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Sample preparation optimization for assay of active pharmaceutical ingredients in a transdermal drug delivery system using experimental designs

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Abstract

A simple but very effective sample preparation method is discussed for a matrix or drug-in-adhesive type of transdermal drug delivery system (TDS). The method is a one-step extraction using a methanol/water solvent system. Because of the unique design and physical property of the delivery system, special considerations were taken in selection of sample solvent, sample container and extraction enhancement device. The main focus of the article is on method optimization using experimental designs. A Plackett–Burman design was used to screen multiple method factors including extraction solvent strength, extraction solvent volume, shaking speed of a reciprocating shaker, and shaking time. Later, two of the factors were studied in more details using a 4×5 general factorial design. From the experimental results, the so-called main effects plots and interaction plots were generated using a statistical software. The plots are helpful in choosing the method conditions.

Keywords: Transdermal drug delivery system; Plackett–Burman design; General factorial design; Sample preparation

1. Introduction

Recently, there has been resurgence in development of transdermal delivery systems (TDS or transdermal patch) for therapeutic use because of its better safety profile, better bioavailability, and better patient compliance. TDS can be divided into two categories: the active and passive transdermal systems. The active TDS uses active assisting means, including ultrasound (Sonoporation), laser, iontophoresis and electroporation, to push the drug through the skin. The passive TDS allows the active pharmaceutical ingredient (API) to defuse through the skin layers to achieve drug delivery. [1–3] This paper discusses a particular type of TDS, the so-called drug-in-adhesive matrix (DIAM) system in the context of sample preparation considerations.

The importance of sample preparation has received active discussions in the literature [4–7]. The sample preparation procedure is a pivotal part of an analytical method for quantitative analysis of different products, including pharmaceutical products [8]. The development of a sample preparation method involves selection of suitable reagents, materials and apparatus (sample solvent, container, extraction enhancement devices, filtration devices, etc.), and selection/optimization of method factors (organic solvent concentration, pH, temperature, extraction time, energy level, etc.). The initial selection of sample preparation reagents and materials is based on knowledge of the formulation design and physical properties of the API and the intended purpose of the method. The sample preparation procedure will impact the method's accuracy, repeatability and laboratory-to-laboratory reproducibility as well as its simplicity, safety, and time and cost-effectiveness.

Development of sample preparation method for TDS, particularly the DIAM type of TDS, has proved a challenge due to its unique physical properties. A DIAM system is composed of three layers: the backing, which is usually a piece of flexible polymer; the adhesive layer, which also contains

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the API; and the protective release liner, which is removed before the delivery system is used. The fact that TDS is not designed to release the API(s) in aqueous media makes the sample preparation for a DIAM system difficult. The conventional procedures designed for the common dosage forms such as tablets or capsules will not work. The tackiness of the system makes the sample preparation even more difficult because it will readily attach to the container or fold up on itself potentially resulting in poor recovery.

In this article, we report a simple but effective sample preparation method for the DIAM system. The procedure is a one-step extraction using methanol/water as sample solvent and utilizes a reciprocating shaker to provide agitation. We also demonstrate the use of factorial experimental designs to optimize four method factors including sample solvent strength, sample solvent volume, shaking speed, and shaking time. Compared with one-factor-at-a-time experiments, a factorial experiment is more efficient in multi-factor optimization. More importantly, when the multiple independent variables of a method will generate a maximum point (an optimized condition), the one-factor-at-a-time experiments can easily miss the optima, whereas the factorial experiments will give a combination near the maximum [8]. In this study, we report a two-step optimization process. First, a 10-experiment set Plackett–Burman design was used to screen the four operating factors. This type of design is called the fractional factorial design [9], and has been used elsewhere in method development and validation [10–16]. Plackett–Burman designs are often used to screen a number of factors using a relatively small number of experiments to identify the factors that have the greatest effect on the response variables. In the second step, a 4×5 general factorial design was used to allow for a more detailed examination of two chosen factors.

2. Experimental

2.1. Chemicals and reagents

HPLC-grade methanol was purchased from EM Science (An affiliate of Merck KGaA, Darmstadt, Germany). HPLC-grade equivalent water was obtained from an in-house Millipore Milli-Q-Gradient ultrapure water system (Millipore, USA). This study also involves a proprietary Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) compound, which is identified as API_J&J, and a proprietary transdermal product, which is identified as DIAM_J&J.

2.2. Apparatus

A 4-oz straight-sided round, wide-mouth glass jar (70 mm height $\times$ 50 mm i.d.) with 0.030 mm PTFE disc-lined cap was used as the container for sample preparation. A reciprocating shaker (Model HS501, IKA Works, USA) with a stroke length of 3 cm was used to provide agitation in sample preparation.

2.3. Sample preparation method

Solutions for each DIAM_J&J system were prepared by carefully placing one sample into a 4-oz wide-mouth glass jar, making sure that the adhesive-side faces up and does not attach to the wall of the jar. Subsequently, 25.0 mL of sample solvent (70% methanol, unless otherwise specified) was added to the jar via pipette and the jar capped tightly. Next (immediately after solvent addition) samples were placed on a reciprocating shaker at a frequency of 150 rpm for 3 h (unless otherwise specified). After the shaking was completed, samples from each glass jar were immediately transferred into HPLC vials for sample analysis.

2.4. Computer software

Minitab, the statistical software, was purchased from Minitab Inc. (State College, PA, USA).

2.5. HPLC analysis of samples

A Waters (Milford, MA) Alliance HPLC system equipped with a photodiode array detector was used for the sample analysis. The Waters Millennium32 software was used to acquire, store, and process the chromatographic data and to report results. All chromatographic runs were performed using a Supelco (Bellefonte, PA, USA) Discovery® RP Amide C16 column (4.6 mm $\times$ 250 mm, 5 μm particle size) and water (A) and acetonitrile/methanol (50/50, B) mobile phases. The gradient elution was programmed to start with 45% and end with 68% B in 23 min with no holding time at a flow rate of 1.0 mL/min. UV detection at 220 nm, column temperature of 40 °C, and an injection volume of 25 μL were used in the method.

3. Results and discussion

3.1. Selection of extraction method and solvent system

Two different approaches were considered for sample preparation of the DIAM_J&J system. In one approach the adhesive layer was dissolved in hexane. Then a liquid–liquid extraction step is performed using methanol and water. An aliquot of the aqueous phase was then used for HPLC analysis. One of the major disadvantages of this approach is that the drug delivery system self-folds as soon as it is in contact with hexane, which can cause incomplete recovery of the API. Additional measures had to be taken to prevent this from happening, which had the potential of introducing contaminants. The second approach, which is the topic of this article, was to use an aqueous solvent to extract the API without dissolving the adhesive layer. This approach is based on the fact that the API has very limited solubility in the adhesive phase and the adhesive layer is relatively thin, which will allow the API to diffuse into the extraction solvent in an acceptable time