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Characterization of a new degradation product of nifedipine formed on catalysis by atenolol: A typical case of alteration of degradation pathway of one drug by another

Tarun Handa [a], Saranjit Singh [a,*], Inder Pal Singh [b]

[a] Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar 160 062, Punjab, India
[b] Department of Natural Products, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar 160 062, Punjab, India

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ABSTRACT

An increasing interest is being shown throughout the world on the use of fixed-dose combinations of drugs in the therapy of select diseases, like cardiovascular diseases, due to their multiple advantages. Though the main criterion for combining drugs in a single dosage form is the rationale, but consideration like stability of formulation is equally important, due to an added aspect of drug–drug interaction. The objective of this study was to evaluate interaction among the drugs in an antihypertensive combination of nifedipine and atenolol. Nifedipine is a known light sensitive drug, which degrades via intra-molecular mechanisms to nitro- and nitroso-pyridine analogs, along with a few minor secondary products that are formed through inter-molecular interactions amongst primary degradation products and their intermediates. Atenolol is reasonably stable weakly basic drug that is mainly hydrolyzed at acetamide terminal amide moiety to its corresponding carboxylic acid. To the best of our knowledge, there is no known information on chemical compatibility among the two drugs. The present study involved subjecting of nifedipine, atenolol and their combination to a variety of accelerated and stress conditions. HPLC studies revealed formation of a new product in the mixture of two drugs (~2%), which was also generated from nifedipine alone, but at trace levels (<0.1%). The product was isolated by preparative chromatography and subjected to indepth studies for its characterization. Ultra-violet, FT-IR, mass spectrometric and nuclear magnetic resonance spectroscopic studies highlighted that the principal photo-degradation pathway of nifedipine was modified and diverted in the presence of atenolol. To verify the same, a study was conducted employing two other β–blockers with similar structures to atenolol, and the same product was formed in relatively higher quantity therein also. The new product is postulated to be produced as a result of rearrangement of hydroxylamine intermediate, known to be involved in the generation of nitro- and nitroso-pyridine photo-degradation products of nifedipine.

1. Introduction

Fixed-dose combinations (FDCs) are gaining wide popularity as they overcome the inconvenience and chances of missed doses with multiple individual drugs. Yet combining of two or more drugs, just for the sake of improving therapeutic convenience, is discouraged unless the basic criterion of rationality is fulfilled. Also, there are other associated important issues during pharmaceutical development of FDCs and similar multi-drug products [1]. A critical aspect is the possibility of drug–drug incompatibility, which may happen in addition to usual interactions among formulation ingredients and primary packaging. The drug–drug interaction can lead to newer degradation products. Also, possibility exists of catalysis of the degradation of one drug by another, thus increasing the chances of degradation products exceeding specification thresholds, which is a typical reason today for recall of the drug products from the market [2]. For example, we previously established that in the case of four-drug anti-tuberculosis FDC containing rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride, the first two drugs chemically interacted with each other to form isonicotinyl hydrazone [3] and interestingly, the remaining two drugs catalyzed this reaction [4]. We even observed similar type of chemical complexity among the drugs and excipients that were proposed to be contained in a polypill for the treatment of cardiovascular diseases (CVDs) [5,6].

The present study forms a part of an on-going project in our laboratory on the study of chemical incompatibility among the drugs contained in FDC/multi-drug formulations. We report herein the generation of a novel degradation product of nifedipine,

* Corresponding author. Tel.: +91 172 2214682; fax: +91 172 2214692.
E-mail address: ssingh@niper.ac.in (S. Singh).

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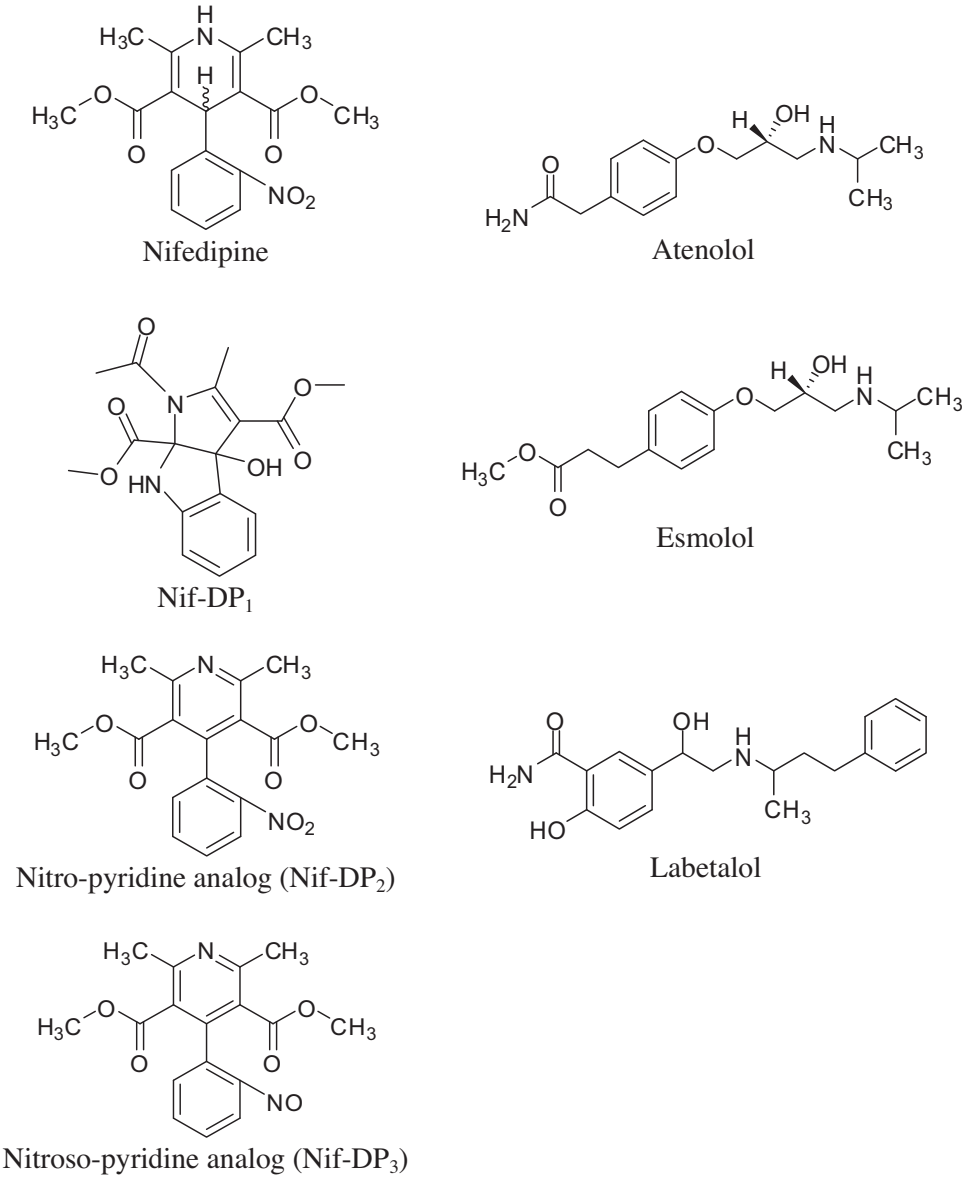

Fig. 1. Structures of nifedipine, targeted product (Nif-DP_1), nitro-pyridine analog of nifedipine (Nif-DP_2), nitroso-pyridine analog of nifedipine (Nif-DP_3), and β-blockers atenolol, esmolol and labetalol.

whose formation was enhanced by the presence of atenolol in a combination formulation. Nifedipine is dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, which belongs to dihydropyridine type of calcium channel blocking agents. On the other hand, atenolol is 2-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)acetamide and it belongs to *N*-alkyl-2-aryl-(3-aminopropan-1,2-diol) type of β-receptor blocking agents. Their structures are shown in Fig. 1. The two drugs, when prescribed in combination for various indications associated with CVDs, are indicated to have better therapeutic claims, especially when either of the individual drugs fails to adequately control the blood pressure. Although, there is no reduction in doses of individual drugs, the main benefits are drawn from the better control of hypertension and lowering of incidences of the side-effects [7–9]. There is no reported effect of one drug on the gastric/intestinal absorption of the other, but biotransformation of nifedipine in the presence of atenolol was found to be significantly higher in the case of male rats liver homogenates, which was opposite to that in the female rats [10]. The individual degradation chemistry of both the drugs is reported in the literature [11–14]. Nifedipine is known to be unstable to ultra-violet (UV) as well as visible light, and undergoes photolysis via intra-molecular mechanisms, mainly to nitro- and nitroso-pyridine analogs [13], whose structures are shown in Fig. 1. A few minor secondary products are also formed through inter-molecular interactions amongst primary degradation products and their intermediates [14]. On the other hand, atenolol is known to degrade mainly through hydrolysis of its acetamide terminal amide moiety to corresponding carboxylic acid [15]. Additionally, Medana et al. have reported various aliphatic and aromatic hydroxyl products, which were generated through TiO_2 catalyzed photodegradation [16]. To the knowledge of the authors, there is no previous report regarding physico-chemical interaction between nifedipine and atenolol, when present together in a combination.

2. Experimental

2.1. Drugs and reagents

Nifedipine and atenolol were provided gratis by Unique Pharmaceutical Laboratories (Mumbai, India) and Dr. Reddy's