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Short communication

Application of pressurized liquid extraction technology to pharmaceutical solid dosage form analysis

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Abstract

The technique of pressurized liquid extraction has been evaluated for the extraction of active ingredients from pharmaceutical dosage forms using montelukast sodium oral chewable tablets as a model. The extraction method was optimized for the number of extraction cycles, extraction time, extraction solvent composition and temperature. Samples were extracted using two cycles of water for 2 min with a cell temperature of 40 °C and a pressure of 1.0×10^4 kPa, to disintegrate the tablet, followed by three cycles of methanol for 3 min at 70 °C and 1.0×10^4 kPa, to solubilize montelukast sodium. The method demonstrated an extraction efficiency of 98.2% of label claim and an RSD of 1.3% ($n=10$), as compared to 97.6% and an RSD of 0.9% obtained using a validated mechanical extraction method.

Keywords: Pressurized liquid extraction; Extraction method; Pharmaceutical analysis; Montelukast sodium

1. Introduction

The most common approach for tablet formulation sample preparation is either to grind the tablets to a powder and then mechanically agitate an aliquot of the powder with a suitable solvent or to allow the tablets to disintegrate in water for a period of time, prior to the extraction step. The extraction is achieved by liquid extraction and is usually accelerated by mechanical manipulation. The operation is performed manually and is often time-consuming. With the demand for increased productivity, faster analysis times and reduced solvent usage, there is an increased trend towards automating these labor-intensive activities, using robotic tablet processing workstations [1,2]. These systems offer complete automation of the sample preparation process with the possibility for on-line or off-line quantitation. Several alternate sample extraction techniques are also being developed that offer selective extraction of analyte from the sample matrix, increased speed, reduced solvent usage and potential for automation [3–6]. They include supercritical fluid extraction (SFE), microwave-assisted extraction (MAE) and pressurized liquid extraction (PLE). PLE, while similar in approach to SFE, uses solvents, rather than a supercritical fluid, at elevated temperatures and pressures for extraction of selected components from solid or semi-solid samples. PLE is used widely in environmental [7,8], herbal [9] analyses and in the

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dairy/food industry [10]. However, many of the features of PLE make it attractive for potential use in pharmaceutical laboratories [11].

In this study, PLE was evaluated using the extraction of montelukast sodium, an LTD4 antagonist indicated for control of asthma, from oral chewable tablets as a model. The effects of the number of extraction cycles, extraction time, solvent composition and temperature on recovery of montelukast sodium from the tablet matrix were studied. The PLE method was used for the determination of content uniformity of montelukast sodium in chewable tablets and the results were compared to those obtained with a validated method using mechanical extraction.

2. Experimental

2.1. Instruments

Pressurized liquid extractions were performed using a model ASE 200 instrument from Dionex (Sunnyvale, CA, USA), equipped with an ASE 200 solvent controller and integrated collection unit with 26 collection vial positions. Stainless steel (22-ml) extraction cells and 40-ml amber collection vials were used throughout the study. Quantitative analysis of montelukast sodium in PLE extracts was carried out using a HP1050 Series HPLC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a quaternary pump operated at 0.9 ml/min, an autosampler with injection volume of 10 μl, a variable wavelength UV detector set at 389 nm and a temperature-controlled column compartment maintained at 50 °C. An Inertsil phenyl column, 5 μm, 100×3.0 mm I.D. (Ansys Technologies, Lake Forest, CA, USA) and water–acetonitrile (50:50, v/v) modified with 0.2% trifluoroacetic acid as mobile phase were used. Multichrom version 2.1-1 (Thermo LabSystems, Cheshire, UK) was used to collect the chromatographic data.

2.2. Materials

Omnisolve acetonitrile and methanol, HPLC grade (EM Science, Gibbotown, NJ, USA), trifluoroacetic acid (TFA), sequanal grade (Pierce, IL, USA) and Milli-Q water were used.

Standard solutions of montelukast dicyclohexyl amine salt (DCHA), from Merck (Rahway, NJ, USA) were prepared in water–methanol (25:75, v/v) at a concentration of 0.025 mg/ml. Montelukast sodium 5 mg oral chewable tablets were used as the model pharmaceutical dosage form in this study.

2.3. Procedures

A typical PLE sequence consists of loading the sample in an extraction cell, preheating the cell for 5 min, filling the extraction cell with solvent, heating and pressurizing the cell, adding fresh solvent to the cell and finally purging of the solvent from the cell using nitrogen gas. Throughout the study, the solvent volumes were kept at 60% of the extraction cell volume and divided among the cycles if more than one cycle was specified. A volume of 13.2 ml, 6.6 ml or 4.4 ml of the fresh solvent was flushed through a 22-ml cell when one, two or three extraction cycles, respectively, was selected. The content of the collection vials was transferred into a volumetric flask and diluted to volume with methanol. An aliquot of this solution was centrifuged at 14,000 rev./min for 5 min prior to analysis. Each result reported for the method development phase was the mean of at least three sample preparations.

For comparison, the same lot of tablets was analyzed with a validated method using mechanical assisted extraction. One intact tablet was transferred into a volumetric flask and allowed to completely disintegrate in 50 ml water. The flask was then filled to 80% of its volume with methanol, mechanically agitated for 60 min, cooled to room temperature and diluted to volume with methanol. An aliquot of the sample solution was then centrifuged at 14,000 rev./min for 5 min prior to injection onto the column.

3. Results and discussion

Preliminary extraction experiments were performed with the samples loaded into the cells as either an intact tablet or ground tablet powder with 50%, 75% and 100% (v/v) of methanol in water as the extraction solvent. The ground tablet samples were prepared by grinding a number of tablets to a fine powder and an aliquot of the powder equivalent

to one tablet mass was weighed into an extraction cell. The extractions were initially performed using one 5-min extraction cycle with the cell temperature maintained at 40 °C and the pressure at 1.0×10^4 kPa. The results are summarized in Fig. 1.

Highest recoveries of montelukast sodium were obtained with ground tablets using 75% and 100% methanol as the extraction solvent. The recovery of montelukast sodium from the intact tablets was highest using 50% methanol as the extraction solvent. Tablets did not disintegrate when the extraction was performed with 75% and 100% methanol in water, while they did disintegrate in the cells using 50% methanol. Additional experiments were performed using a two-step process where water was used to disintegrate the tablet, followed by the addition of methanol to solubilize montelukast sodium. Due to limitations in the instrument design, multiple extractions using different extraction solvents on the same sample cell in a single method is not feasible. It was necessary to run two methods on the same sample cell and collect the resulting extracts in separate vials. The samples were subjected to either one cycle of water for 5 min or two cycles of water for 2 min to disintegrate the tablet, followed by one extraction cycle of methanol for 5 min. The temperature and the pressure of the cells were maintained at 40 °C and 1.0×10^4 kPa. The extracts from the water cycle (~17% of label claim of montelukast sodium recovered) and methanol cycle were combined and diluted to volume with methanol. The results showed a mean recovery of 89% of label claim, independent of whether the tablets were disintegrated with one cycle for 5 min or two cycles for 2 min. The data compare favorably with 83% of label claim obtained with extraction of the ground tablet using methanol as the extraction solvent (Fig. 1). As a result, further experiments were carried out using intact tablets and two water cycles for 2 min. Experiments were designed to optimize the number of methanol extraction cycles, the extraction time, the extraction solvent composition and temperature.

3.1. Number of extraction cycles and extraction time

To study the effect of the number of extraction cycles and extraction time on recovery of montelukast sodium from the tablet matrix, experiments were performed using two cycles of water for 2 min followed by one, two or three extraction cycles of methanol for 3 or 5 min. The data are shown in Fig. 2. Separating the extraction step into two or more cycles improves the extraction efficiency since it allows fresh solvent to be introduced into the cell and maintains a favorable solvent/sample equilibrium. However, increasing the extraction time from 3 to 5 min and the number of extraction cycles to three had little or no effect on the recovery.

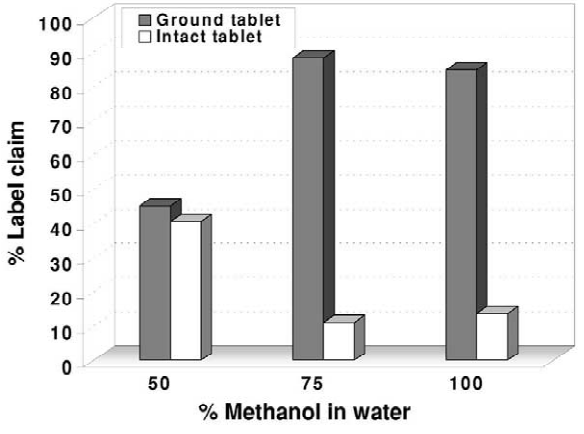

Fig. 1. Effect of extraction solvent composition on recovery of montelukast sodium from various sample preparations.

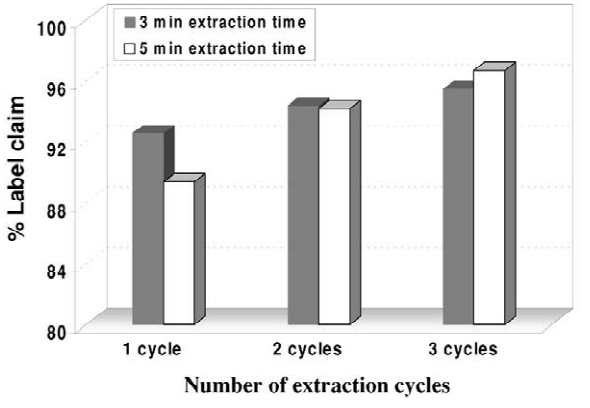

Fig. 2. Effect of number of extraction cycles and extraction time on recovery of montelukast sodium from intact tablets.

3.2. Extraction solvent composition

The effect of extraction solvent composition on the recovery was studied using three extraction cycles of 3 or 5 min and 100%, 75% and 50% (v/v) methanol in water as the extraction solvent (Fig. 3). Methanol (100%) provided the highest recovery of montelukast sodium. The results showed no significant differences in the recoveries of montelukast sodium when using an extraction time of 3 or 5 min.

3.3. Effect of temperature

The effect of cell temperature on the recovery of montelukast sodium was studied at 40, 50, 70 and 100 °C, using three extraction cycles of 3 min and methanol as the extraction solvent. Since montelukast sodium is thermally unstable in solution, montelukast sodium degradate levels were also monitored. Elevated temperatures increase montelukast sodium solubility and also increase its desorption kinetics from the tablet matrix by decreasing the viscosity of the solvent. Best recoveries were obtained at 70 °C without significant increase in montelukast sodium degradate levels.

3.4. Determination of content uniformity of montelukast sodium in chewable tablets

The optimized PLE procedure was used to determine the content uniformity of montelukast sodium in chewable tablets. Individual tablets were disintegrated in water using two cycles of 2 min at 40 °C and 1.0×10^4 kPa, followed by an extraction with methanol using three cycles of 3 min at 70 °C and 1.0×10^4 kPa. For comparison, the tablets were also analyzed with a validated method using mechanical extraction. The PLE method gave a mean recovery of 98.2% of label claim and an RSD of 1.3% ($n=10$), which compares favorably with 97.6% and RSD of 0.9% ($n=10$) obtained with the procedure using mechanical extraction. The comparison reflects not only differences in extraction procedure but also small differences in the tablet populations used.

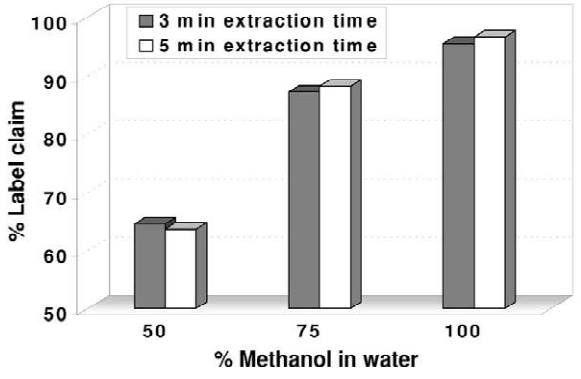

Fig. 3. Effect of extraction solvent composition on recovery of montelukast sodium from intact tablets.

4. Conclusion

The technique was demonstrated to be suitable for the extraction of montelukast sodium from intact chewable tablets. The future application of PLE may be extended to other pharmaceutical dosage forms and perhaps shows most promise for formulations where drug extraction efficiency is problematic using conventional extraction techniques. However, to handle a large number of samples efficiently and for the technique to compete effectively in the marketplace with other tablet automated sample preparation systems, design changes to the current equipment will be necessary. The current system is only capable of processing a maximum of 24 samples at a time. Sample throughput could be improved by (1) increasing the number of sample cells, (2) processing the samples simultaneously rather than sequentially and (3) eliminating/minimizing post-extraction manipulation of sample extract by providing the capability to customize multiple extractions and collection of resulting extracts.

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