Original Article

Development of single *in vitro* dissolution method for fixed-dose combination of atorvastatin and aspirin

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ABSTRACT

Introduction: This investigation aimed to develop and validate a dissolution method for a combination of atorvastatin and aspirin tablets using the ultraviolet (UV) spectrophotometric method. The analytical method was developed by UV spectrophotometry using the absorbance ratio method which involves the measurement of absorbance at two wavelengths 246 nm as the λ_{max} of atorvastatin and 212 nm for aspirin as isoabsorbtive point. The method was validated according to ICH guidelines which include accuracy, precision, specificity, linearity, and analytical range. Furthermore, the stability and solubility of both the drugs in different media, that is, water and phosphate buffer of different pH were studied. **Procedure:** Based on this, the established dissolution conditions were 900 mL of 0.2 M phosphate buffer pH 6.8 as dissolution medium at 37±0.5°C, using USP apparatus II at a stirring rate of 75 rpm for 1 h. The corresponding dissolution profiles were constructed, and all the selected brands showed more than 80% drug release within 45 min. **Results:** Thus, the proposed dissolution method and analytical method can be applied successfully for the quality control of atorvastatin and aspirin in marketed tablets.

Keywords: Dissolution, atorvastatin, ICH guidelines, aspirin, ultraviolet spectrophotometric method

INTRODUCTION

A combination of two or more drugs in a single pharmaceutical formulation is known as a fixed-dose combination. As a rule, two drugs to be combined should have approximately equal plasma half-life, and the ratio of doses of each component should depend on an apparent volume of distribution and plasma concentrations. The rationale of using fixed-dose combinations includes (i) improved patient compliance – simplified disease management for chronic diseases such as HIV, diabetes, hypertension, and asthma, (ii) better efficacy-synergistic mechanism improved absorption, distribution, metabolism, and excretion and drug resistance, and (iii) simplified/cost-effective handling and distribution – mainly for HIV drugs.[1] The dissolution test is a simple and useful *in vitro* tool that can provide valuable information about drug release similarity among different batches and brands. It describes manufacturing reproducibility, product performance similarity, and biological availability of drugs from its formulation. Therefore, it is considered as one of the most important quality control parameters for solid pharmaceutical dosage forms.[2] Atorvastatin belongs to the category of antihyperlipidemic drugs, and aspirin belongs to a non-steroidal anti-inflammatory drug. Both the drugs belong to BCS Class II, that is, high permeability low solubility.[3] Atorvastatin is (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl4-(phenyl carbamoyl)-5-propane-2-yl pyrrol-1-yl]-3,5 dihydroxy heptanoic acid , a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase which is an early rate-limiting step in cholesterol biosynthesis. The inhibition of synthesis leads to the consumption of intracellular cholesterol, which increases the expression of low-density lipoprotein (LDL) receptors on hepatocytes resulting in a fall in serum LDL cholesterol concentration to about 40% and high systemic disappearance of LDL cholesterol.[4] Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of its actions. Other actions are the result of acetylation of certain macromolecules, including COX.[5]

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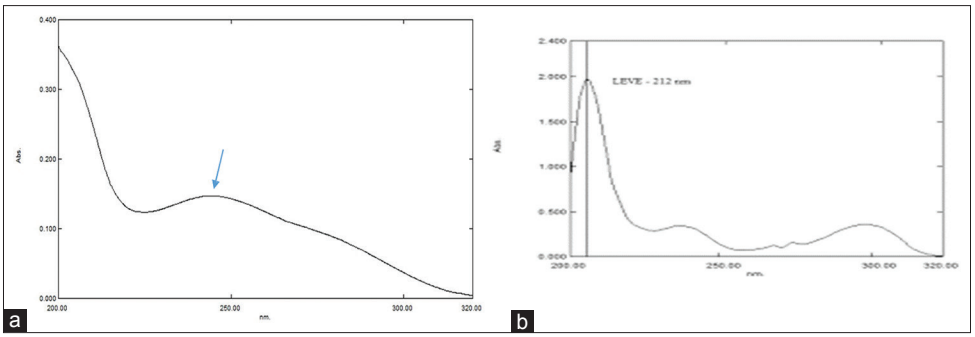


Figure 1: (a) Ultraviolet (UV) spectra of ATOR in methanol: Water (b) UV spectra of ASP in methanol: Water

MATERIALS AND METHODS

Materials

Atorvastatin and aspirin were received as gift samples from Cipla Pvt Ltd. (Mumbai, India). Potassium dihydrogen orthophosphate and sodium hydroxide pellets were procured by SD Fine Chem LTD. (Mumbai). All reagents and solvents used were of analytical grade.

Methods

Ultraviolet (UV) method development and validation

An accurately weighed quantity of ATORVA and ASP (10 mg) each was transferred in a 100 mL volumetric flask, dissolved in a sufficient quantity of methanol. The volume was made up to the mark with water to get the concentration 100 µg/mL. An aliquot (1 ml) of this solution was diluted with methanol: Water in a 10 mL volumetric flask up to mark to get final concentration 10 µg/mL. The standard solution of ATORVA and ASP was scanned in the range of 200–400 nm in 1.0 cm cell against methanol: Water (50:50) using a UV spectrophotometer (Shimadzu, Japan) and spectra were recorded to determine the λ_{max} of both the drugs. Figure 1a and b show the spectra of ATORVA and ASP drugs.

Dissolution method development

The best dissolution medium was selected on the basis of the solubility studies. Various dissolution conditions were tested for the development of a suitable dissolution method for the dissolution study of ATORVA and ASP capsules. The following parameters were finalized:

Medium: 0.2 M Phosphate buffer pH 6.8
Volume: 900 ml
Apparatus: USP type II (Paddle)
rpm: 75
Temperature: 37°C ± 0.5°C
Timepoint: Within 45 min, the drug release is more than 85%.

Preparation of test solution

A capsule was dropped into each of the six dissolution vessels of the dissolution apparatus USP type II (Dissolution tester, USP Model: TDT-06P, Electrolabs, India) containing preheated dissolution medium to 37°C, 0.2 M phosphate buffer pH 6.8 after testing the sink conditions. A 5 ml aliquot of the sample was withdrawn at 5, 10, 20, 30, 45, and 60 min intervals replacing 5ml of dissolution medium each time.

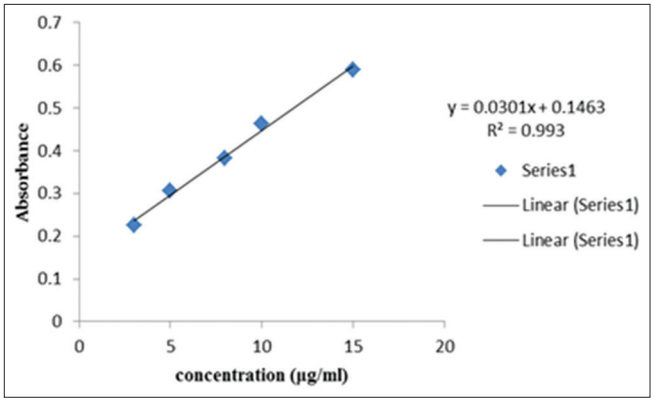


Figure 2: Linearity curve of ATORVA in methanol: Water

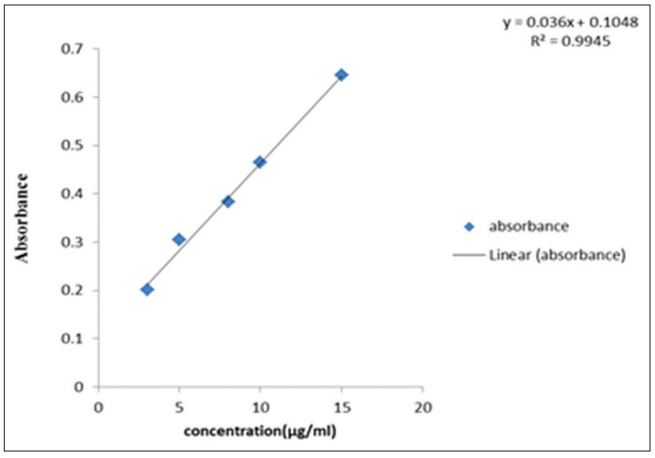


Figure 3: Linearity curve of ASP in methanol: Water

RESULTS AND DISCUSSION

Determination of λ_{max}

The UV spectra for the linearity of both the drugs (ATORVA and ASP) are shown in Figures 2 and 3.

Linearity and range

For the determination of linearity, sample solutions of different concentrations were prepared for ATORVA and ASP. The absorbance of the above solutions was measured at 246 nm and 212 nm, respectively, for ATORVA and ASP. A graph of absorbance versus concentration is plotted and the correlation coefficient was calculated.

Linearity overlain spectra of ATORVA are shown in Figures 4a and b.

Beer's law is obeyed in a concentration range of 5 to 20 µg/mL for ATORVA and 5–20 µg/mL for ASP.

Dissolution method development

The dissolution of ATORVA and ASP capsule was carried out in 900 ml of 0.2 M phosphate buffer pH 6.8 maintained at 37°C ± 0.5°C in paddle apparatus at 75 rpm for 60 min. The diluted samples of dissolution were analyzed UV spectrophotometrically, and percent

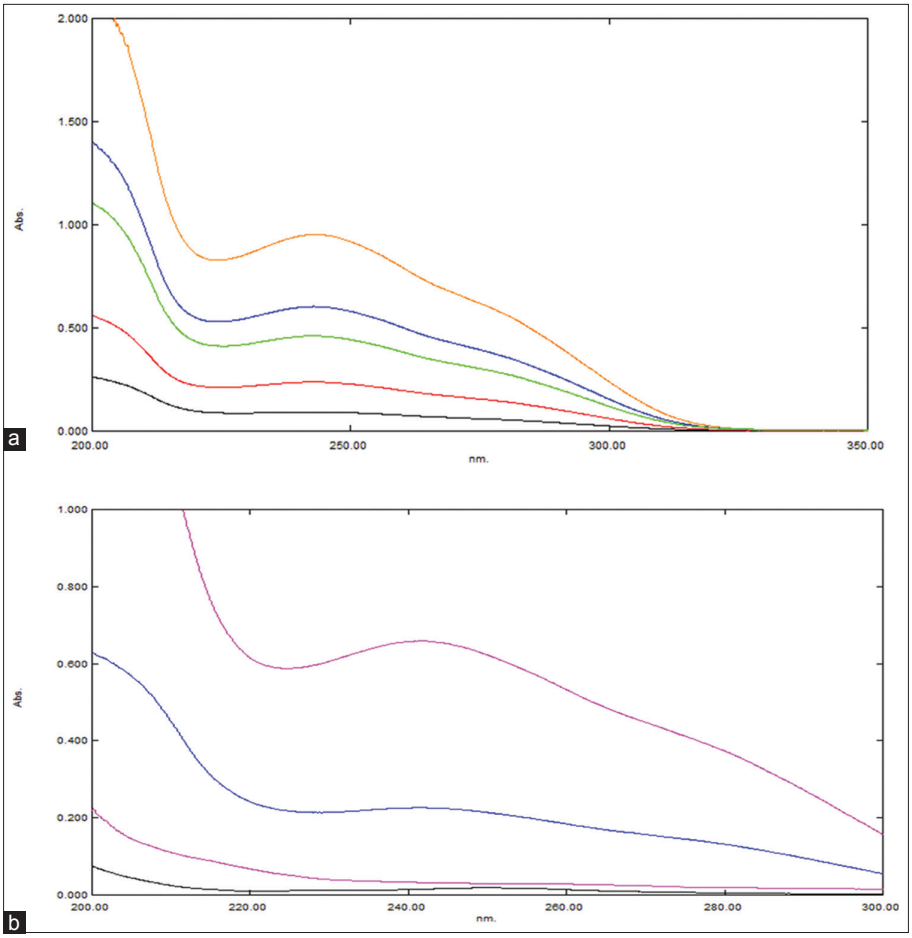
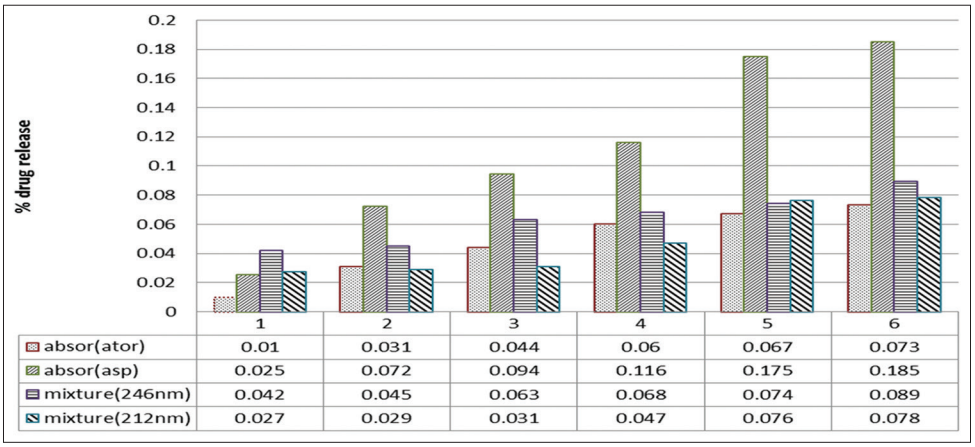


Figure 4: (a) Linearity overlain ultraviolet (UV) spectra of ATORVA, (b) linearity overlain spectra of ASP



	1	2	3	4	5	6
absor(ator)	0.01	0.031	0.044	0.06	0.067	0.073
absor(asp)	0.025	0.072	0.094	0.116	0.175	0.185
mixture(246nm)	0.042	0.045	0.063	0.068	0.074	0.089
mixture(212nm)	0.027	0.029	0.031	0.047	0.076	0.078

Figure 5: Dissolution data graph showing percent drug release of ATORVA, ASP, and mixture in dissolution media

drug release is calculated and graph is plotted between drug release verus time. The dissolution profile of ATORVA and ASP at 75 rpm was performed, and percent drug release at 50 rpm was <85% release. Hence, 75 rpm is set as the dissolution rate for ATORVA and ASP capsules.

Assay and result

The release pattern of APIs from the formulation for individual and combination was studied according to the time which was determined from the calibration curve drawn after the analysis with the UV spectrophotometric method. The percent release pattern of an individual drug as well as both the drugs in combination in the given marketed fixed-dose combination in Figure 5.

CONCLUSIONS

The dissolution method was developed and validated for ATORVA and ASP capsules using the UV spectrophotometric method that the method was validated according to ICH guidelines which include accuracy, precision, specificity, linearity, and analytical range. Stability and solubility of both the drugs in different media, that is, water and phosphate buffer pH 7.2 were studied. Dissolution conditions were 900 mL of 0.2 M phosphate buffer pH 6.8 as dissolution medium at 37 ± 0.5°C, using USP apparatus II at a stirring rate of 75 rpm for 1 h. Thus, the proposed dissolution method and analytical method can be applied successfully for the Quality control of ATORVA and ASP in marketed capsules.

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