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Original Research Paper

Preparation and evaluation of taste masked oral suspension of arbidol hydrochloride

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ABSTRACT

The purpose of this study was to cover the bitter taste of arbidol hydrochloride (ARB) and develop dry suspension with combination of solid dispersion and flavors. Taste masking was successfully done by solid dispersion using octadecanol as the carrier by fusion method. Suspending agents, carriers and other excipients were selected. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) were performed to identify the physicochemical interaction between drug and carrier, DSC analysis indicated that ARB was amorphous in the solid dispersion, FTIR spectroscopy showed no interaction between drug and carrier. Taste masking was evaluated on six volunteers with a score of 4.9. The results demonstrated successful taste masking. Water was used to study the *in vitro* dissolution performance of the three formulations of commercial tablet, capsule and self-made suspension. The self-made suspension showed a lower and slower release, the insoluble carrier octadecanol blocked the drug dissolving from the solid dispersion. It was indicated from the primary stability study, the self-made suspensions were sensitive to high temperature, high humidity and strong light conditions, they should be stored in sealed containers away from heat, light and humidity.

1. Introduction

ARB (1-methyl-2-phenyl-thiomethyl-3-carboxy-4-dimethylaminomethyl-5-hydr-oxy-6-bromoindole hydrochloride monohydrate) (Fig. 1) is a small indole-derivatives molecule used for the treatment and prevention of infections by influenza A, B viruses, A/H1N1 is included [1]. ARB was listed in Russia in 1993 and in China in 2006, for the control of influenza and other acute respiratory virus infection [2–4]. It is proved that ARB is efficient to reduce the duration of illness and to prevent the development of post-influenza complications [5]. Moreover, despite years of clinical trials and application reveal that, ARB show high efficacy, minor adverse effect, and no drug resistance [6–9]. A major problem in the development of an oral solid dosage form of ARB is its intensely bitter taste, leading to poor patient compliance. To overcome the above problem, we try to develop a bitterness-covered ARB for dry suspension.

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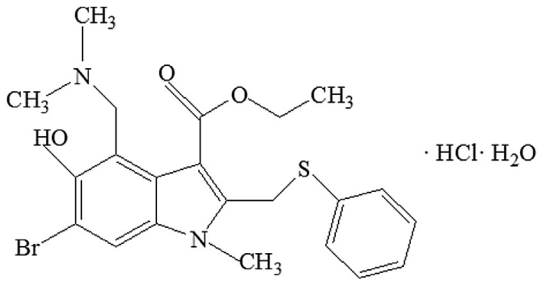

Fig. 1 – Chemical structure of ARB.

The commercially available products include tablets and capsules. It is estimated that 50% of the population have problem of swallowing tablets and capsules, especially the pediatric and geriatric population [9]. Dry suspension has been used to address the problem. In addition to good patient compliance, there are many advantages of dry suspension, such as safety, stability, convenience and ease absorption.

Without changing its safety and efficacy, a drug's taste has to be masked and techniques are being adapted to meet this need, especially for the pediatric and juveniles patients. These are as follows: taste masking with flavors, taste masking by granulation, microencapsulation, ion exchange resins, solid dispersion method, bitterness inhibitor. When single approach for taste masking is not very successful for highly bitter drugs, using combination of various taste masking technologies is found to be a more efficient strategy [9]. Amongst the strategies mentioned, we choose the combination of flavors with solid dispersion [10].

Solid dispersion have been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting method, hot melt extrusion, solvent evaporation method, spray drying, supercritical fluid precipitation and so on [11,12].

In our study, melting method was chosen owing to their effective taste masking and ease of industrial production. To prepare ARB solid dispersion, octadecanol was used as the carrier, then flavors such as sucrose, mannitol, aspartame and orange flavor were added.

2. Materials and methods

2.1. Materials

Arbidol hydrochloride was purchased from Sichuan Baili Pharmaceutical Co., Ltd. (China). Arbidol hydrochloride commercial tablet was purchased from Shiyao Group Pharmaceutical (Shijiazhuang) Co., Ltd. (China). Arbidol hydrochloride commercial capsule was purchased from Shijiazhuang Siyao Co., Ltd. (China). Xanthan, mannitol, orange flavor concentration and aspartame were purchased from Beijing Fengli Jingqiu Commerce and Trade Co., Ltd. (China). Sodium carboxymethyl cellulose and hydroxypropyl cellulose were kindly supplied by Anhui Sunhere Pharmaceutical Excipients Co., Ltd. (China). Arabic gum, octadecanol, sucrose, citric acid, poloxamer 188, glyceryl monostearate, sodium dodecyl sulfate, pentane sulfonate and ammonium dihydrogen phosphate were purchased from Tianjin Bodi Chemical Co. Ltd. (China). Sunset yellow dye was purchased from Shanghai Institute Dye Co. (China). PEG6000 and phosphoric acid was purchased from Tianjin Kermel Chemical Reagent Co., Ltd. (Tianjin, China). Methanol of chromatographic grade was purchased from Concord Technology Co., Ltd. (Tianjin, China).

2.2. Methods

2.2.1. Preparation of solid dispersions

Conventional melting method was used in our work. Several typical carriers with a low melting point including PEG6000, citric acid, octadecanol, poloxamer 188 and glyceryl monostearate were evaluated using organoleptic evaluation and *in vitro* dissolution study.

Different carriers were heated at 70 °C directly to melt entirely, then the mixture of ARB and sucrose with a ratio of 1:2 was slowly added to the carriers with constantly stirring. After totally dispersed, the melted mixture was solidified in an ice-bath under vigorous stirring until forming particles. After dried at room temperature for 2 h, the final solid dispersion was crushed, pulverized and screened by 40# mesh; particles with diameters under the size were chosen for further use.

2.2.2. Organoleptic evaluation [13]

The objective of this study was to conduct and evaluate the palatability of different formulations of ARB dry dispersion. Taste evaluation was done on a team of 3 members. Each volunteer took dispersion equivalent to 100 mg ARB in the mouth for 15 s and then spit out. The taste score between 1 and 5 was given to evaluate the taste of formulation. Namely, the scores were set as follows: 1 (Distasteful, equivalent to ARB taste), 2 (Slightly taste, ARB taste remaining fairly), 3 (Mean, ARB taste remaining to some extent), 4 (slightly tasty, ARB taste slightly remaining), 5 (Tasty, no taste of ARB).

2.2.3. In vitro dissolution study

The *in vitro* dissolution test was studied using a ChP2010 Type2 dissolution apparatus (paddle method), and all the tests were carried out in triplicate. The temperature of the dissolution medium (a volume of 900 ml purified water) was maintained at 37 ± 0.5 °C with stirring from a paddle at 75 rpm. A certain amount of samples equivalent to 100 mg ARB were used in all of the dissolution tests. At prescheduled time intervals (5, 10, 15, 20, 30, 45, 60 min), samples aliquots were withdrawn and filtered (0.45 μm membrane, Millipore) immediately, then replaced with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and the concentration of ARB was determined using on a UV spectrophotometer (Beijing Rayleigh Analytical Instrument Co.) at 257 nm.

2.2.4. Differential scanning calorimetry analysis

Thermal analysis of octadecanol, raw arbidol hydrochloride, powdered sucrose, physical mixture, and the solid dispersion of the three substances were performed on a DSC 1 (Metter Toledo, Greifensee, Switzerland). Samples each 2–5 mg was