European Journal of Pharmaceutical Sciences 106 (2017) 352–361

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Modeling and comparison of release profiles: Effect of the dissolution method

Sara Cascone

Department of Industrial Engineering, University of Salerno, via Giovanni Paolo II 132, 84084 Fisciano, (SA), Italy

ARTICLE INFO

Keywords:
Dissolution
Diclofenac
In vitro release
USP apparatuses

ABSTRACT

During the last decades, the study of the in vitro dissolution of pharmaceuticals has been strongly encouraged by the FDA in order to determine its relationship with the in vivo bioavailability of a drug. In this work immediate and extended release formulations containing diclofenac, a BCS class II drug, were studied using different dissolution methods. The release profiles obtained in USP Apparatus II and USP Apparatus IV were evaluated and compared to determine the effect of the fluid dynamic conditions on the release. The influence of the mixing conditions (i.e. the paddle rotation speed in USP Apparatus II or the inlet flow rate in USP Apparatus IV) on the drug release were evaluated, finding that, for the extended release formulations, they do not affect significantly the release profile. An in vitro device simulating the peristaltic contractions of the stomach during the digestion was used to simulate fluid dynamics closer to the real physiology. The tablets were found to behave in a completely different way if tested in the artificial stomach.

Both model-independent and model-dependent approaches were used to compare and fit the dissolution profiles, respectively. Fit factors were used as indicators of similarity of two dissolution profiles; model equations (such as zero-order, first-order, or Korsmeyer-Peppas equations) were used to fit the experimental data. With the identification of the best fitting model by the use of correlation factors and Akaike Information Criterion, the transport phenomena that determine the behavior of each formulation were identified.

1. Introduction

In order to determine the bioavailability of a drug administered from a solid dosage form, two key phenomena must be taken into account: the dissolution of the pharmaceuticals, which is related to the solubility of a drug, and the active ingredient absorption, which is related to its permeability. The U.S. Food and Drug Administration (FDA) encourages pharmaceutical companies to study the relationship between in vivo drug bioavailability and in vitro dissolution (Chow and Fanny, 1997). For this reason, during the years, in vitro dissolution testing has played a critical role in pharmaceutical development and manufacturing, often guiding the design of new formulations and the development of more efficient dosage forms (Baxter et al., 2005). In order to use in vitro dissolution profiles as indicators of in vivo bioavailability, of bioequivalence, or to develop in vitro-in vivo correlations, reliable release data, obtained in defined physiochemical and hydrodynamic conditions, are necessary (Pillay and Fassihi, 1998). The reproduction of the physiological biochemical processes and fluid dynamics experienced by an orally administered pharmaceutical form is a very complex and challenging task, which has been faced by several scientist, that developed several methods to reproduce dissolution conditions closer to the real physiology (Cascone et al., 2016b).

Within the Biopharmaceutics Classification System (BCS), diclofenac sodium is BCS class II active pharmaceutical ingredient (Chuasuwan et al., 2009), which means low solubility and high permeability compound. In the case of Class II compounds, drug dissolution might be the rate-limiting step for drug absorption (Hurtado y de la Peña et al., 2003). According with the USP recommendations, the dissolution method for extended release tablets of diclofenac provides the use of the USP Apparatus II, set at 37 °C with a paddle rotation of 50 rpm (Convention, 2010). Concerning the immediate-release tablets, it was recommended to perform dissolution in 900 mL of SIF (Simulated Intestinal Fluid) at 50 rpm in USP Apparatus II (Chuasuwan et al., 2009). Moreover, for different formulations, if no USP methods are available, the dissolution test should be performed using a method recommended by FDA (Anand et al., 2011), which can be easily found online (U.S., Food and Drug Administration, 2005). Concerning the apparatus selection, even if the USP I and II apparatuses are the most used for determining the dissolution profiles, it is recognized that the USP IV apparatus offers many advantages in the study of poorly-soluble drugs (Beyssac and Lavigne, 2005; Bhattachar et al., 2002; Brown et al., 2004). The aim of this work is to compare the effect of the dissolution

E-mail address: scascone@unisa.it.

http://dx.doi.org/10.1016/j.ejps.2017.06.021
Received 28 March 2017; Received in revised form 9 May 2017; Accepted 12 June 2017
Available online 14 June 2017

method (in terms both of dissolution apparatus used and of mixing conditions) on the release profiles of several pharmaceuticals. Thus, starting from a conventional dissolution USP Apparatus II, the same pharmaceutical forms were tested in a flow-through cell apparatus (USP IV apparatus), and using an in vitro apparatus simulating the stomach (artificial stomach) with the aim of comparing the dissolution profiles obtained. Since in this work several diclofenac-based formulations are analyzed, in order to level out the dissolution media used (necessary to isolate the effect of mixing conditions on dissolution profiles), the methods described in the USP general chapter (Chapter < 711 >) concerning the dissolution, Method A (Convention, 2012), are used.

During the last decades, the regulatory authorities have placed more emphasis on the meaningful comparison of dissolution profile data in order to: i) develop in vitro/in vivo correlations, which can reduce costs in the development of new formulations; ii) establish final dissolution specifications for the pharmaceutical dosage form; iii) establish the similarity of pharmaceutical dosage forms (O'hara et al., 1998). Since the 1990s, scientists started to develop methods useful to compare dissolution profiles (Ruiz and Volonte, 2014), ranging from the use of the similarity factors, to the more recent and sophisticated computer softwares (Zhang et al., 2010). The use of similarity factors, which will be described in the next section, has been widespread diffused, since they reduce the complexity of the description of a dissolution profile, providing a single value describing two curves composed of several points each (Costa et al., 2003). During the years, several mathematical models have been published, in order to elucidate the water and drug transport mechanisms during the dissolution of a solid dosage form, since they determine the final release profiles. Some literature reviews well describes the feature of these models (Caccavo et al., 2017; Dash et al., 2010; Lokhandwala et al., 2013; Singhvi and Singh, 2011). With the further aim of modeling the diclofenac drug release profiles from different pharmaceutical formulations, in order to assess the influence of the dissolution method on the release profiles, in this work the dissolution data will be compared and analyzed using both model-independent and model-dependent approaches.

2. Materials and methods

2.1. Materials

Three different tablet types were used, all of them containing diclofenac as active ingredient: a commercial immediate release formulation (Voltaren® 50 mg, Novartis Farma Spa, Origgio, VA, Italy), characterized by a gastro-resistant behavior; a commercial extended release formulation (Diclofenac DOC Generici 100 mg, Milan, Italy); a tablet composed exclusively by the active ingredient and a polymer matrix. In order to obtain the last formulation, mixtures of HPMC K15M (Methocel K15M Premium Grade from Colorcon, UK) and diclofenac (CAS number 15307-79-6 from Sigma Aldrich) 50:50 w/w powders were used. The cylindrical matrices (375 mg, 13 mm diameter, about 2 mm thickness) were prepared by compressing for 5 min the powder in a tableting machine (Specac PN3000), equipped with flat-faced punches with a force of 50 kN (realized by a Carver Press).

2.2. Dissolution in USP apparatuses

In order to reproduce the gastrointestinal environment, two different dissolution media were used during the test. To reproduce the acidic stomach environment, a medium at pH 1 was used, obtained mixing 6.25 mL of HCl (37% w/w solution, CAS number 7647-01-0) up to a volume of 750 mL. After 2 h, the medium was neutralized to simulate the intestinal environment.

Concerning the dissolution in the USP Apparatus II (AT7Smart, Sotax, Allschwil, Switzerland), the tablets were immersed into the USP II vessel at a constant temperature of 37 °C, setting the paddle rotation speed at 50, 75, or 100 rpm. After 2 h, the medium was neutralized adding an alkaline solution containing 16 g of sodium phosphate tribasic dodecahydrate (CAS number 10101-89-0, Delchimica Scientific Glassware) in 250 mL of deionized water to obtain a final pH value of 6.8. During the dissolution, samples of the medium were withdrawn in order to determine the amount of drug released during the time.

Concerning the dissolution in the USP Apparatus IV (CE7 SMART, Sotax, Allschwil, Switzerland), large tablet cells (diameter 22.6 mm) were used. In the bottom cone of the cell, a red glass bead (about 5 mm diameter) was inserted to prevent the leakage of the material through the inlet section. Above the red bead, a certain amount of smaller glass beads was inserted in order to ensure a laminar flow inside the cell and to avoid a high flow-induced stress on the tablet surface during the dissolution. The tablets were positioned on a sample holder above the glass beads. A filtration system was positioned at the inner top part of the cells to ensure the undissolved particles retaining. The temperature was set at 37 °C and kept constant during the dissolution, the flow rates used were 4, 8, or 16 mL/min. In the first part of dissolution, the medium at pH 1 was used, after 2 h, the medium was changed with the buffer solution at pH 6.8, obtained as previously described. Fresh medium was continuously fed into the cell, which means that the system was used in an open loop configuration (Fotaki, 2011). The outlet medium was stored in a different tank, samples of this medium were withdrawn in order to determine the amount of drug released during the time.

All the dissolutions were performed in triplicate to ensure the reproducibility of the data.

2.3. Dissolution in the artificial stomach

In order to evaluate the effect of the fluid dynamics on release profiles, a non-conventional in vitro device was used to test the commercial extended release formulation. The artificial stomach is described in Cascone et al. (2016a). Briefly, the device is composed by a chamber, simulating the human stomach, on which circular contractions are applied. The contractions start in the antral zone and they are realized stronger at the bottom (the region close to the valve simulating the pylorus) to reproduce the real physiology. The contractions are realized by the means of a camshaft rotation which, connected with the stomach by belts, shrinks the stomach alternately in three different positions with a frequency of three contractions per minute. The whole device was hold into an external chamber maintained at temperature of 37 °C and the same contraction strength was used for all the runs. The tablet was inserted inside the artificial stomach and maintained suspended at a fixed position by a wire to limit the contact with the stomach walls or bottom, which can alter the release surface and then the release profile. In order to analyze the effect of the contraction strength on the drug release, the dissolution was performed at two different position in the stomach. The first type of dissolution was performed maintaining the tablet suspended close to the bottom of the stomach (identified with h in Fig. 3D), immediately below the third (and the strongest) contraction. The second type of dissolution was performed maintaining the tablet suspended between the first and the second contractions (identified with h_2 in Fig. 3D), which corresponds approximately to the middle height of the stomach chamber. In order to verify the drug distribution along the artificial stomach height, at the same time, samples of the dissolution medium were withdrawn both from the bottom (through the emptying valve) and from the top of the device (immediately below the free liquid surface). In this way it was possible to identify a distribution of the drug concentration along the stomach height, caused both by the drug diffusion and by the mixing generated by contractions. In order to compare the dissolution patterns obtained in the artificial stomach and in the conventional apparatuses, the same dissolution medium at pH 1 was used for the first 2 h of dissolution. After 2 h, the stomach content was carefully transferred into a