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ORIGINAL ARTICLE

A pragmatic approach to the analysis of a combination formulation

Noshin Mubtasim [a], **Eva Rahman Kabir** [a,*], **Ashis Kumar Podder** [a], **Subrata Bhadra** [b]

[a] *Department of Pharmacy, BRAC University, Dhaka, Bangladesh*
[b] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Bangladesh*

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Method validation

Abstract The aim of the paper was to formulate a combined oral dosage form of rosuvastatin calcium and amlodipine besylate and to develop and validate an analytical method to be adopted for both routine quality control assay and *in vitro* dissolution studies of the formulation.

The proposed combination formulation has shown compatibility with the chosen excipients, verified through FT-IR study. A novel gradient RP-HPLC method was developed and validated according to the ICH guideline which was found to be suitable for the simultaneous estimation of rosuvastatin calcium and amlodipine besylate from the formulation. The retention time of 2.7 and 6.08 min allows the analysis of large amount of samples with less mobile phase which makes the method economic. The dissolution profiles of both the drugs in different dissolution medium were encouraging which makes the combination formulation of rosuvastatin calcium and amlodipine besylate superior and effective in achieving patient compliance.

Abbreviations: RP-HPLC, reverse phase high performance liquid chromatography; THF, tetrahydrofuran; CVD, cardiovascular disease; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; Ca^{2+}, calcium; PDA, photo diode array; LC, liquid chromatography; FT-IR, Fourier Transform Infrared spectroscopy; IR, infrared; µg, microgram; ml, milliliter; FDA, Food and Drug Administration; USP, United States Pharmacopeia; µl, microliter; % RSD, percentage relative standard deviation; LOD, limit of detection; LOQ, limit of quantitation; BP, British Pharmacopeia; ICH, International Conference on Harmonization

* Corresponding author at: Flat 503, Concord Nessa, House 16, Road 59, Gulshan, Dhaka, Bangladesh. Tel.: +880 1714073632.
E-mail address: eva.kabir@gmail.com (E.R. Kabir).

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1. Introduction

Cardiovascular diseases such as coronary heart disease, cerebrovascular disease, atherothrombosis, ischemic heart disease, and peripheral arterial disease are found to be prevalent among different age groups of people especially among the young generation. According to a report by Saquib et al., the death rate from cardiovascular diseases (CVD) would be 4 times higher in 2010 and 21 times higher in 2025 compared to its corresponding rate in 2003 (Saquib et al., 2012). Hypertension and dyslipidemia are important, modifiable cardiovascular (CV) risk factors that frequently coexist, and together have an effect on CV risk that may be greater than expected from the simple addition of the risk associated with each condition (Blank et al., 2005).

2. Need of combination therapy

Novel drug delivery systems are constantly being developed for various purposes such as the expansion of markets and indications, the extension of product life cycles, or the generation of opportunities. Even after advancement in the management of cardiovascular diseases (CVD) during the last several years, they are still the main cause for morbidity and mortality (Gowda et al., 2012). Many hypertensive symptoms of hyperlipidemic patients may be reduced using the combination formulation of antihyperlipidemic and antihypertensive agents. Combined dosage form of two or more drugs has been proven useful in multiple therapies as they offer better patient compliance than a single drug. It is well recognized that a single drug, even when used in maximal recommended dosage will control no more than 50% of a hypertensive population (Shaikh et al., 2010). On the other hand, the skillful use of two or more agents in combination can improve hypertension control rates to well above 80% (Shaikh et al., 2010). Therefore, the rational for combination therapy is to encourage the use of lower doses of drug to reduce patient's blood pressure with the goal to minimize dose dependent side effects and adverse reactions (Atram et al., 2009). The fixed-dose combination containing the antihypertensive agent amlodipine and the cholesterol lowering agent atorvastatin is the first combination of its kind designed to treat two risk factors for cardiovascular disease (Bashir et al., 2011). Atorvastatin has rapid access to non-hepatic tissues due to the hydrophobicity which results in some undesirable side effects. These unwanted side effects associated with combined dosage of atorvastatin and amlodipine may be reduced when rosuvastatin is used in place of atorvastatin. An assortment of techniques has been described for the quantification of rosuvastatin alone or in combination with other products (Gowda et al., 2012). The reverse phase-high performance liquid chromatography (RP-HPLC) methods described for simultaneous determination of rosuvastatin and amlodipine in pharmaceutical preparations (Banerjee and Vasava, 2013; Tajane et al., 2012) however, is not developed for *in vitro* dissolution profile of rosuvastatin calcium and amlodipine besylate from their combination drug products. Since no systemic studies on the design and development of such a combination formulation or its *in vitro* dissolution study are currently available in literature, we took an attempt to develop a suitable formulation and assay method which can be used further to characterize the *in vitro* dissolution profile of rosuvastatin calcium and amlodipine besylate. Therefore, a simple, accurate, efficient and reproducible reverse phase HPLC method has been developed and validated for the simultaneous determination of rosuvastatin calcium and amlodipine besylate at 240 nm in combined tablet dosage form and has been applied successfully for *in vitro* dissolution studies.

Rosuvastatin, chemically described as bis [(E)-7 [4-(4-fluorophenyl)-6 isopropyl-2[methyl (methyl-sulphonyl) amino] pyrimidin-5-yl] (3R, 5S) -3, 5-dihydroxyhept-6-enoic acid] (Fig. 1), is another member of the drug class statin. It is hydrophilic and this makes it hepatoselective. This drug may thus be considered as a substitute of atorvastatin to formulate a new combination of drug for dose-related reduction in systolic blood pressure, diastolic blood pressure and low density lipoprotein cholesterol in patients with co-morbid hypertension and dyslipidemia. It competitively inhibits HMG-CoA reductase enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis (Reddy et al., 2011).

Amlodipine besylate, chemically described as 3-ethyl-5-methyl(±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5 pyridinedicarboxylate, monobenzenesulphonate (Fig. 2), is a long-acting dihydropyridine class of calcium channel blocker, approved for treating hypertension and both vasospastic and chronic, stable angina (Blank et al., 2005). It selectively inhibits the transmembrane influx of Ca^{2+} ion across L-type calcium channels, without changing serum calcium concentration. Thus it relaxes the muscles lining the arteries and lowers blood pressure. It also expands coronary arterioles which increases the flow of blood to the heart and prevents heart pain (angina) resulting from reduced flow of blood to the heart that is caused by coronary artery spasm (contraction). It is more vasoselective with lower negative inotropic effects and reflex tachycardia is less prominent since fluctuations in plasma levels are less pronounced with these agents (Drug information reference, 2003).

3. Materials and methods

The present research started with the development of a proposed combination formulation of a statin with a calcium channel blocker. Excipients, used for the preparation of the combined formulation tablets of rosuvastatin and amlodipine, were initially chosen on the basis of the existing formulation of atorvastatin and amlodipine and their compatibility with the

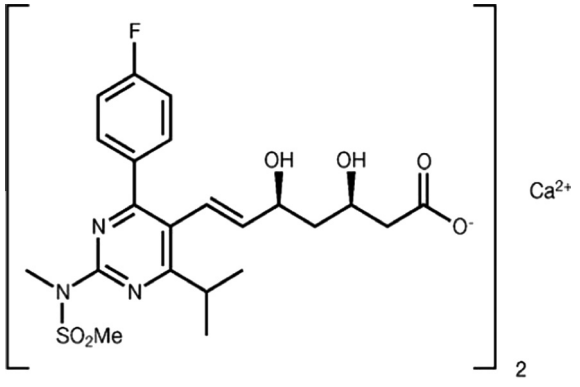

Figure 1 Structure of rosuvastatin calcium.