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Ultrasound influence on the solubility of solid dispersions prepared for a poorly soluble drug

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ABSTRACT

Solid dispersions have been successfully used to enhance the solubility of several poorly water soluble drugs. Solid dispersions are produced by melting hydrophilic carriers and mixing in the poorly water soluble drug. Supersaturation is obtained by quickly cooling the mixture until it solidifies, thereby entrapping the drug. The effects of using ultrasound to homogenize the molten carrier and drug mixture were studied. In particular, the increase in drug solubility for the resulting solid dispersions was analyzed. Piroxicam, which has very low water solubility, was used as a model drug. A full factorial design was used to analyze how sonication parameters affected the solubility and *in vitro* release of the drug. The results show that the use of ultrasound can significantly increase the solubility and dissolution rate of the piroxicam solid dispersion. Pure piroxicam presented a solubility of 13.3 μg/mL. A maximum fourfold increase in solubility, reaching 53.8 μg/mL, was observed for a solid dispersion sonicated at 19 kHz for 10 min and 475 W. The *in vitro* dissolution rate test showed the sonicated solid dispersion reached a maximum rate of 18%/min, a sixfold increase over the piroxicam rate of 2.9%/min. Further solid state characterization by thermal, X-ray diffraction and Fourier transform infrared analyses also showed that the sonication process, in the described conditions, did not adversely alter the drug or significantly change its polymorphic form. Ultrasound is therefore an interesting technique to homogenize drug/carrier mixtures with the objective of increasing the solubility of drugs with poor water solubility.

1. Introduction

Piroxicam (PRX) is a nonsteroidal anti-inflammatory drug with many therapeutic uses [1,2]. According to the Biopharmaceutical Classification System, this drug is classified as Class II, presenting low solubility at physiological pH and high permeability through the intestinal membrane [3,4].

Drug solubility and dissolution rate are very important properties to its absorption, presenting a crucial impact on its bioavailability. Poorly soluble drugs, such as PRX, usually present low solubilities and dissolution rates, leading to low and irregular bioavailability and a sub-optimal efficacy [5–7]. The increasing number of new drugs with poor solubility has made increasing drug solubility one of the major current challenges for the pharmaceutical industry [5,7,8].

Several techniques have been proposed to increase the solubility of poorly soluble drugs. Among these, solid dispersions made through the melt method and using hydrophilic carriers have been widely used [4,9–11]. In this method, the drug is mixed with a melted carrier, and then this mixture is cooled abruptly. The heating followed by rapid cooling results in supersaturation and the entrapment of the drug in the solidified carrier matrix. The structure of the solid dispersions obtained, and consequently the drug solubility, will be affected by the cooling rate and degree of supersaturation [12].

Ultrasound has been widely applied in cleaning materials [13], cell disruption [14], organic synthesis [15], substance crystallization [16], bioactive compound extraction [17,18] and food extraction [19,20]. However, although ultrasound has often been used in multi-disciplinary fields, little attention has been given to the application of ultrasound in the pharmaceutical field. Currently, there are a small number of studies that aimed to use ultrasound for pharmaceutical formulations [7]. This shows that the use of ultrasound in different pharmaceutical processes is still little explored.

In a solid–liquid system under action of ultrasound, the solid dissolution is governed by an increased rate of mass transfer

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Nomenclature

ANOVA	analysis of variance
DSC	Differential Scanning Calorimetry
FT-IR	Fourier Transform Infrared Spectroscopy
P	sonication power
PEG 4000	polyethylene glycol 4000
PM	physical mixture
PRX	piroxicam
RM	percentage of drug released per minute
SD	solid dispersion without sonication
SEM	Scanning Electron Microscopy
SSD	sonicated solid dispersion
T	sonication time
TGA	Thermogravimetry
TRP	time to reach the plateau
VGLM	Visual General Linear Model
XRPD	X-ray Powder Diffraction

[21–23]. Thus, the use of sonication during the mixture of drug and carrier in the production of solid dispersions could intensify the drug dissolution process. By using ultrasound to homogenize a drug in the melted carrier, it may be possible to increase the amount of drug solubilized in the carrier before cooling [21,22]. After rapid cooling, the resulting solid dispersions would have a higher amount of entrapped drug in the carrier matrix. This would translate as an increase in solubility and dissolution rate of the solid dispersion in water.

Ultrasonic homogenization involves a great variety of interdependent effects, and the extent of its action depends on the conditions of sonication [21,24]. Therefore, the study of the factors involved in the sonication process is of great importance in predicting responses and optimizing methods. To study the different factors in this process, full factorial design is a robust and valuable tool. It has been used over the years and especially to study pharmaceutical processes [25,26].

The aim of the present work was to use a full factorial design ($3^2 + 2$) to evaluate the effect of ultrasonic homogenization conditions during the mixture of the PRX and the melted carrier. The factors studied were sonication time and sonication power. The solid dispersions produced by rapid cooling of the PRX/carrier mix were then evaluated based on the solubility and dissolution rate of the drug. A solid dispersion produced without the use of sonication (SD) and a physical mixture (PM) of PRX and the carrier were also produced and studied for comparison. The sonicated solid dispersion (SSD) with the largest water solubility and dissolution rate, as well as the solid dispersion without sonication and the physical mixture of PRX, were further characterized to verify whether the sonication process promoted any physicochemical modifications to the drug during the production process.

2. Materials and methods

2.1. Materials

PRX obtained from Pharmanostra Ltda (Rio de Janeiro, RJ, Brazil) was used as the model poorly water soluble drug. Polyethylene glycol 4000 (PEG 4000) purchased from Henrifarma Ltda (São Paulo, SP Brazil) and Poloxamer 407 supplied by Viafarma Ltda (São Paulo, SP, Brazil) were used as hydrophilic carriers. Deionized water was used to prepare the solutions. All other materials used were of analytical grade. Hydrochloric acid and sodium chloride used to prepare the simulated gastric fluid without pepsin were purchased from Synth (Diadema, SP, Brazil).

2.2. Physical mixture preparation

PRX, PEG 4000 and Poloxamer 407 are solid at room temperature. Physical mixtures of these substances were prepared by manually mixing them until a uniform mixture was obtained. Before mixing, the carriers were crushed and sieved and particles with sizes between 600 and 710 μm were mixed with PRX. The PRX, PEG 4000 and Poloxamer 407 were put in a suitable flask in the proportions of 1:8:1 by weight and shaken for 10 min. This proportion of drug and carriers was defined by preliminary experiments not presented in this study.

2.3. Solid dispersion preparation by melt method using ultrasound

Solid dispersions were prepared in the same proportion of drug and carrier used in the physical mixture. Therefore, sonicated solid dispersions were prepared by the melt method using PRX, PEG 4000 and Poloxamer 407 in the proportions of 1:8:1, respectively. PEG 4000 and Poloxamer 407 have a melting point of approximately 60 °C and 55 °C, respectively, as measured in item 3.3.2. Therefore, the carriers were first melted and heated to around 70 °C. Then PRX was added and the sample was homogenized by sonication (Fig. 1), using an ultrasonic probe DR500 (Unique Ltda, Indaiatuba, SP, Brazil) with a frequency of 19 kHz, tip diameter of 13 mm and maximum power rated at 500 W. The sample temperature was monitored in all experiments, as sonication tends to heat the sample. Temperatures did not rise above 75 °C after sonication with the use of water to cool the sample, as shown in Fig. 1. After sonication, the dispersions were immediately placed in a freezer and cooled for 24 h at −12 °C. The solidified dispersion was then crushed and sieved. Once again only particles with sizes between 600 and 710 μm were used to control for particle size when comparing to the physical mixture.

The sonication time (X_1) and power (X_2) for each experiment were determined using a full factorial design with three levels and two factors, plus two replicates at the central point ($3^2 + 2$), for a total of 11 experiments. The choice of these factors and of maximum and minimum values for theses parameters was based on previous experiments performed in our laboratory. Sonication time, specifically, was chosen so that no visible degradation of the drug would occur. Table 1 shows the factors and the levels studied in their coded and non-coded values.

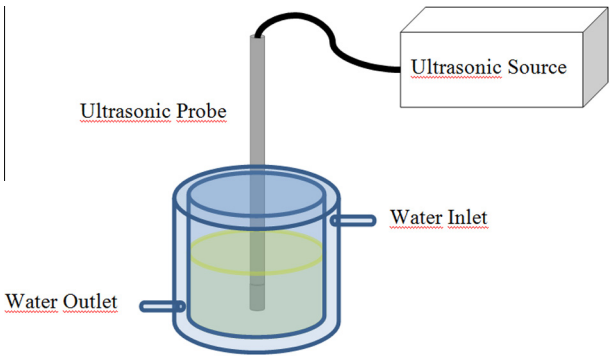

Fig. 1. Scheme of homogenization with an ultrasonic sonicator.