International Journal of Pharmaceutics 477 (2014) 643–649

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Preformulation study of fiber formation and formulation of drug-loaded microfiber based orodispersible tablets for in vitro dissolution enhancement

Péter Szabó [a,b], Barnabás Kállai-Szabó [a], István Sebe [b], Romána Zelkó [b,*]

[a] Gedeon Richter Plc., Formulation R&D, Gyomroi Str. 19-21, Budapest H-1103, Hungary
[b] University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hogyes Endre Str. 7-9, Budapest H-1092, Hungary

ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form 3 November 2014
Accepted 5 November 2014
Available online 6 November 2014

Keywords:
High-speed rotary spinning
Microfibers
Hydroxypropyl cellulose
Orodispersible tablet
Dissolution enhancement

ABSTRACT

Preformulation study of rotary spun hydroxypropyl cellulose fibers was carried out using the combination of textural characterization of gels in the concentration range of 42–60% w/w and optical microscopic evaluation of formed fibers. High adhesiveness values resulted in bead formation at lower polymer concentration, meanwhile fiber formation was hindered when high adhesiveness values were associated with high polymer content. The optimum gel concentration for fiber formation was given to 50% w/w.

Drug loaded microfibers were prepared using a model drug of biopharmaceutical drug classification system class II. Fibers were milled, sieved and mixed with tableting excipients in order to directly compress orodispersible tablets. Hardness, friability, in vitro disintegration time values complied with the pharmacopoeial requirements. In vitro dissolution profiles obtained from three distinct dissolution media (pH 1.0; 4.5; 6.8) were quite differentiated compared to the compressed physical mixture of the same composition. Difference and similarity factors confirmed that the drug dissolution from microfiber based formula was almost independent from the pH value of the media. X-ray diffraction patterns indicated that the drug embedded in microfibers was in amorphous state, and the decrease of *o*-Ps lifetime values suggested that fiber formation enabled the development of a more ordered fibrous system.

1. Introduction

The spread of combinatorial chemistry and high throughput screening in the pharmaceutical research have led to increased amount of drugs with higher molecular weight, higher lipophilicity, and poorer water solubility (Lipinski, 2000). The undesirable physicochemical characteristics of new drug candidates can be attributed to the presence of the phenomenon of molecular obesity (Hann and Keseru, 2012). Regarding their disadvantageous ADME behavior, the increasing proportion of new drug candidates with poor water solubility poses challenge for the pharmaceutical industry. According to the biopharmaceutical drug classification system, active pharmaceutical ingredients in class II and in class IV can be characterized by low water solubility. While in case of chemical entities in class II in vitro–in vivo correlation can be expected, in case of drugs in class IV limited or no in vitro–in vivo correlation can be found due to the low permeability (Amidon et al., 1995). Even though it is reported that the in vitro dissolution enhancement of pharmaceutically active compounds of class II is not necessarily resulted in the consequent improvement of bioavailability, the most widely accepted formulation approach of these drugs focuses on the facilitation of in vitro dissolution (Sarnes et al., 2014).

Different techniques are used in the formulation processes of drugs of poor water solubility in order to increase their solubility, and thereby their bioavailability in peroral dosage forms. Over the last decade hot-melt extrusion has gained popularity as a possible way in the formulation of drugs of poor solubility and as a result of its limited bioavailability (Repka et al., 2007). Other approaches focusing on particle size reduction have also become important, thus nanotechnology has emerged as the most promising discipline. Several nanosized drug delivery systems were developed in order to improve solubility, bioavailability, tolerability, toxicity of drug candidates such as micelles, microspheres, dendrimers, solid–lipid nanocarriers, and self-emulsifying drug delivery systems (Agrawal et al., 2014).

* Corresponding author. Tel.: +36 1 2170927; fax: +36 1 2170927.
E-mail address: zelko.romana@pharma.semmelweis-univ.hu (R. Zelkó).

http://dx.doi.org/10.1016/j.ijpharm.2014.11.011
0378-5173/

Drug loaded polymer fibers are also intended to enhance the solubility of poorly soluble drugs. Various spinning techniques are used in the production of polymer fibers. The most frequently applied method is electrospinning, where the fiber formation from polymer solutions is induced by high voltage (Huang et al., 2003). Other techniques such as melt spinning, high speed rotary spinning are also suitable for manufacturing polymer-based nano- and microfibers (Badrossamay et al., 2010; Nakata et al., 2007; Sebe et al., 2013). Polymeric fibers have several favorable properties, such as high specific surface area, high porosity and the ability to include the active pharmaceutical ingredient in amorphous state (Huang et al., 2003; Verreck et al., 2003). However interest in fiber-based formulations have been growing recently due to their potential applicability in release-modification and solubility improvement (Okuda et al., 2010; Verreck et al., 2003; Yu et al., 2010), the main interest focuses on parenteral and topical dosage forms, while hardly any attention is given to formulations intended for oral administration.

In high speed rotary spinning technique, the formed centrifugal force and the solvent evaporation give rise to the fiber formation. The applied rotary speed, the composition of the polymeric solution and the inner diameter of the wall orifices are the main parameters which affect the microstructure of the fibers (Badrossamay et al., 2010). Both electrospinning and high speed rotary spinning are capable for production of micro- and nanofibers. While conventional electrospinning process is limited by its low productivity, with high speed rotary spinning fibers can be produced with a higher rate. Although the lowest the fiber diameter the highest the specific surface, which is beneficial for the dissolution, the processibility of nano-sized drug delivery systems can be cumbersome. A typical example for this problem is the production of tablets from fibers which must be milled in order to blend them with conventional tableting excipients of a size range of a few micrometers. Huge particle size differences can be resulted in segregation and consequently inhomogeneity of tablets (Williams, 1976).

In recent years, research on the formulation of orodispersible tablets has become very popular due to their pharmaceutical and therapeutic benefits. The easy administration, the rapid liberation, and the increased bioavailability of the incorporated drug are the most important properties which can be effectively utilized in the formulation of drugs (Bandari et al., 2008).

Hydroxypropyl cellulose is considered as common pharmaceutical excipient, since it has a wide application area in both solid, semisolid and fluid dosage forms (thickening, coating, emulsifying agent). The advantageous solubility properties of the polymer, it is soluble in both water and in organic solvents, make its usage a reasonable choice in the formulation of drugs of poor water solubility. The fundamental assumption was based on the common dissolution medium of the polymeric base and the active ingredient. The latter was also dissolved in organic solution thus forming a homogeneous polymeric gel for fiber formation with high speed rotary spinning technique, which could have an impact on the dissolution of the drug.

Versatility of texture analysis is leading to its increasing importance in the measurement of textural properties of different dosage forms. The method is capable for the characterization of solid, semi-solid, and fluid systems. In a previous paper authors showed that measuring textural properties is a good alternative to obtain rheological and mechanical information either about liquid crystalline and solid fibrous systems (Szabó et al., 2014).

The aim of this study was to track the fiber formation of hydroxypropyl cellulose using gels of different concentrations and elucidate the texture-structure relationship. Furthermore, we intended to demonstrate the importance of the high speed rotary spinning technique in the formulation of the poorly soluble drugs using a model drug substance. The produced drug-loaded microfibers were proposed to be processed in order to develop orodispersible tablets.

2. Materials and methods

2.1. Materials

Hydroxypropyl cellulose (Klucel® ELF, Mw ~40,000, moles of substitution of 3.8, Ashland, USA), citric acid monohydrate (Molar Chemicals, Hungary) was used in the fiber formation process. A semisynthetic alkaloid derivative model drug was selected from the biopharmaceutical classification system class II and can be characterized with the following physicochemical properties: Mw < 500, pK_a = 7.1 (with one basic centre), water solubility < 5.1 μg/ml, log*P* 4–5. In the preparation of the drug stock solution diluted ethanol (3:1 volume ratio) was made by the mixing of 75 ml of ethanol (96% v/v%, Reanal, Hungary) and 25 ml of distilled water. Potassium dihydrogen phosphate (Molar Chemicals, Hungary), sodium hydroxide (Molar Chemicals, Hungary), and distilled water were applied in the preparation of the dissolution media. The excipients of the orally disintegrating tablets were as follows: microcrystalline cellulose (Vivapur® 102 MCC) as filler and disintegrant, mannitol (Mannogem® EZ, SPI Pharma) as filler, milled polyethylene glycol 1500 (Macrogol 1500, Hungaropharma) as lubricant, equimolar mixture of milled citric acid anhydrate, and sodium bicarbonate as effervescent agent and croscarmellose sodium (Vivasol®, JRS Pharma) as superdisintegrant.

2.2. Preparation of drug stock solution

5.000 g of model drug was measured into a 50.00 ml volumetric flask, and then it was suspended with about the half of the necessary amount of diluted ethanol (3:1 volume ratio). When a lactescent dispersion was formed, 3.000 g of citric acid monohydrate was added. The dispersion was carefully shaken until a clear solution was obtained, then the solution was diluted to 50.00 ml with the solvent mixture.

2.3. Preparation of hydroxypropyl cellulose gels

Hydroxypropyl cellulose gels were prepared in a beaker by addition of the necessary amount of distilled water. After careful homogenization, the samples were covered with paraffin tape and stored at room temperature (T = 25 °C) for one hour. These samples were used in the preparation of the fibers by high-speed rotary spinning. 15 min before the beginning of the texture analysis 10 g of each sample was put in a small cylindrical glass container (internal diameter: 23 mm, height: 30 mm), which was fixed to the basis of the texture analyzer. Hydroxypropyl cellulose gels of 42–60% w/w concentrations were prepared for the texture analysis. Based on the results of the texture analysis the optimum polymer concentration was 50% w/w therefore gels containing model drug was prepared by the addition of the same amount of Klucel ELF hydroxypropyl cellulose and model drug stock solution. After careful homogenization the gels were covered with paraffin tape, and stored at room temperature (T = 25 °C) for one hour.

2.4. Texture analysis

Three parallel gel samples of each concentration were analyzed using Brookfield CT3 Texture Analyzer with 4500 g load cell (Brookfield Engineering Laboratories, Inc., USA). The test was performed with a cylindrical probe (TA-5, black delrin, diameter: 12.7 mm, length: 35 mm). The compression type test was carried out performing one cycle. The pretest speed, test speed, and the