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Ziprasidone nanocrystals by wet media milling followed by spray drying and lyophilization: Formulation and process parameter optimization

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ABSTRACT

The aim of work was to prepare and characterize Ziprasidone nanosuspension to achieve enhance solubility and *in vitro* dissolution. The media milling technique was utilized for production of nanosuspension and the effect of amount of milling agent, milling time, volume of water, stirring speed and type of stabilizers on particle size and size distribution was studied. The optimized nanosuspension was subjected to spray drying and lyophilization which than characterized for fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), *in vitro* dissolution study, X-ray diffraction (XRD) and field emission scanning electron microscopy (FE-SEM). FTIR and DSC studies showed compatibility of Ziprasidone with selected excipients. DSC study also revealed that crystalline form of Ziprasidone in spray dried and lyophilized nanosuspension was remained same as to that of pure Ziprasidone. XRD of spray dried and lyophilized nanosuspension showed same diffraction pattern as that of the pure Ziprasidone only crystallinity was decreased. Around 8 fold increase in saturation solubility was observed. *In vitro* dissolution of spray dried and lyophilized nanosuspension was significantly higher. The rod like nanocrystals were observed in FE-SEM studies which were present on surface of sphere in spray dried nanosuspension and dispersed in matrix like structure in lyophilized nanosuspension.

1. Introduction

Ziprasidone is an atypical antipsychotic agent used for the treatment of schizophrenia, mania and bipolar disorder. It was first approve in United states in 2001 and commercially it is available as Geodon® immediate release (IR) capsules for oral use and intramuscular injection [1]. Despite of its high safety and efficacy, it suffer from low oral bioavailability (60%) [2]. Ziprasidone HCl has high lipophilicity (c log P = 3.6) and poor solubility (intrinsic solubility of 0.3 μg/ml) its solubility in simulated bio relevant fluids was estimated to be 4–5 μg/mL [3]. Thus Ziprasidone shows solubility and dissolution rate limited absorption. Various approaches have been investigated to enhance the solubility and dissolution of ziprasidone like complexation with β-cyclodextrin, solid dispersions, ball milling and cryogrinding, coated crystal by spray drying, lipid based drug delivery systems, etc. [1,2,4–7]. The limited work is available for solubility and dissolution enhancement via nanosuspension. Thus in this article attempts has been made to enhance the solubility and dissolution of Ziprasidone via nanosuspension technique.

Pharmaceutical nanosuspension is colloidal dispersions of pure drug nanoparticles with the particle size typically in the range of 200–600 nm, stabilized by suitable surfactants [8]. On reducing the particle size to nano scale, the surface area will increase which will enhance the rate of dissolution as per Noyes–Whitney equation [9]. Method of preparation of nanosuspension can be broadly classified into two categories: bottom-up processes (Anti solvent precipitation) and top-down processes (Media milling and high pressure homogenization) [8,10,11]. But due to low cost, fast and easy to scale up, media milling is wildly used for the preparation of nanosuspension [12,13]. In this technique, particle size reduction is

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achieved due to mechanical attrition of drug particles with the milling media [14].

The primary objective of this work was to develop and evaluate nanosuspension of ziprasidone and to optimize the process and formulation parameters of media milling technique. The secondary objective was to improve the physical stability of the optimized nanosuspension by spray drying and lyophilization.

2. Materials and methods

2.1. Materials

Ziprasidone was obtained as s gift sample from Cadila Healthcare Ltd, India. Vitamin E TPGS was obtained from ISO CHEM, France, Poloxamer 407 and Poloxamer 188 were obtained from BASF, Mumbai, India, Polyvinylpyrrolidone K-30 (PVP K-30), Polyvinyl alcohol (PVA), Hydroxy propyl methyl cellulose (HPMC E5) and Mannitol were purchased from Himedia, Mumbai, India. Distilled water was used as a dispersion media. Zirconium oxide beads of 0.1 mm diameter were purchased from BioSpec Inc., USA. All other materials used were of analytical grade.

2.2. Methods

2.2.1. Preparation of nanosuspension by media milling method

Nanosuspension was prepared by wet media milling technique. The Drug (2%w/v) was dispersed in aqueous solution containing 1% w/v stabilizer. The resulting suspension was poured in to a glass vial containing zirconium oxide beads as milling media and exposed to stirring at fixed speed using a magnetic stirrer for preset time period [15].

2.2.2. Preliminary work for screening of variables

Preliminary studies were performed to determine the ideal conditions for preparation of nanosuspension by wet media milling. The parameters studied were amount of milling agent, milling time, volume of suspension, stirring speed and type of stabilizer. The batches were prepared according to Table 1.

2.2.2.1. Amount of milling agent and milling time. Zirconium oxide beads were used as milling agent. Nanosuspension was prepared by varying the amount of milling beads. Milling operation were carried out by taking four different amount of milling beads (2.5, 5, 7 and 10 g m.) and samples were taken at different time intervals (3,6, 9 and 12 h) and particle size and PDI were determined.

2.2.2.2. Volume of water. Nanosuspensions were prepared by taking different volume of water (5, 7 and 10 ml; batches b17, b18 and b19). Milling was carried out by taking 7 gm of Zirconium oxide beads and 1000 rpm stirring speed. Poloxamer 407 (1%w/v) was used as stabilizer and milling was carried out for 6 h for the preparation of ziprasidone nanosuspension and prepared nanosuspensions were evaluated with respect to particle size and PDI.

2.2.2.3. Stirring speed. Milling operation was carried out at four different milling speed (500, 1000, 1500 and 2000 rpm; batches b20, b21, b22 and b23) and the prepared nanosuspension were evaluated with respect to particle size and PDI.

2.2.2.4. Type of stabilizers. Particle stability and the particle's physical properties are depend on the stabilizer used. In this study different polymeric stabilizers like PVA, PVP K-30, HPMC, non-ionic surfactants like Poloxamer 407, Poloxamer 188, Vitamin E TPGS and tween 80 and ionic surfactant like SLS were taken for selection of suitable stabilizer. Prepared nanosuspensions were evaluated with

Table 1
Composition of formulations.

Batch code	Amount of milling beads (gm)	Milling time (h)	Volume of water (ml)	Stirring speed (rpm)	Stabilizer
b1	2.5	3	5	1000	Poloxamer 407
b2		6			
b3		9			
b4		12			
b5	5	3	5	1000	Poloxamer 407
b6		6			
b7		9			
b8		12			
b9	7	3	5	1000	Poloxamer 407
b10		6			
b11		9			
b12		12			
b13	10	3	5	1000	Poloxamer 407
b14		6			
b15		9			
b16		12			
b17	7	6	5	1000	Poloxamer 407
b18			7		
b19			10		
b20	7	6	5	500	Poloxamer 407
b21				1000	
b22				1500	
b23				2000	
b24	7	6	5	1000	PVA
b25					PVP k 30
b26					HPMC
b27					Poloxamer 188
b28					Poloxamer 407
b29					Vit E TPGS
b30					Tween 80
b31					SLS
b32					Vit E TPGS + SLS