
Development of Fast Dissolving Tablets of Nisoldipine by Solid Dispersion Technology using Poloxamer 407 and Poloxamer 188

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INTRODUCTION
Drugs which belong to class II of biopharmaceutical classification system are characterized by high membrane permeability, slow dissolution rate and high per oral dose. The solubility or dissolution rate of a drug in this category is therefore a key factor in determining the rate and extent of its absorption.1 Solid dispersion technology can be used to enhance the dissolution rate of BCS class II drugs thereby improving their bioavailability. Enhancement of dissolution rate is important to attain the suitable blood concentration for increased therapeutic effect, as their dissolution rates are typically the rate limiting step for bioavailability. Several methods have been reported for enhancement of solubility and dissolution rate of poorly aqueous soluble drugs, namely increasing the surface area by reducing the particle size, use of surfactants, preparation of water soluble complexes, pro drug approach, salt formation of the drug, decreasing the crystallinity of the drug through the formation of solid solutions. The most common method is reducing the particle size by micronization technique. The technique is disadvantaged by the greater tendency of size reduced particles to stick together which leads to formation of larger agglomerates which in turn leads to reduction in effective surface area for dissolution. Now a days the most effective method to improving the dissolution rate is the use of solid dispersion technique but this is reliant on optimization of carrier and solvent.2 The solid dispersions are two component systems consisting of a hydrophilic carrier in which the drug is incorporated. The solid dispersion technology provides the possibility to reduce the drug particle size almost to a molecular level and increased wettability.3 In addition to this, a transformation of the drug from the crystalline form to amorphous form can occur, which can be beneficial since dissolution of an amorphous drug does not require energy to break up the crystalline lattice. Another interesting method to improve the dissolution of solid dispersion tablet is with the incorporation of superdisintegrants, because superdisintegrants do not irritate the gastrointestinal tract and can be used at low amounts in the formulations.4 Crospovidone, croscarmellose sodium and sodium starch glycolate were used as superdisintegrants. Nisoldipine is an anti hypertensive agent which may be used alone or in combination with other agents in the management of hypertension and it belong to BCS class II category, therefore solid dispersion technique can be used to enhance the dissolution rate of drug.9 Nisoldipine is a 1,4–dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nisoldipine prevents calcium dependent smooth muscle contraction and subsequent vasoconstriction. Poloxamer 407 (P 407) and poloxamer 188(P 188) were used as the carriers for the preparation of solid dispersions with nisoldipine. Poloxamer is a synthetic block copolymer of ethylene oxide and propylene oxide widely used in pharmaceutical preparations.5

MATERIALS AND METHODS
Materials
Nisoldipine, poloxamer 407 and poloxamer 188 were obtained from orchid chemicals &Pharmaceutics Ltd, Chennai. All other chemicals were of reagent grade and used without purification.

Preparation of solid dispersions and physical mixtures
The physical mixtures of nisoldipine were prepared by mixing the drug with P 407 and P 188 separately in a mortar for 2-3 min until a homogeneous mixture was obtained. The resulting mixture was stored in a vacuum desiccator for one week.

In solvent evaporation method dichloromethane and ethanol was used as solvent and five different ratios of drug and polymer were used (1:1, 1:2, 1:3, 1:4, 1:5) to prepare solid dispersions of nisoldipine.6 Respective amount of carrier was dissolved in required amount of dichloromethane and ethanol taken in a conical flask to get a clear completely soluble polymeric solution by using magnetic stirrer. The weighed amount of

ABSTRACT
Objective: The aim of the present study is to design oral fast-release tablets of nisoldipine and to optimize the drug dissolution profile by modifying the carrier concentration. Poloxamer 407 and Poloxamer 188 were selected as carriers for preparing the solid dispersion (SD) by solvent evaporation method with different drug polymer ratios. Methods: The prepared solid dispersions were analyzed for physical state, drug:carrier interactions by X-ray diffraction, infrared spectroscopy, differential scanning calorimetry and scanning electron microscopy. Results: The dissolution studies revealed that all solid dispersions showed increased dissolution rate when compared to pure nisoldipine. Among the two polymers used, poloxamer 407 (P 407) was found to be better than poloxamer 188(P 188) in the enhancement of dissolution efficiency. The tablets were formulated using solid dispersion of nisoldipine containing poloxamer 407 as carrier. Conclusion: The results exhibited that poloxamer 407 SD based tablets gave a significantly higher release of nisoldipine when compared with control tablets. Infrared spectral studies showed that there was no interaction between the nisoldipine and its formulation with different carriers used in the preparation of solid dispersions. X-ray diffraction studies revealed that the degree of crystallinity of nisoldipine decreased when the concentration of carriers increased, which showed that the drug is in amorphous nature.

Key words: Fast dissolving tablets, Poloxamer 407, Poloxamer 188, Solid dispersion, Superdisintegrants.

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DEVELOPMENT OF FAST-DISSOLVING TABLETS OF AMLODIPINE BESYLATE BY SOLID DISPERSION TECHNOLOGY USING POLOXAMER 407 AND POLOXAMER 188

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ABSTRACT

Objective: Amlodipine besylate is a calcium channel blocker used in the treatment of hypertension which is practically insoluble in water. The present study aims to design oral fast-release tablets of amlodipine besylate and to optimize the dissolution of the drug by altering the carrier concentration.

Materials and Methods: Poloxamer 407 (P407) and poloxamer 188 (P188) were selected as carriers for the preparation of solid dispersion (SD) by the solvent evaporation method with different drug-polymer ratios. The prepared SDs were evaluated for the physical state, drug-carrier interactions by X-ray diffraction (XRD), infrared spectroscopy, differential scanning calorimetry, and scanning electron microscopy.

Results: From the dissolution studies, it is confirmed that all SDs showed increased dissolution rate when compared to pure amlodipine besylate. Among the two polymers used, P407 was found to be better than P188 in enhancing dissolution efficiency. The tablets were prepared using SD of amlodipine besylate containing P407 as a carrier. The results showed that P407 SD-based tablets gave a significantly higher release of amlodipine besylate when compared with control tablets. The infrared spectral studies showed that there was no significant interaction between amlodipine besylate and its formulation with different polymers used in the preparation of SDs. XRD studies revealed that the degree of crystallinity of amlodipine besylate reduced when the concentration of carriers increased, which reveals that the drug is in amorphous nature.

Conclusion: The combination of SD technology and using superdisintegrants in the formulation is a promising approach for preparing efficient, fast-dissolving tablet of poorly water-soluble drugs, viz. amlodipine besylate.

Keywords: Amlodipine besylate, Calcium channel blocker, Fast-dissolving tablets, Poloxamer 407, Poloxamer 188, Solid dispersion, Superdisintegrants.

INTRODUCTION

Drugs which come under the Class II of BCS system are characterized by high membrane permeability and slow dissolution. The poor aqueous solubility of the drug and their low dissolution rate in the gastrointestinal fluids often lead to insufficient bioavailability and are one of the most difficult problems in pharmaceutical technology. It is estimated that more than 35% of the known drugs and more than 25% of the newly discovered drugs possess such problems [1]. Solid dispersion (SD) technology can be used to enhance the dissolution rate of BCS Class II drugs, thereby improving their bioavailability. The enhancement of dissolution rate of the drug is important to attain suitable blood concentration for enhanced therapeutic effect as their dissolution rates are typically the rate-limiting step for bioavailability [2]. There are several methods employed for improving the solubility and dissolution rate of poorly aqueous soluble drugs, such as increasing the surface area by reducing the particle size, using surfactant systems, salt formation of the drug, prodrug approach, preparation of water-soluble complexes, and reducing the crystallinity of the drug. The most common method is decreasing the particle size by micronization technique. The technique is disadvantaged by the higher tendency of size reduced particles to stick together which leads to the formation of larger agglomerates which in turn leads to a decrease in effective surface area for dissolution. Nowadays, the most effective method to improve the dissolution rate is the use of SD technique [3]. The SDs are two-component systems consisting of a hydrophilic carrier in which the drug is incorporated. The SD technology gives the possibility to reduce the drug particle size almost to a molecular level and increased wettability [4]. In addition to this, the crystalline drug is transformed to amorphous form, which can be beneficial, since the dissolution of an amorphous drug does not require energy to break up the crystalline lattice [5].

Another method to improve the dissolution of SD tablets is by the addition of superdisintegrants because they do not irritate the gastrointestinal tract and can be used in low amounts in the formulations [6]. Cross croscarmellose sodium, crospovidone, and sodium starch glycolate were used as superdisintegrants [7]. Amlodipine besylate is a calcium channel blocker which may be utilized in the management of hypertension, and it belongs to BCS Class II category. One of the biggest problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Hence, SD technique can be used to improve the dissolution rate of the drug. The drug works by slowing down the rate at which calcium moves into heart, blood vessel walls, allowing better blood flow. Poloxamer 407 (P407) and poloxamer 188 (P188) were used as the carriers for the preparation of SDs with amlodipine besylate [8]. Poloxamer is a synthetic block copolymer of ethylene oxide and propylene oxide and used widely in pharmaceutical preparations [9].

MATERIALS AND METHODS

Materials
Amlodipine besylate, P407, and P188 were obtained from Orchid Chemicals & Pharmaceuticals Ltd., Chennai. All other chemicals were of reagent grade and used without purification.

Preparation of SDs
Dichloromethane and ethanol were used as the solvent, and five different ratios of drug and carrier were used (1:1, 1:2, 1:3, 1:4, 1:5).