P-02

Transformation of Cilostazole Nanosuspension into Nanocrystal to Increase the Product Stability and Dissolution Rate

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1. Introduction

Low aqueous solubility is the major problem encountered during formulation development of new chemical entities as well as for the generic development (1). Compounds with poor aqueous solubility cause slow dissolution, generally show erratic and incomplete absorption leading to low bioavailability, when administered orally (2).

Cilostazol (CLZ) is the second molecule after Pentoxifylline to receive U.S. FDA approval for the treatment of Intermittent Claudication. CLZ is one of many molecules belong to Biopharmaceutical Classification System (BCS) Class II. based on poor water solubility and high permeability.

Nanosuspensions referred to colloidal dispersions of submicron sized drug particles which are stabilized by addition of a suitable polymer and/ or surfactant, and the mean particle size below 1000 nm. Conversion of a nanosuspensions into a solid products can stabilize them both physically and chemically (3).

2. Methods

2.1. Preparation of nanosuspension of CLZ: Study of ideal composition and optimal milling program. Prepared nanosuspensions were investigated to the characterization of particle size distribution, zeta-potential, thermodynamic solubility.

2.2. Optimized nanosuspension and presuspension were solidified by preparing matrix pellets via the extrusion/spheronization method. Physical properties of pellets were investigat-

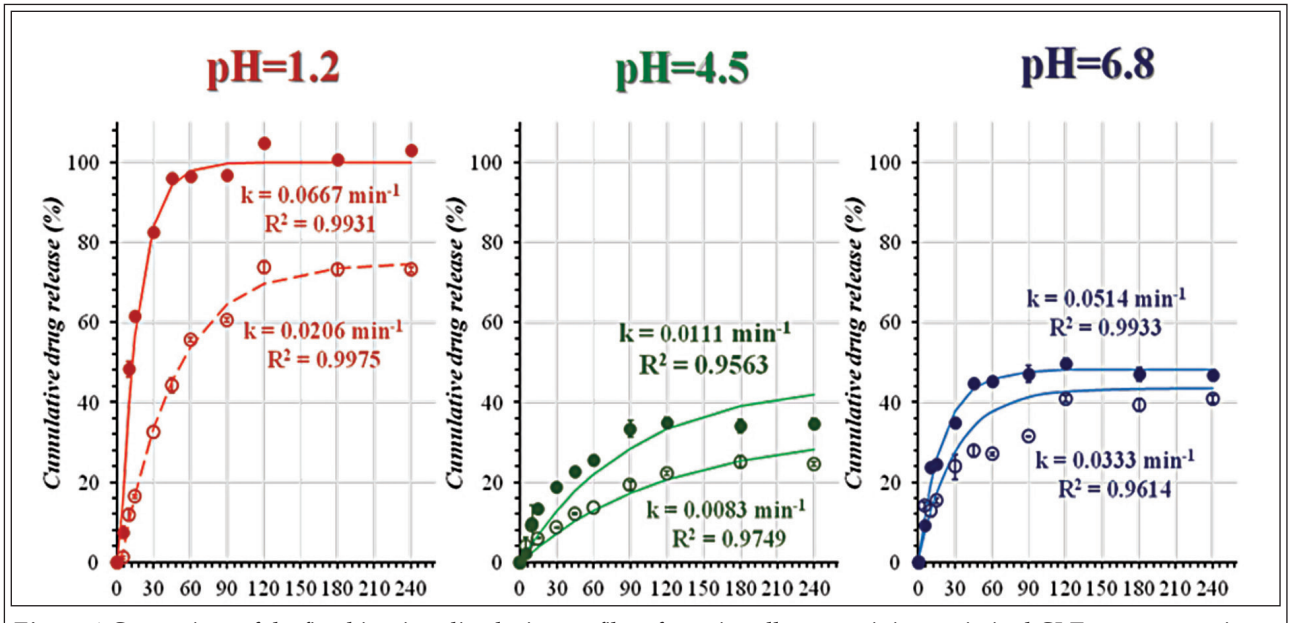

Figure 1 *Comparison of the fitted in-vitro dissolution profiles of matrix pellets containing optimized CLZ nanosuspension (●), matrix pellets containing unmilled dispersion (◦) in various, aqueous-based buffer solutions (pH=1.2, pH=4.5, pH=6.8), n=3, mean values ± SDs*

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ed (shape/size analysis; flow properties and compressibility).

2.3. In vitro dissolution studies.

2.4. Solid state characterization of matrix pellets: Powder X-ray Diffractometry (PXRD); Differential Scanning Calorimetry (DSC).

3. Results

3.1. In case of CLZ milling, combination of ionic and nonionic emulsifiers and increasing of milling speed and milling time have significantly reduced the mean particle size, the polydispersity index (PDI) and also have a positive impact on physical stability indicated by the tendency of Zeta-potential values.

3.2. The roundness and aspect ratio are informative shape parameters, while the maximum Feret diameter can be used to demonstrate the mean particle size of pellets (4). The roundness of these formulations were perfect. The flowability and compressibility of these formulations were excellent.

3.3. Dissolution rate of matrix pellets, demonstrated a significant improvement in medium at pH=1.2, while were diminishing in medium at pH=4.5 and pH=6.8.

3.4. Solid state characterization of pulverized matrix pellets with Differential Scanning Calorimetry (DSC) and Powder X-ray Diffractometry (PXRD) indicated the transformation of CLZ Form A to amorphous form during extrusion process.

4. Conclusions

We have managed to prepare matrix pellets containing CLZ amorphous nanocrystals by 'top-down' surfactant assisted media milling approach and extrusion. Particle size reduction and amorphization due to extrusion with surface-active agents had a significant impact on dissolution rate constant of CLZ. Solid state characterization of pulverized matrix pellets with Differential Scanning Calorimetry (DSC) and Powder X-ray Diffractometry (PXRD) indicated the transformation of CLZ Form A to amorphous form during extrusion.

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