17% DHL) due to various attrition forces inherited in mixing, granulation and compression processes and heat imparted during the blister packing process.

An increased amount of degradation products with time has also been shown in the tablets manufactured by wet granulation method, suggesting the role of excipients and the method of manufacturing on the degradation of the tablet formulations. Results also show that

Table 4: Assay of lovastatin, HAL and DHL in wet-granulated tablets stored in different packaging material

Type of packaging	Initial results			Test results after 12 months storage at 25±2°C		
	% Lovastatin	% HAL	% DHL	% Lovastatin	% HAL	% DHL
Glass bottles	99.4±0.31	0.67±0.2	0.45±0.09	98.76±0.23	0.91±0.36	0.58±0.04
PVC/Alu foil blisters	99.4±0.31	0.67±0.2	0.45±0.09	98.18±0.18	1.19±0.28	0.62±0.03
Alu/Alu blisters	99.4±0.31	0.67±0.2	0.45±0.09	98.94±0.21	0.79±0.30	0.53±0.08

*Each value is mean of five observation±SD. SD: Standard deviation, HAL: Hydroxy acid lovastatin, DHL: Dehydro lovastatin, Alu: Aluminum

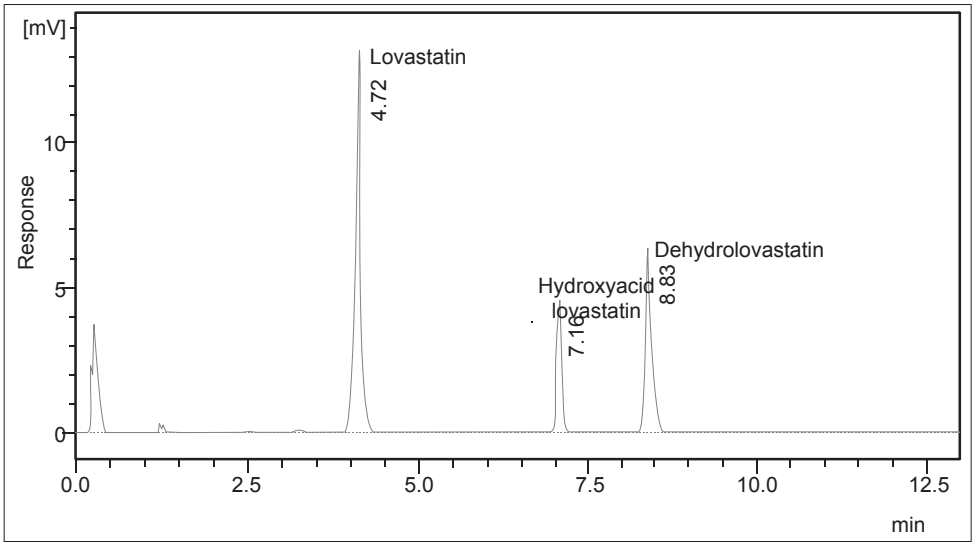

Fig. 1: HPLC chromatogram of lovastatin and formulation adjuvants spiked with hydroxy acid lovastatin and dehydro lovastatin

packaging material influences significantly the stability of tablets as shown in Table 4. All tablets packed in Alu/Alu blisters showed maximum stability as compared to those stored in glass bottles and PVC/Alu foil blisters respectively. The increased degradation in PVC/Alu foil blisters may be due to less integrity (pin holes) of PVC, which offers comparatively less protection against environmental changes [14]. Decreased stability in glass bottles may also be attributed to less protection of the tablets against degrading factors.

CONCLUSION

The contents of degradation products in lovastatin obtained from different sources were different showing that they are originated from the manufacturing stage of the API. The varying contents of the degradation products in tablets manufactured by different methods initially and with time indicate that the manufacturing process and excipients also have important role in the generation of degradation products. Furthermore, packaging material significantly affect the stability of the tablets during storage. Therefore, all these conditions and factors must be considered and controlled during formulation, manufacturing, and storage of the compound and its formulated products.

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