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THE MICROWAVE-ASSISTED SOLVENT EXTRACTION OF PROPRANOLOL FROM TABLETS

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ABSTRACT

A rapid alternative technique for the extraction of propranolol from tablets is reported. Traditionally, propranolol has been extracted using sonication, but this has proved to be significantly solvent consuming. In this study, propranolol has been extracted successfully from tablets using an optimised microwave-assisted solvent extraction (MASE) method. The optimum conditions for MASE for this application were: extraction solvent, methanol; extraction time, 45 s (5 s heat and 40 s cool); and extraction solvent volume, 5.00 mL. The recovery of propranolol from tablets by the optimised MASE method was 89.8% with a RSD of 3.7%. This performance was acceptable and comparable with sonication. The determination and identification of the extracts was performed using high-performance liquid chromatography with ultraviolet detection at 290nm. A domestic microwave oven was used for the study, because an industrial MASE apparatus was uncompetitive with sonication with respect to extraction time due to the amount of time required to cool the sample following microwave heating. Safety considerations for domestic microwave ovens are discussed, including the use of a novel two-vial sample cell.

Keywords: High-performance liquid chromatography, microwave-assisted solvent extraction, propranolol, sonication, tablets.

INTRODUCTION

One use of microwaves presently being studied is as a rapid heat source for the solvent extraction of soluble organic substances from insoluble matrices. The sample and solvent are contained together in a closed, non-metallic extraction vessel housed inside the microwave oven. Polar solvent molecules become excited by the microwave radiation and rotate faster, generating heat (Chang, 1998). Consequently, the solvent warms up much more quickly than in conventional heating. Furthermore, a higher temperature liquid has more solvating power, so accelerating the desorption of solute molecules from the sample surface, and lower viscosity, so improving solvent penetration into matrix pores. The resultant higher pressure also facilitates solvent penetration, and keeps the solvent safely below its boiling point. Consequently, less solvent may be required to extract the same amount of material and extraction can be faster. Solute recovery can also be improved compared to conventional solvent extraction.

Conventional solvent extraction methods can have major disadvantages, such as the use of significant amounts of toxic and corrosive organic solvents. Many organic solvents are expensive to buy and dispose of, as well as posing an environmental health hazard. Consequently, microwave-assisted solvent extraction (MASE) is proposed as an alternative with the potential advantage of the reduced use of hazardous solvents. For such exploitation in chemical analysis, the extraction should ideally be quantitative, reproducible, efficient, and compare favourably with existing extraction methods.

Medicinal drugs in tablets are routinely extracted as part of quality control programmes in the pharmaceutical industry. Pharmaceutical companies prepare tablets dosed with drug at a known concentration. Dosed drugs are then extracted to confirm the level of inclusion. In this regulated environment, a recovery of greater than 90% and a relative standard deviation (RSD) of less than 5% is required.

Microwave-assisted solvent extraction has already seen some use for pharmaceutical applications. As an illustration, Labbozzetta *et al.* (2005) extracted naproxen from suppositories and found advantages over conventional methods. Woźniakiewicz *et al.* (2008) extracted tricyclic antidepressants from human serum quantitatively and reproducibly. There have only been a few reports in the chemical literature of the MASE of drugs from tablets. Eskilsson *et al.* (1999) reported the MASE of felodipine and its degradation product from tablets. Average recoveries were just below 100% and competitive with a validated ultrasonication method. Interestingly, the MASE method could be used successfully without the need for reducing the tablet to a powder. This was achieved by using a 5% methanol in

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acetonitrile extraction solvent. Methanol dissolved the outer covering layer and acetonitrile made the inner matrix swell, fragmenting the tablet into small pieces, and releasing the analytes. Eight years later, Hoang *et al.* (2007) applied MASE to the extraction of active pharmaceutical ingredients from solid dosage forms including tablets. They found that MASE gave results comparable with validated mechanical extraction procedures. In the same year, Lee *et al.* (2007) compared MASE, accelerated solvent extraction, and Caliper Life Sciences Tablet Processing Workstation II with a conventional manual extraction method for the extraction of a compound from spray dried dispersion tablet formulations. They found that all three modern extraction methods were faster than the traditional method. More specifically, MASE was slower than the Tablet Processing Workstation II, but gave a higher recovery than accelerated solvent extraction. A year later, Nickerson *et al.* (2008) also found that these same three modern extraction methods gave significantly reduced sample preparation times compared to the standard method for the extraction of active pharmaceutical ingredients from controlled release tablet formulations.

This study describes a MASE method to recover the well-known beta-blocker propranolol (as the hydrochloride) from tablets quantitatively and reproducibly. Propranolol is used to treat hypertension (Windholz, 1976). Sonication, the existing extraction method, uses significant amounts of methanol, a toxic organic solvent. It is anticipated that MASE may consume less solvent and complete the extraction faster. Quantitation was by high-performance liquid chromatography (HPLC) with ultraviolet detection at 290nm**.**

MATERIALS AND METHODS

Instrumentation, reagents and standards

The industrial microwave apparatus was purchased from Milestone, Sorisole, Italy. The domestic microwave oven was manufactured by Bosch, England, UK. An ultrasonic bath was obtained from JAC, Kodo, Japan. The HPLC instrument was procured from Dionex, Germering, Germany. The propranolol hydrochloride tablets (40 mg per 200 mg tablet) were produced by AstraZeneca, Macclesfield, UK and obtained from Sultan Qaboos University Hospital Pharmacy. Pure propranolol hydrochloride (99%), methanol (HPLC grade), and ethanol (HPLC grade) were obtained from Sigma Aldrich, Steinheim, Germany. The ammonium formate (99.995%+) was procured from Sigma Aldrich, St. Louis, MO and trifluoroacetic acid (TFA) (99.9%) was purchased from Panreac, Barcelona, Spain. The deionised water used in some of the extraction solvents and HPLC mobile phase was produced in-house by passing tap water through a TKA DI 800 mixed-bed water demineraliser (Niederelbert, Germany).

Sample preparation

Twenty pink tablets of propranolol hydrochloride were weighed and ground using a pestle and mortar to give a pinkish powder. The powdered tablets were cone and quartered until an appropriate amount was left for use as a sub-sample.

Microwave-assisted solvent extraction with an industrial microwave apparatus

About 100mg of sample were weighed accurately (±0.1mg) into a Teflon extraction vessel, followed by 15.00mL of methanol and a magnetic stir bar. A reference vessel, used for temperature control, was also assembled. The vessels were put inside the microwave irradiation chamber. The power was set to 1000W and the heating cycle was 5 min at 80^{o}C and 1 bar. Once the extraction programme was completed, high temperature and pressure were reached inside the vessels, so it was necessary to cool them down for 30 min before opening them. Once the vessels had cooled to room temperature, the extract was filtered through Whatman paper #1 and diluted to 25.00mL with methanol. Then, 5.00mL of that solution was diluted to 10.00mL with methanol ready for analysis by HPLC. The extractions were performed in triplicate.

Microwave-assisted solvent extraction with a domestic microwave oven

Sample (33.3mg) was weighed directly and accurately (±0.1mg) into a tared 9.50mL hinged-lid vial (EP290 Polyvial®, LA Packaging, Yorba Linda, CA). Using a micropipette, 2.50, 3.75, or 5.00mL of extraction solvent were added to the sample. The lid was snapped shut and the vial shaken and placed inside a 50mL polypropylene centrifuge tube from Bibby Sterilin, Stone, UK. The cap was screwed on to the centrifuge tube. The two-vial system was then put inside the microwave oven and heated at 600W for 5 s. Then, it was removed from the oven, the screw cap of the outer tube removed, the tube inverted and the smaller, inner vial removed and placed upright in an ice-salt bath for 40 s. For a 90 s extraction time, this heating and cooling procedure was repeated once more. The resulting extract was filtered by pouring into a 5mL plastic syringe (Terumo, Leuven, Belgium) attached to a 13 mm diameter, 0.2-µm pore size filter unit (Schleicher and Schuell, Dassel, Germany) with a small glass sample tube underneath. The plunger of the syringe was pressed down. The filtered extracts were then ready for analysis by HPLC. The extractions were performed in triplicate.

Safety considerations for the domestic microwave oven

The industrial microwave apparatus has built-in safety features, such as sensors for monitoring temperature and pressure, and for the detection of solvent leaks. The domestic microwave oven, however, does not.

Consequently, a careful and considered approach needs to be adopted when using the latter apparatus for extraction purposes with flammable organic solvents.

One safety measure used in this study was to place a 9.50mL vial containing the tablet sample and extraction solvent inside a 50-mL tube. This step exploits Boyle's law (Zumdahl and Zumdahl, 2007). If the pressure inside the smaller, inner vial becomes dangerously high during microwave heating, the hinged lid pops open. The larger volume of the screw-capped outer tube causes a decrease in the pressure, allowing the analyst time to switch off the oven before the pressure rises again to dangerous levels. This two-vessel arrangement also prevents vapours of flammable organic solvents entering the heating chamber.

Another precaution taken in this study was the use of a weighted clear plastic safety shield in front of the oven during the extractions. The shield was obtained from Aldrich, Steinheim, Germany.

Sonication

The sonication extraction method was that used by Shinde *et al.* (1993). About 200 mg of the powdered propranolol tablets were weighed accurately (±0.1mg) and transferred to a 50.00 mL volumetric flask. Then, 30.00 mL of methanol was added and the flask kept in an ultrasonic water bath at 22ºC for 5 min and finally diluted to the mark with methanol. The solution was filtered through Whatman paper #1 ready for analysis by HPLC. The extractions were performed in triplicate.

High-performance liquid chromatography

Quantitation was by isocratic HPLC using a method developed by Law and Appleby, (1996). A 15cm × 4.6mm i.d. strong cation-exchange column (Hichrom, Reading, UK) was employed to separate the components in the extracts. The mobile phase was 0.02 *M* ammonium formate in methanol-water (80:20, v/v). The pH of the mobile phase was adjusted to 2.45 by the addition of TFA. The mobile phase was pumped at a flow rate of 1 mL/min by a Dionex P580 pump. In order to facilitate the introduction of sample solutions into the HPLC system, a Rheodyne 8125 injection valve (Cotati, CA) fitted with a 20µL loop was needed. The loop was flushed with 100µL of sample solution immediately prior to injection. A Dionex UVD170S ultraviolet detector was used to quantify and confirm the presence of propranolol in the extracts and was set at 290nm. A DTK Pentium III computer loaded with the Dionex Chromeleon Chromatography Information Management System Software was used to observe the detector response and provide quantitative data. The peak for propranolol appeared at about 8.3 min.

RESULTS AND DISCUSSION

An industrial MASE apparatus was considered first for the extraction of propranolol from tablets. The initial experiment gave the following promising result: 84.0 ± 3.6% (n = 3). Its use was, however, curtailed because of the long cooling stage required (30 min) that made the process uncompetitive with sonication with respect to extraction time. Consequently, attention was switched to a domestic microwave oven, and the subsequent reduction in scale, where cooling time was much faster (40 s).

In this study with the domestic microwave oven, three different variables were optimised: extraction solvent, extraction solvent volume, and extraction time.

Optimisation of extraction solvent

Four different extraction solvents were used: methanol, ethanol, ethanol-aqueous 1 *M* TFA (96.2:3.8, v/v), and 0.02 *M* ammonium formate in ethanol-water (80:20, v/v). This final extraction solvent was adjusted to pH 2.45 by the addition of TFA. Ethanol and ethanol-based extraction solvents were tried as less hazardous alternatives to methanol and methanol-based ones. Methanol-aqueous 1 *M* TFA (96.2:3.8, v/v) has been used to extract propranolol successfully from rodent food (Williams *et al.*, 1996). A solution of 0.02 *M* ammonium formate in methanol-water (80:20, v/v) at pH 2.45 is a successful HPLC mobile phase for the separation of propranolol (Law and Appleby, 1996).

The average recoveries of propranolol from tablets were very close to 90% for each of the four extraction solvents (Table 1). Analysis of variance (Morgan, 1991) showed that there was no significant difference at the 5% probability level between recoveries of propranolol using the four different extraction solvents. Methanol was chosen as the optimum extraction solvent of the four, because it gave the best precision (lowest RSD). In addition, it was the cheapest of the four extraction solvents. Furthermore, it did not require any time-consuming preparation, unlike ethanol-aqueous 1 *M* TFA (96.2:3.8, v/v) and 0.02 *M* ammonium formate in ethanol-water (80:20, v/v).

Table 1. Recoveries by MASE of propranolol from tablets using different extraction solvents. Solvent volume, 5.00 mL; extraction time, 90 s; number of replicates, 3.

Extraction solvent	Recovery ± RSD (%)
Methanol	88.5 ± 1.2
Ethanol	89.3 ± 5.6
Ethanol-aqueous 1 *M* TFA (96.2:3.8, v/v)	87.9 ± 7.1
0.02 *M* ammonium formate in ethanol-water (80:20, v/v) at pH 2.45	89.3 ± 4.8

Optimisation of extraction solvent volume

Three volumes of methanol were studied: 2.50mL, 3.75mL, and 5.00mL. It was found that 5.00mL gave the highest average recovery of the three volumes tried (Table 2). Furthermore, average recovery increased steadily with increasing extraction solvent volume. This inferred that the highest volume of the solvent gave the greatest solubility of the drug. Volumes of extraction solvent greater than 5.00mL may have given higher recoveries, but solvent volume was limited to 5.00mL by the equipment used. Larger volumes of solvent increased the frequency of the inner vial popping open.

Table 2. Recoveries by MASE of propranolol from tablets using different volumes of extraction solvent. Solvent, methanol; extraction time, 90 s; number of replicates, 3.

Extraction solvent volume (mL)	Recovery ± RSD (%)
2.50	74.8 ± 1.6
3.75	78.9 ± 2.7
5.00	82.7 ± 1.8

Optimisation of extraction time

The last variable to be investigated was extraction time. Two times were tried: 45 and 90 s. It was found that the average recovery of propranolol was greater when extracting for 45 s (91.3 ± 3.6%) than for 90 s (88.7 ± 3.6%). The *t*-test (Morgan, 1991) at $P = 0.05$ showed that there was no significant difference between the recovery of propranolol at the two different times. In both cases, recoveries were about 90% and the RSDs were an acceptable 3.6%. Consequently, 45 s was chosen as the optimum extraction time.

In summary, the optimum extraction conditions for MASE were extraction solvent, methanol; solvent volume, 5.00mL; and extraction time, 45 s.

There was some variation of recovery by MASE from experiment to experiment given the same extraction conditions. As an illustration, the following recoveries and RSDs were obtained when methanol was the extraction solvent, extraction time was 90 s, and extraction solvent volume was 5.00mL: 88.5 ± 1.2% (Table 1), 82.7 ± 1.8% (Table 2), and 88.7 ± 3.6% (Optimisation of extraction time). The 82.7% result is significantly lower than the 88.5 and 88.7% recoveries at the 5% probability level. This was presumably because an external standard was used during the study. The use of an internal standard, such as atenolol, may have given better reproducibility from experiment to experiment.

Comparison of MASE with sonication

The optimised MASE method was compared with the literature technique, sonication, for the extraction of propranolol from tablets. It was found that sonication gave significantly higher recovery of the drug from the tablets at the 5% probability level and better precision (as measured by RSD), but recovery by MASE and its associated precision were acceptable (Table 3). Furthermore, MASE gave a faster extraction and used less extraction solvent and sample.

Table 3. Comparison of MASE with sonication for the extraction of propranolol from tablets. Number of replicates, 3.

Variable	MASE	Sonication
Recovery (%)	89.8	99.5
RSD (%)	3.7	0.5
Solvent volume (mL)	5.00	30.0
Extraction time (s)	45	300
Sample size (mg)	33.3	200.0

CONCLUSIONS

It can be concluded that MASE is a viable alternative to the conventional extraction method for the recovery of propranolol from tablets. It has been shown that MASE recovery and precision data were acceptable. In addition, MASE was significantly faster and used less solvent than sonication. Propranolol recovery by MASE was significantly lower than by sonication. To improve recovery by MASE, it is suggested for the future that the volume of extraction solvent be increased. To overcome the problem of vial popping when using larger volumes of solvent with the present sample cell arrangement, larger volume inner vials can be purchased. Another suggestion is to increase microwave power from the present 600 W to, for example, 1000 W. The use of greater power should heat the extraction solvent faster, producing a higher temperature solvent in the sample vial for the same extraction time. Since solubility is usually greater at higher temperature, one might reasonably expect greater recovery of propranolol from the tablet. In addition to use as a sample pre-treatment step in pharmaceutical industry quality control programmes, the MASE method described in this study could also be applied successfully to student laboratory classes. The use of a novel two-vial sample cell has allowed safe use of the domestic microwave oven. Furthermore, the domestic microwave oven has been demonstrated to be advantageous compared to an industrial extractor for applications where the extraction time is relatively short. A univariate approach was taken in this study. This cautious approach was adopted, because it was unknown in advance whether the results would be reproducible since sample size was modest and the experiments were performed on a small scale. It was found that recoveries were generally reproducible despite the small scale used. Armed with this knowledge, it can be proposed that a full- or fractional-factorial approach

could also be applied to the MASE of propranolol from tablets successfully. Chemometrics is not a panacea though. Poor reproducibility with an experimental design approach can lead to anomalous results and wrong conclusions being made.

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REFERENCES

Chang, R. 1998. Chemistry. p. 382-383. McGraw-Hill, New York, N.Y.

Eskilsson, CS., Bjorklund, E., Mathiasson, L., Karlsson, L. and Torstensson, A. 1999. Microwave-assisted extraction of felodipine tablets. Journal of Chromatography A. 840:59-70.

Hoang, TH., Sharma, R., Susanto, D., Di Maso, M. and Kwong, E. 2007. Microwave-assisted extraction of active pharmaceutical ingredient from solid dosage forms. Journal of Chromatography A. 1156:149-153.

Labbozzetta, S., Valvo, L., Bertocchi, P. and Manna, L. 2005. Focused microwave-assisted extraction and LC determination of the active ingredient in naproxen-based suppositories. Journal of Pharmaceutical and Biomedical Analysis. 39:463-468.

Law, B. and Appleby, JRG. 1996. Re-evaluation of strong cation-exchange high-performance liquid chromatography for the analysis of basic drugs. Journal of Chromatography A. 725:335-341.

Lee, C., Gallo, J., Arikpo, W. and Bobin, V. 2007. Comparison of extraction techniques for spray dried dispersion tablet formulations. Journal of Pharmaceutical and Biomedical Analysis. 45:565-571.

Morgan, E. 1991. Chemometrics: Experimental Design. Wiley, Chichester, UK.

Nickerson, B., Arikpo, WB., Berry, MR., Bobin, VJ., Houck, TL., Mansour, HL. and Warzeka, J. 2008. Leveraging elevated temperature and particle size reduction to extract API from various tablet formulations. Journal of Pharmaceutical and Biomedical Analysis. 47:268-278.

Shinde, VM., Desai, BS. and Tendolkar, NM. 1993. Simultaneous determination of propranolol hydrochloride and hydrochlorothiazide in tablets by quantitative TLC. Indian Drugs. 31:192-196.

Williams, JR., Morgan, ED. and Law, B. 1996. Comparison of supercritical, subcritical, hot, pressurized and cold solvent extraction of four drugs from rodent food. Analytical Communications. 33:15-17.

Windholz, M. 1976. The Merck Index. Merck, New Jersey, USA. pp 1016.

Woźniakiewicz, M., Wietecha-Posłuszny, R., Garbacik, A. and Kościelniak, P. 2008. Microwave-assisted extraction of tricyclic antidepressants from human serum followed by high performance liquid chromatography determination. Journal of Chromatography A. 1190:52-56.

Zumdahl, SS. and Zumdahl, SA. 2007. Chemistry. Houghton Mifflin, New York, USA. 181-184.

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