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Effect of glucosamine HCl on dissolution and solid state behaviours of piroxicam upon milling

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ABSTRACT

Piroxicam is a non-steroidal anti-inflammatory drug that is characterised by low solubility and high permeability. In order to improve the drug dissolution rate, the co-grinding method was used as an approach to prepare piroxicam co-ground in the carriers such as glucosamine hydrochloride. As, this amino sugar (glucosamine HCl) has been shown to decrease pain and improve mobility in osteoarthritis in joints, therefore, the incorporation of glucosamine in piroxicam formulations would be expected to offer additional benefits to patients. The effect of the order of grinding on the dissolution of piroxicam was also investigated. Co-ground drug and glucosamine were prepared in different ratios using a ball mill. The samples were then subjected to different grinding times. In order to investigate the effect of the grinding process on the dissolution behaviour of piroxicam, the drug was ground separately in the absence of glucosamine. Mixtures of ground piroxicam and unground D-glucosamine HCl were prepared. Physical mixtures of piroxicam and glucosamine were also prepared for comparison. The properties of prepared co-ground systems and physical mixtures were studied using a dissolution tester, FTIR, SEM, XRPD and DSC. These results showed that the presence of glucosamine HCl can increase dissolution rate of piroxicam compared to pure piroxicam. Generally, all dissolution profiles showed the fastest dissolution rate when ground piroxicam was mixed with unground glucosamine. This was closely followed by the co-grinding of piroxicam with glucosamine where lower grinding times showed the fastest dissolution. The solid state studies showed that the grinding of piroxicam for longer times had no effect on polymorphic form of piroxicam, whereas mixtures of piroxicam–glucosamine ground for longer times (60 min) converted piroxicam polymorph II to polymorph I.

1. Introduction

The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Piroxicam is a member of the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis and a variety of other acute and chronic musculoskeletal disorders, dysmenorrhea and as ordinary analgesics [1,2]. According to the Biopharmaceutical Drug Classification System (BCS) proposed by Amidon et al., 1995 [3], piroxicam is a class II drug with low solubility and high permeability. Its pharmacokinetic pattern is characterised by slow and gradual absorption via the oral route and a long half-life of elimination, thus giving a prolonged therapeutic action but also a delayed onset of anti-inflammatory and analgesic effect [4].

Glucosamine is a naturally occurring, highly water soluble, non-toxic compound that has been shown to decrease pain and improve mobility in osteoarthritic joints of humans when given orally [5,6]. This has led to its popular use as a nutritional supplement in both humans and dogs. This monosaccharide (glucosamine) is one of a family of amino sugars and is a weak base. Due to the instability of glucosamine its salts, either hydrochloride or sulphate, are used in therapy [7]. Al-Hamidi et al. showed the ability of glucosamine as a hydrophilic carrier to enhance the dissolution rate of carbamazepine (CBZ) in solid dispersion formulations [8]. The increase in dissolution rate was due to the hydrophilic nature of

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glucosamine and this in turn improves the wettability of carbamazepine. This work therefore explores the use of D-glucosamine HCl as a potential excipient to improve the dissolution rate of piroxicam by use of a co-grinding approach. Solid sate characterisation should be determined to make sure grinding and glucosamine do not japrodize piroxicam's stability. It has been reported that piroxicam has two polymorphic forms. Form I (β, cube shape) has higher melting point compared to form II (α, needle shape). Anhydrous piroxicam is colourless irrespective of the polymorphic form (this is a neutral molecules of piroxicam). Piroxicam monohydrate has yellow colour [9]. It was reported that amorphous piroxicam is also yellow and the yellow colour of amorphous piroxicam is attributed to charged piroxicam molecules [10].

The incorporation of glucosamine HCl in piroxicam formulations will give additional benefit to those patients that need to take anti-inflammatory drug alongside D-glucosamine HCl (G-HCl), as this amino sugar is able to decrease pain and improve mobility in osteoarthritic joints. Therefore, the aim of the present study is to improve the dissolution rate of piroxicam in the presence of G-HCl via co-grinding technique. The effect of the order of grinding on the dissolution of piroxicam was also investigated. The physicochemical characteristics of the prepared co-ground systems, morphology of particles and their solid state were also studied to enable the investigation of any possible interaction/incompatibility between drug and G-HCl.

2. Materials and methods

2.1. Materials

Piroxicam and D-(+)-glucosamine hydrochloride (G-HCl) were purchased from Sigma (USA). All materials were of analytical grade and used as obtained. The dissolution media (pH 1.2), was prepared according to the USP method using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK).

2.2. Preparation of physical mixtures of drug–carrier

Physical mixtures of piroxicam were prepared by mixing piroxicam and D-(+)-glucosamine hydrochloride (as hydrophilic carrier) in a Turbula blender (Type T2C, Switzerland) for 10 min. Different ratios of drug:carrier (4:1, 2:1, 1:1, 1:2 and 1:4) were prepared to enable comparison. After mixing, the powders were stored in screw-caped glass vials at room temperature until required.

2.3. Preparation of co-ground mixtures of drug–carrier

Co-grinding of different ratios of drug to carrier (4:1, 2:1, 1:1, 1:2 and 1:4) was achieved using a ball mill (Fritsch, Germany). The total amount of drug:carrier was kept constant for all formulations (20 g) during the co-grinding process. The volume of the mill chamber was 250 mL. Eight steel balls with diameter 20 mm were used. The vibration rate was 400 rpm. All drug:carrier ratios were subjected to different grinding times of 1, 10, 30 and 60 min.

In order to investigate the effect of the grinding process on the dissolution behaviour of piroxicam, the drug was ground separately in the absence of G-HCl. A mixture of ground piroxicam and unground G-HCl was then prepared by mixing them in the Turbula®® blender for 10 min. In order to ascertain the effect of grinding on G-HCl, the carrier was also ground in the absence of piroxicam and then their physical mixtures prepared. Physical mixtures of the ground piroxicam and ground G-HCl were prepared with different ratios using the same methodology as described above for the physical mixtures. Different ratios of drug:carrier (4:1, 2:1, 1:1, 1:2 and 1:4) were prepared in all cases for comparison.

2.4. Solubility measurements of piroxicam

Solubility measurements of piroxicam were performed according to a published method [11]. An excess of piroxicam was added to 10 mL of pH 1.2 aqueous solutions with different concentrations of G-HCl (1, 5, 10 and 15%, w/v). The capped test tubes were shaken at 37 °C for 24 h. The resulting suspensions were then filtered through a 0.45-μm membrane filter. The filtrates were diluted (using the pH 1.2 solution) to achieve appropriate absorbance. The diluted solutions were analysed to determine the piroxicam concentration using a UV spectrophotometer (Shimadzu 160A) at 333 nm. A calibration curve was then generated using different concentrations of piroxicam in pH 1.2 aqueous solutions; the curve had a correlation coefficient of 0.999. All solubility tests were carried out in triplicate.

2.5. Particle size analysis

Particle size distribution of all formulations was conducted using a Sympatec laser diffraction particle size analyzer (Clausthal-Zellerfeld, Germany). The average particle diameters ($D_{10\%}$, $D_{50\%}$, and $D_{90\%}$) were calculated automatically using the software provided. In this technique, a laser beam is passed through the sample, and different size particles diffract the light at different angles to produce a particle size distribution. Approximately 2–3 g of the sample was transferred into the funnel of the VIBRI. The sample container was cautiously tapped against the funnel to ensure all the content was transferred. A test reference measurement was performed with the HELOS sensor using WINDOX software followed by a standard measurement. This was to ensure the material was flowing through the vibrating chute into the groove of the rotary table.

2.6. Scanning electron microscopy

Electron micrographs of piroxicam ground mixtures were obtained using a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. The samples were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were taken to facilitate the study of the morphology of the ground mixtures.

2.7. Fourier transform infrared (FT-IR)

The FT-IR spectra (650–4000 cm^{-1}) of piroxicam ground mixtures and physical mixtures were recorded using ATR with a FT-IR spectrophotometer (PerkinElmer, UK). After obtaining sharp peaks of reasonable intensity, the spectra were the result of averaging 4 scans at a resolution of 1 cm^{-1}.

2.8. Differential scanning calorimetry (DSC)

Samples of ground or physical mixtures of drug:carrier (3–6 mg) was placed in standard aluminium pans (40 μL) sealed with a lid containing a hole. The crimped aluminium pans were heated from 20 to 350 °C at a scanning rate of 10 °C/min under nitrogen gas. The enthalpy, onset temperatures and melting points of the samples were automatically calculated using the software provided (Mettler-Toledo, Switzerland).