Journal of Drug Delivery Science and Technology 43 (2018) 369–378

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Albendazole nanocrystals: Optimization, spectroscopic, thermal and anthelmintic studies

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ARTICLE INFO

Keywords:
Nanocrystals
Antisolvent precipitation
Fourier transform infrared spectroscopy
X-ray diffraction
Differential scanning calorimetry
Anthelmintic bioassay*Chemical compounds studied in this article:*
Albendazole (PubChem CID:2082)
Formic acid (PubChem CID:284)
Polyvinylpyrrolidone (PubChem CID:6917)

ABSTRACT

Albendazole is a broad spectrum anthelmintic. Its efficacy is often limited by poor intestinal absorption mainly due to its low aqueous solubility. One of the best approaches to enhance aqueous solubility and dissolution of drug is nanoparticles. In the present study nanocrystals of albendazole were prepared by antisolvent precipitation technique followed by spray drying. The nanocrystals were optimized using 3^2 full factorial design considering stabilizer concentration and stirring speed as independent variable and dissolution efficiency as dependent variable. The prepared formulations were subjected for spectroscopic, thermal and dissolution studies. The results of FTIR showed that the drug was compatible with the excipients. The dissolution from nanocrystals was much more faster then pure albendazole. The particle size of nanocrystals was 277 nm. The XRD showed that there were no significant difference in the diffraction pattern of pure Albendazole and nanocrystals, crystalline habit modification happened in the nanocrystals. The lower melting point and enthalpy in physical mixture and in nanocrystals compare to pure Albendazole was reported in DSC study. TEM image of nanocrystals indicated rectangular nanoparticles. Gas chromatography study showed that the amount of residual solvent was less than the permissible limits. The optimized nanocrystals showed better anthelmintic activity compared to pure Albendazole.

1. Introduction

Albendazole is a broad spectrum anthelmintic first approved for human use in 1982 [1,2]. It is effectively used in experimental and clinical chemotherapy of different intestinal and systemic parasitosis. Despite its general use against systemic parasites, its efficacy is often limited by poor intestinal absorption mainly due to its low aqueous solubility. Therefore long treatments and high doses are required to reach optimal plasma concentrations [3]. Efficacy of albendazole can be enhanced by improving its aqueous solubility and dissolution. Different studies have been carried out to improve the aqueous solubility and dissolution rate of albendazole, such as the preparation of solid dispersions [4] (Torrado, Torrado et al., 1996), co grinding [5], inclusion complexes [6], complexation with povidone [7] etc.

In recent years, nanoparticles engineering technique has gain an importance for the enhancement of drug solubility. Unlike micronization, nanonization often increases the solubility as well as the dissolution rate. The nanocrystals are principally the crystals with a size in the nanometres range and being composed of 100% drug without any matrix material [8,9]. Nanocrystals can be formulated by two basic techniques, the top down technology and bottom up technology [10]. The top down technology i.e. media milling and high pressure homogenization [8], basically depends on mechanical attrition to convert large crystalline particles into nanoparticles. These techniques produce nanoparticles that are mostly crystalline but high energy or pressure is required to achieve nano size particle. In contrast, bottom up processes involve dissolution, followed by precipitation or drying. The mechanical energy input is thus minimal as compared to top down technology more over these bottom up processes were reported as a simple and cost effective approach with scale up potential [11,12]. The major drawback of bottom up technique is to maintain the nano size of crystals. During process Oswald ripening may increase particle size. This problem can be overcome by stabilizers or by drying. Drying can provide prolong stabilization [11]. Freeze drying and spray drying are two commonly used methods to convert nanosuspension into redispersible dry powders [13,14]. Compared with freeze drying, spray drying is reported as more cost effective and easier to be implemented directly after antisolvent precipitation in continuous production process [11].

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https://doi.org/10.1016/j.jddst.2017.11.003
Received 30 January 2017; Received in revised form 2 November 2017; Accepted 4 November 2017
Available online 07 November 2017
1773-2247/

The aim of this study was to improve dissolution of albendazole by nanocrystals. The nanocrystals were prepared by antisolvent precipitation method followed by spray drying. The formulation was optimized using 3^2 full factorial design considering stabilizer concentration (A) and stirring speed (B) as independent variables and dissolution efficiency as dependent variable. The optimized nanocrystals were evaluated for spectroscopic, thermal, dissolution and anthelmintic study.

2. Materials and methods

2.1. Materials

Albendazole was obtained as a gift sample from GlaxoSmithKline Pharmaceuticals Ltd. Polyvinylpyrrolidone (PVP K30) was purchased from HiMedia. Formic acid and hydrochloric acid (HCl) were obtained from Merck. Sodium hydroxide (NaOH) was purchased from LobaChemie.

Indian Earthworm species *Eiseniafoetida* was collected from Anand Agriculture University. All earthworms were of approximately equal size (8–10 cm).

2.2. Method of preparation of albendazole nanosuspension

Albendazole nanosuspension was prepared by antisolvent precipitation method. Albendazole was dissolved in formic acid then the organic solution of albendazole was added drop wise into aqueous solution containing stabilizer under continuous stirring at 1200 rpm until homogenous milky suspension was obtained.

2.2.1. Spray drying (SD) of albendazole nanosuspension

Solidification of selected albendazole nanosuspension was achieved using spray drying technique (Model: LU222 Advance, Make: Labultima), equipped with a high performance cyclone, with inlet temperature 110 °C; outlet temperature 60–70 °C; feed rate 1 mL/min; aspiration 70 Nm^3/hr.

2.3. Characterization of nanoparticles

2.3.1. Fourier transform infrared spectroscopy

The drug excipients compatibility study was carried out using Fourier Transform Infrared Spectroscopy (FTIR). FTIR of PVP K30, pure Albendazole, Physical mixture of Albendazole and PVP K30 were carried out by potassium bromide disc method. A pinch of samples were grinded with potassium bromide and the mixture was converted in to a disc. The disc was kept in a sample holder of FTIR spectrophotometer (Model: Nicolet 6700 Make: Thermoscientific USA). The FTIR spectrum was recorded over the region 4000-400 cm^{-1}.

2.3.2. Particle size analysis

Particle size was measured by dynamic light scattering technique. A pinch of sample was dispersed in distilled water and sonicated for 50 s and particle size was measured using particle size analyser (Model: NanoS90 Make: Malvern).

2.3.3. Saturation solubility

Excess amount of nanocrystals and pure drug powder were dispersed in 10 mL of 0.1 N HCl. The dispersion was shaken at 50 rpm & 37 °C for 72 h using orbital shaking incubator. The filtered sample solutions were analysed using a UV–visible spectrophotometer (Model: UV- 1800 Make: Shimadzu) at 307.8 nm after appropriate dilution.

2.3.4. In vitro dissolution studies

Dissolution behavior of albendazole nanocrystals was studied by USP type II apparatus (paddle) using 900 mL of 0.1 N HCl as dissolution medium stirred at 50 rpm. The Nanocrystals (100 mg equivalent drug) were accurately weighed and introduced directly into the dissolution medium. 4 mL sample was withdrawn at regular time intervals (5, 10, 15, 30, 60, 90, 120 and 150 min), and replaced by fresh dissolution medium. Samples were filter and appropriately diluted with 0.1 N NaOH. Samples were analysed spectrophotometrically (Model: UV-1800 Make: Shimadzu) at wavelength of 307.8 nm using 0.1 N NaOH as a blank [15]. Dissolution efficiency was calculated using equation (1) [16].

$$\text{Dissolution efficiency(DE)} = \frac{\int_{t_1}^{t_2} y.dt}{y_{100}(t_2 - t_1)} \times 100 \quad (1)$$

Table 1
Operation conditions of headspace auto sampler and Gas chromatograph.

Headspace auto sampler		Gas chromatograph	
Oven temperature	95 °C	Column	Capillary column
Needle temperature	100 °C	Oven temperature	45 °C for 5 min
Transfer line temperature	110 °C	Heating rate	10 °C/min up to 120 °C
Thermostatic time	20 min	Injection temperature	220 °C
Carrier gas	Nitrogen	Carrier gas	Nitrogen

Table 2
Anthelmintic bioassay.

Group No.	No of earth worms	Test Sample	Concentration (mg/mL)	Paralysis Time (min)	Death Time (min)
1	6	Control (distilled water)	–		
2	6	Albendazole Pure drug	8	75 ± 3	104 ± 4
3	6	Albendazole Nanocrystals	8	49 ± 4	71 ± 4

2.3.5. X-ray diffraction study (XRD)

X-ray diffraction analysis was carried out to detect the crystallinity of pure albendazole and nanocrystals using a D2 phaser X-Ray diffractometer (Model: D2 phaser, Make: Bruker, USA). The powder was placed in a sample holder & scanned from 10 to 80° (2θ).

2.3.6. Differential scanning calorimetry (DSC)

The DSC study of PVP K30, pure Albendazole, Albendazole/PVP K30 physical mixture and PVP K30 stabilized Nanocrystals were carried out using a differential scanning calorimeter (Model: Pyris 1 DSC, Make: Perkin Elmer, USA). Approximately 2.5 mg samples were accurately weighed and sealed in standard aluminum crucibles with a single hole punched in the lid. An empty pan of the same type was employed as a reference. The DSC instrument was calibrated using the melting point of indium (156.6 ± 0.3) as a standard. DSC scans of each sample were performed at a heating rate of 10 °C/minute in the temperature range of 45–300 °C. The DSC cell was purged with a stream of nitrogen at a rate of 50 mL min^{-1}.

2.3.7. Transmission electron microscopy (TEM)

The morphological evaluation of nanocrystals was performed by TEM (Model: Tecnai 20, Make: Philips, Holland). A pinch of nanocrystals were dispersed in distilled water and sonicate using bath sonicator for 30 s. Two drops of prepared sample were put on to a 300 mesh carbon coated copper grid. The grid was placed in to a sample holder and all images were acquired at an accelerating voltage of 200 kV.