Formulation Development and Optimization of Nitrendipine Nanosuspension with Improved Pharmacokinetic Characteristics

Anand Shah¹, Vipul Patel² and Sunny Shah³

¹Bhagwant University, Rajasthan, India, ²S.K.Patel College of Pharmaceutical Education & Research, Kherva, Gujarat, India, and ³B.K. Mody Govt. Pharmacy College, Rajkot, Gujarat, India.

Received August 16, 2012; accepted March 16, 2013

ABSTRACT

Poorly water-soluble drugs such as nitrendipine (~2.0 µg/ml at 37°C in water) offer challenging problems in drug formulation as poor solubility is generally associated to poor dissolution characteristics and thus to poor oral bioavailability. To enhance these characteristics, we prepared and evaluated nitrendipine nanosuspension using the nanoprecipitation technique. The important process parameters, the concentration of nitrendipine in the organic phase, concentration of surfactant in the anti-solvent, and starring speed were evaluated using 3³ full factorial designs. It was observed that the concentration of nitrendipine in the organic phase, concentration of surfactant in the anti-solvent, and starring speed significantly affect the particle size as well as dissolution velocity. Differential scanning calorimetry studies confirmed that the crystallinity of the drug was maintained after the nanoprecipitation suggesting that improved dissolution of nitrendipine nanosuspensions could be attributed to reduction in particle size. This formulation may offer a superior pharmacokinetic profile due to nanotechnological design.

KEYWORDS: Nanosuspension; Dissolution Enhancement; Nanoprecipitation; Mean Particle Size.

Introduction

Nitrendipine is a dihydropyridine calcium channel antagonist with a very low solubility for the treatment of hypertension (Santiago et al., 1990). Nitrendipine is classified as a Class II API (poorly soluble and highly permeable) by the Biopharmaceutics Classification System (BCS) (Fude et al. 2010). The absolute oral bioavailability of this drug is reported to range from about 10% to 20%, depending in part on the dosage form (Soons et al., 1991; Sweetmans et al., 2009).

The basic challenge faced by the researcher for the formulation of such poorly soluble drugs is the low oral bioavailability and erratic absorption of the drugs from the gastrointestinal tract due to their low saturation solubility and dissolution velocity. The low saturation solubility results in a low concentration gradient between the gut and blood vessel and leads to a limited transport of drug (Merisko-Liversidge et al., 2003). For poorly soluble drugs as seen in BCS Class II, the dissolution of the drugs in the gastrointestinal fluid media is the rate limiting step for the absorption of the drugs (Aguilar-Bryan et al., 1995). Hence, for efficient absorption of drugs from the gastrointestinal tract to improve their therapeutic efficacy, there is an imminent need for studies in designing novel strategies for their dissolution enhancement.

There are a number of formulation approaches such as salt formation, pH adjustment, cosolvency, and complexation used for enhancement of dissolution but none of the approaches has achieved the merits of being universal. Micronization of poorly soluble drugs has been applied for many years to improve dissolution velocity of poorly soluble drugs but reducing the drug to micron size does not increase the saturation solubility of the drug, and at such a low saturation solubility as generally observed in BCS Class II drug, the increment in the dissolution characteristics does not help to a great extent (Muller et al., 1999; Rasenack et al., 2003). Consequently, off late nanonisation has been employed for treating the BCS Class II drugs. When the drug is being reduced to nanosized level there is an obvious increase in its saturation solubility assisted by improvement in the dissolution characteristics which could be attributed to the effective increase in particle surface area according to the Ostwald Freundlich equation (Patravale et al., 2004). The drug nanoparticles are generally suspended in an aqueous media and are termed as nanosuspensions.

Nanosuspensions can be prepared using various techniques, namely nanoprecipitation, sonication, high speed homogenization, milling, and high pressure homogenization (Gary et al., 1995; Mullar et al., 1998; Masaaki et al., 1995; Hecq et al., 2005; Mittapalli et al.,...