Available online at www.sciencedirect.com
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 45 (2007) 565–571
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Comparison of extraction techniques for spray dried dispersion tablet formulations

Carlos Lee [a,*], Jenny Gallo [b], William Arikpo [a], Vincent Bobin [a]

[a] *Analytical Research and Development, Pfizer Global Research and Development, Eastern Pt. Road, Groton, CT 06340, USA*
[b] *Department of Chemistry, Michigan State University, East Lansing, MI 48825, USA*

Received 29 May 2007; received in revised form 2 August 2007; accepted 2 August 2007
Available online 15 August 2007

Abstract

Non-traditional sample preparation/extraction techniques that utilized the Caliper Life Sciences Tablet Processing Workstation II (TPW II), Microwave Assisted Extraction (MAE), and Accelerated Solvent Extraction (ASE) were evaluated for the extraction of Compound A from a 50 mgA, 15% Spray Dried Dispersion (SDD) immediate released (IR) tablet formulation. The TPW II consistently provided complete recoveries with very short preparation/extraction times (~30 min). MAE also provided complete recovery of the API from the tablet formulation, but required approximately twice the extraction time, while ASE provided the lowest recovery of the three non-traditional techniques. The sample preparation/extraction efficiencies of the three non-traditional techniques were compared to that of the 5.5 h long manual method.

Keywords: Tablet Processing Workstation, TPW; Microwave Assisted Extraction, MAE; Accelerated Solvent Extraction, ASE; Extraction; Sample preparation; Automated; Spray Dried Dispersion; Low potency

1. Introduction

Development of suitable, robust, and efficient sample preparation/extraction procedures for solid oral dosage formulations has and continues to be a challenge for analytical chemists. The development of solubility enhancing formulations and/or controlled released formulations such as Spray Dried Dispersions further adds to the analytical complexity, due to the gelling effects of the polymers used in these types of formulations. Hydroxypropyl cellulose, HPC, and hydroxypropyl methyl cellulose, HPMC, which are often used in Spray Dried Dispersion formulations, are known to gel in the presence of various solvents, including water. This gelling can trap the active pharmaceutical ingredient, API, within the tablet matrix, affecting recovery [1,2]. Conventional sample preparation/extraction approaches involving techniques such as sonication and mechanical shaking are often inadequate to efficiently and quantitatively extract the API from the drug product matrix [3]. The need for the development of non-tradition, automated, efficient, and robust sample preparation/extraction techniques for solid oral dosage forms, especially those involving Spray Dried Dispersions and other complex formulations, are critical and necessary. The purpose of this research was to evaluate three non-traditional and automated sample preparation/extraction techniques for the extraction of Compound A active from a 15% Spray Dried Dispersion immediate released (IR) tablet formulation. The three non-traditional techniques investigated were the Zymark Tablet Processing Workstation II (TPW II), Microwave Assisted Extraction (MAE), and Accelerated Solvent Extraction (ASE). Compound A, a 50 mgA, 15% Spray Dried Dispersion tablet formulation in development at Pfizer, Inc was analyzed by the three non-traditional techniques and the sample preparation/extraction efficiencies compared to that of the 5.5 h manual sample preparation/extraction procedure.

2. Experimental

2.1. Compound A

Compound A is a 15% Spray Dried Dispersion tablet formulation under development at Pfizer, Inc., for the treatment of diabetes. The 50 mgA IR tablet formulation (900 mg

* Corresponding author. Tel.: +1 860 686 0339; fax: +1 860 686 5219.
E-mail address: Carlos.W.Lee@Pfizer.com (C. Lee).

0731-7085/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2007.08.011

tablet weight) was chosen because the current manual sample preparation procedure was very tedious, time-consuming and involved. An opportunity existed to reduce sample preparation/extraction time by utilizing non-traditional techniques. The aqueous solubility of the active in 0.1N NaOH is 0.97 mgA/mL and decreases significantly with decreasing pH (solubility in 0.1N HCl is 0.0004 mgA/mL). The active is very soluble in acetone (3.5 mgA/mL) and in acetonitrile (1.1 mgA/mL). The formulation composition of the tablet is as follows: Compound A (333.3 mg/tablet, 15% SDD); microcrystalline cellulose (324.8 mg/tablet); hydroxypropyl cellulose (45.0 mg/tablet); dibasic calcium phosphate (142.9 mg/tablet); crospovidone (45.0 mg/tablet); magnesium stearate (intra-granular) (4.5 mg/tablet); and magnesium stearate (extra-granular) (4.5 mg/tablet).

2.2. Manual sample preparation

The manual sample preparation procedure developed for this IR tablet formulation has a preparation time of approximately 5.5 h. A tablet is first weighed (∼900 mg) and transferred to a 250 mL volumetric flask. Approximately 25 mL of water is added and the sample is sonicated for 30 min. An additional 25 mL of water is added to the flask and the flask is shaken for 15 min. Acetonitrile (∼150 mL) is added and the flask is shaken for an additional 30 min, followed by sonication for 30 min. The flask is allowed to stand for 90 min, diluted to volume with acetonitrile and then mixed well with swirling and inversion. The resulting sample is sonicated for an additional 30 min and allowed to stand for 90 min. Prior to analysis by HPLC, the samples are filtered with Whatman® Autovial® syringeless filters with 0.45 μm PTFE membrane. The above procedure provides for 100% recovery of the API from the tablet matrix.

2.3. HPLC method conditions

All HPLC analysis was done on an Agilent 1100 HPLC system using a Waters Symmetry Shield RP8 column (4.6 × 150 mL, 3.5 μm). The mobile phase consisted of 57/23/20 (v/v/v) 0.2% $HClO_4$/ACN/MeOH (isocratic). The flow rate was 1.0 mL/min and UV detection at 210 nm was employed. All separations were performed at 35 °C. Injection volume was set at 15 μL. The run time was 25 min. A Whatman® Autovial® syringeless filter with 0.45 μm PTFE membrane was used to filter samples.

2.4. Caliper Life Sciences Tablet Processing Workstation II (TPW II)

The Caliper Life Sciences Tablet Processing Workstation II (TPW II, Caliper Life Sciences, Hopkinton, MA) is an automated bench-top workstation with total tablet assay sample preparation capability. The instrument is designed to automate sample preparation for solid samples, including feeds, blends, powders, capsules, and tablets. A pictorial representation of the system is shown in Fig. 1. The workstation consist of a dispersion/homogenization module, dispersion vessels, robotic arm, balances, sample tube racks, controller and software, solvent pumping system, filtration system and filters, dispersion syringes and valves, vortexer, and sample collection device. The TPW II allows for extraction of up to 100 samples with up to 10 different methods without human intervention. The driving force of the TPW II is its high shear wet grinding homogenizer for particle size reduction. It also has a vortexer for mixing samples following particle size reduction. The TPW II can be connected to an online HPLC system for injection analysis, making it a completely automated system. All data are captured in a Microsoft® Excel Spreadsheet for easy retrieval, providing a complete audit trail. Although the TPW II has been around for several years only a handful of publications could be found in the literature employing it as sample preparation/extraction tool [4–7]. This is very surprising, given the tremendous capability and potential of this fully automated extraction technique to reduce the most tedious and time-consuming part of the analytical process, sample preparation/extraction. A typical sample preparation procedure is shown below:

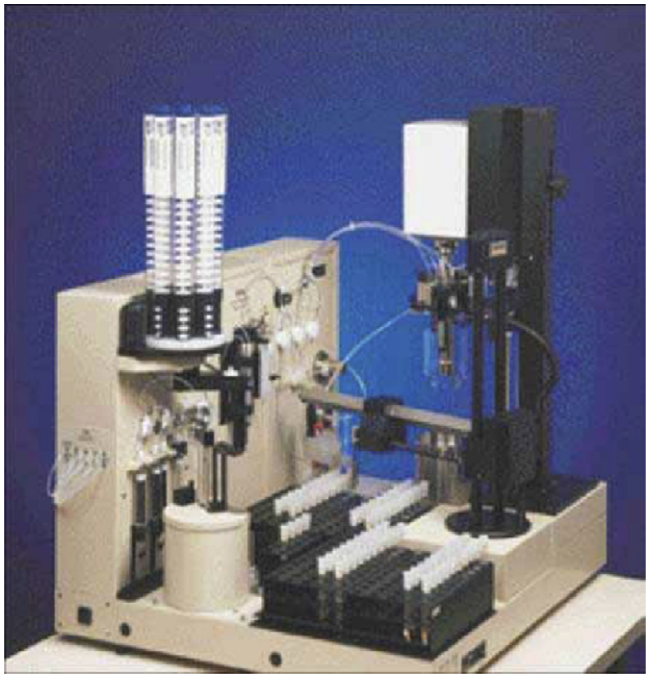

Fig. 1. Caliper Life Sciences Tablet Processing Workstation II.

- Sample and solvent delivered into dispersion vessel.
- Homogenization/particle size reduction (2 K–20 K rpm) and defined pulse length and number of pulses.
- Dilution and mixing.
- Filtration.
- Analysis (HPLC, UV) or collection.
- Cleanup for next sample.

2.5. Microwave Assisted Extraction (MAE)

Microwave Assisted Extraction is a partially automated sample preparation/extraction technique in which extraction solvents are rapidly heated to temperatures 2–3 times higher

than their atmospheric boiling points [8–10]. For example, acetonitrile, with an atmospheric boiling point of ~82 °C has a closed vessel boiling point of 194 °C at 175 psi [8]. This rapid, direct heating of the solvent medium is unique to MAE and leads to shorter sample preparation/extraction times and higher recoveries because of the direct relationship between temperature and solubility, and because of the reduction in solvent viscosity that comes with increasing temperature. Decreasing solvent viscosity leads to increase in diffusion and increase solvent/solute interaction. Additionally, because MAE allows for the sample to be stirred during the heating process, a more homogeneous solution is created and solvent/solute interaction is increased. Current MAE technology allows the operator to control the wattage, temperature, and length of time that goes into the extraction process. Temperature fluctuations are within ±2° and up 40 samples can be processed simultaneously with the CEM MARSExtractor system. Although only polar solvents are microwave absorbers, this drawback of MAE is not generally an issue for solid oral dosage forms, since typical extraction solvents such as acetonitrile, methanol, and water are polar in nature and excellent microwave absorbers. Only a handful of publications have surfaced in the literature utilizing MAE as a sample preparation/extraction tool for solid oral dosage forms. Eskilsson et al. was one of the first to use this technique for extraction of the active ingredient and degradation product from Felodipine tablets [11]. MAE results were comparable to both the manual extraction method and that obtained by ASE. However, because of the ability of MAE to perform extractions in parallel, sample throughput was significantly higher when compared to both the manual method and ASE [11]. Labbozzetta et al. later used MAE for extraction and LC determination of the active ingredient in naproxen-based suppositories [12]. An excellent review of the use of MAE and the principle behind microwave heating was provided by Eskilsson et al in 2000 [9]. A more recent review was completed by Domini et al. in 2006 [10]. The MAE system used in this study was a MARSXtraction System (CEM, Matthews, NC). The system is comprised of a CEM microwave unit with a built-in magnetic stirrer and fiber-optic temperature sensor (Fig. 2). The sample rotor was a 12-position extraction rotor with 100 mL glass vessels.

Fig. 2. CEM MARSXtractor unit.

2.6. Accelerated Solvent Extraction (ASE)

Accelerated Solvent Extraction, like MAE, is an automated solvent extraction technique for solid and semi-solid samples. In ASE, an extraction solvent is pumped through a stainless steel cell (5, 11, 22, or 33 mL cell volumes) containing the sample, held for a specific amount of time at a defined temperature and pressure, and then flushed and filtered into a collection vial. The temperature, pressure and static times are all pre-determined by the scientist. Flush volume cycles can also be applied to the extraction process to improve extraction efficiencies. Up to 24 samples can be processed sequentially in less than 15 min each (Fig. 3). The use of ASE as a sample preparation/extraction tool in the pharmaceutical industry is relatively sparse. Bjorklund et al. first used the technique in 1998 for extraction of Felodipine from tablets [13]. Hoang et al. later used ASE to extract the active ingredient from montelukast sodium oral chewable tablets and

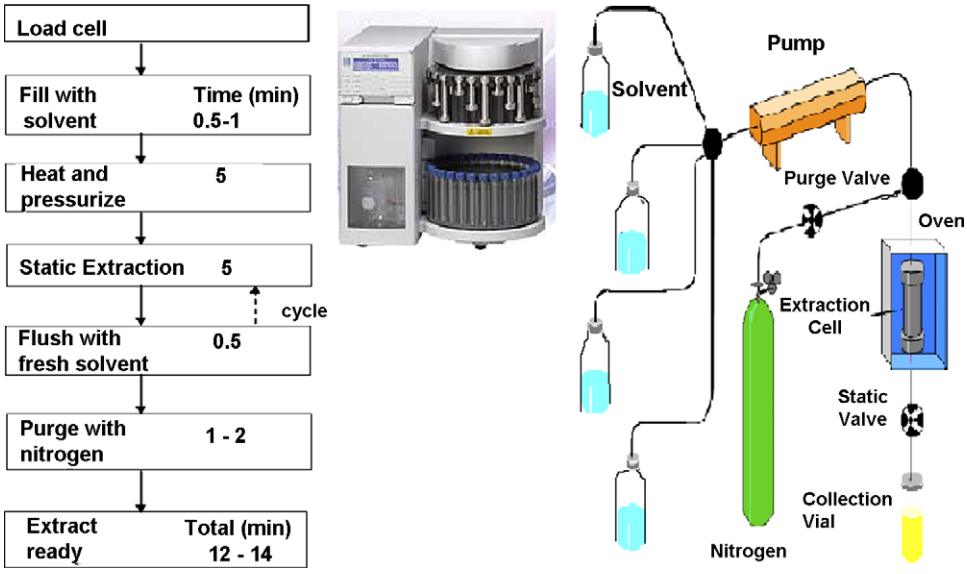

Fig. 3. Dionex ASE 200 extractor with schematic.

Table 1
Optimized TPW II extraction conditions for the 50 mgA Compound A tablet ($n = 10$)

Initial fill volume (mL)	# pulses	Pulse length (s)	Speed (K rpm)	Finish fill volume (mL)	# pulses	Pulse length (s)	Speed (K rpm)	% recovery ($n = 10$)	Total prep time per tablet (min)
100	8	15	10	150	5	10	10	101.4	30

Note: After dilution to volume with 150 mL solvent, the diluted sample was again homogenized to ensure proper mixing/dissolution of the active.

Abend et al. applied the technique to the extraction of ivermectin in a meat-based chewable formulation [14,15].

3. Results and discussions

3.1. TPW II

Sample preparation/extraction were performed on the 50 mgA Compound A tablet using the TPW II. The dissolving solvent used in the manual method, 80/20 ACN/water, was employed. Variables such as initial fill volume, number of pulses, pulse length, and homogenization speed were investigated. It was discovered that the number of pulses and initial fill volume, both impacted the percent recovery and extraction time. The lowest recovery (63%) was obtained with initial fill volumes less than 100 mL and number of pulses less than 5. Low recoveries were also observed with initial fill volumes larger than 150 mL. This is attributed to incomplete homogenization of the tablets as a result of particles floating away from the dispersion unit. The larger volumes facilitate straying of particles from the dispersion unit. The optimized TPW II condition for the Compound A 50 mgA tablet is shown in Table 1. Extraction on 10 tablets yielded quantitative recovery (101.4%) in less than 30 min per tablet.

3.2. Microwave Assisted Extraction

Method development experiments were also conducted on the 50 mgA Compound A tablets using MAE. Variables such as temperature, intact versus broken tablets, and dissolving solvent (mixture versus aqueous first) were evaluated. Significantly lower recoveries (<53%) were obtained at 40 °C for both broken and whole tablets when the premixed dissolving solvent was used as the extraction solvent (Table 2, Methods 11–7). Increasing the extraction temperature to 70 °C provided almost quantitative recovery of the API from the tablets, whether they were broken or whole. MAE performed with aqueous (water) first followed by organic (ACN) provided superior recoveries over the premixed dissolving solvent at 40 °C (Table 2, Methods 8–11). In the aqueous first procedure, a tablet was added to the microwave vessel containing 10 mL of water. The vessel was then microwaved for a prescribed amount of time. The vessel was allowed to cool and 40 mL of ACN was added to the vessel and re-microwaved. Higher recoveries were obtained for both whole and broken tablets. The higher recoveries obtained with the above approach is probably due to the fact that the aqueous environment allows for complete disintegration (increased surface area) of the tablet. The presence of crospovidone, a superdisintegrant in the formulation, promotes the rapid disintegration

Table 2
Extraction of Compound A API from Compound A 50 mgA tablets by MAE using premixed dissolving solvent (80/20 ACN/H_2O) and water (10 mL) first followed by ACN (40 mL)

Method #	Temperature (°C)	Tablet form	Ramp (min)	Hold time (min)	Cool time (min)	Solvent	% recovery	Total prep time (min)
1	40	Broken	5	10	10	80/20 ACN/H_2O	27.5	25
2	40	Whole	5	10	10	80/20 ACN/H_2O	50.0	25
3	40	Broken	5	30	10	80/20 ACN/H_2O	52.0	45
4	40	Whole	5	30	10	80/20 ACN/H_2O	41.2	45
5	70	Broken	5	10	10	80/20 ACN/H_2O	98.4	25
6	70	Broken	5	30	10	80/20 ACN/H_2O	99.9	45
7	70	Whole	5	30	10	80/20 ACN/H_2O	99.5	45
8	40	Whole	1	15/15	5	10 mL H_2O followed by 40 mL ACN	95.8	37
9	40	Whole	1	10/5	5	10 mL H_2O followed by 40 mL ACN	94.8	22
10	40	Whole	1	5/5	5	10 mL H_2O followed by 40 mL ACN	95.2	17
11	40	Whole	7	15/15	5	10 mL H_2O followed by 40 mL ACN	94.3	49
12	40	Whole	7	10/10	5	10 mL H_2O followed by 40 mL ACN	55.1	39
13	40	Whole	7	5/15	5	10 mL H_2O followed by 40 mL ACN	94.3	39
14	40	Whole	1	5/10	5	10 mL H_2O followed by 40 mL ACN	92.9	34
15	40	Whole	10	15/15	5	10 mL H_2O followed by 40 mL ACN	55.8	45
16	40	Whole	10	15/15	5	10 mL H_2O followed by 40 mL ACN	55.8	45
17	40	Whole	5/10	5/30	5	10 mL H_2O followed by 40 mL ACN	100.7	70
18	70	Whole	5/10	5/30	5	10 mL H_2O followed by 40 mL ACN	97.2	60

of the tablet (whole or broken). Addition of the organic component (ACN) facilitates dissolution of the API, thus the higher observed recoveries. Using the premixed dissolving solvent, with only 20% water, probably leads to a slower rate of disintegration and dissolution and thus lower recoveries, especially at lower temperatures. The optimized MAE method with extraction at 40 °C, using whole tablets and the aqueous first approach, is shown in Table 2 (Method 17). Extraction on 10 tablets gave 100.7% recovery of the API from the tablet matrix, with a total preparation/extraction time of 70 min.

3.3. Accelerated Solvent Extraction

Attempts to extract Compound A tablets by ASE (ASE 200, Dionex, Sunnyvale, CA) provided significant challenges. Our initial approach involved crushing one tablet with a pestle while wrapped in a piece of filter paper. The crushed tablet was then carefully transferred to an 11 mL cell, together with the filter paper. The cell was then extracted with the premixed dissolving solvent at temperatures of 40 and 70 °C. As shown in Table 3 (Methods 1–4), recoveries were less than 55%, even at higher temperatures (70 °C) and after up to 5 extractions, with 3 cycles per extraction. It was postulated that the low recoveries obtained for the Compound A tablets by ASE was possibly due to the following three factors: (1) surface area, (2) gelling effect of the HPC polymer present in the formulation and (3) solubility. It was believed that these three factors worked together to prevent quantitative extraction of the API from the tablet matrix. The gelling effect of HPC in the presence of solvents is well known in the pharmaceutical industry [1–3]. Once gelling occurs, the API becomes trapped in the matrix, making extraction very difficult. Gelling also decreases the surface area exposed, preventing complete extraction of the API from the tablet matrix. The ability for both the TPW II and MAE to agitate samples during the extraction process helped to minimize and possibly negate this gelling effect, thus facilitating complete recovery of the API from the tablet matrix.

To minimize the apparent gelling effect of HPC and increase surface area, the use of hydromatrix was investigated. Once the tablet was crushed, it was transferred to a 30 oz amber glass bottle and the bottle was half fill with hydromatrix. The bottle was capped and shaken vigorously to allow the hydromatrix and crushed sample to mix well. The hydromatrix/sample was then transferred to an 11 mL cell and extracted with the premixed dissolving solvent at 70 °C. As shown in Table 3 (Methods 5–7), significantly higher recoveries were obtained using the above-described approach. Commingling the hydromatrix with the crushed tablet helped to minimize gelling/clumping of the tablet formulation on addition of the extraction solvent. Additionally, the presence of hydromatrix helped to increase the surface area of the tablet, facilitating higher recoveries.

The impact of solubility on extraction of the API from the tablet matrix was also investigated. Even with addition of hydromatrix to the extraction procedure, several extractions had to be performed on the cell to get nearly quantitative recovery at 70 °C (Table 3). Because of inherent limitations with the instrument design, performing multiple extractions on a sample/cell

Table 3
Extraction of Compound A tablets by ASE with and without hydromatrix (11 mL cell)

Method #	Temperature (°C)	Tablet form	Static time (min)	# cycles	Flush volume (%)	# extractions	Solvent	% recovery	Total prep time per tablet (min)	Hydromatrix
1	40	Broken	20	3	50	2	80/20 ACN/H_2O	30.7	120	No
2	70	Broken	20	3	50	2	80/20 ACN/H_2O	40.3	120	No
3	70	Broken	20	3	50	5	80/20 ACN/H_2O	54.8	300	No
4	70	Broken	40	3	50	2	80/20 ACN/H_2O	39.4	240	No
5	70	Broken w/sand	10	3	50	3	80/20 ACN/H_2O	96.2	90	Yes
6	70	Broken w/sand	10	3	50	5	80/20 ACN/H_2O	98.1	150	Yes
7	70	Broken w/sand	5	3	50	5	80/20 ACN/H_2O	98.0	75	Yes

Table 4
Extraction of Compound A tablets by ASE with hydromatrix (33 mL cell)

Method #	Temperature (°C)	Tablet form	Static time (min)	# cycles	Flush volume (%)	# extractions	Solvent	% recovery	Total prep time per tablet (min)
1	70	Broken w/sand	10	3	50	1	80/20 ACN/H_2O	89.5	30
2	100	Broken w/sand	10	3	50	1	80/20 ACN/H_2O	90.0	30
3	70	Broken w/sand	10	5	50	2	80/20 ACN/H_2O	96.1	100
4	70	Broken w/sand	20	3	50	2	80/20 ACN/H_2O	97.4	120
5	70	Broken w/sand	30	3	50	2	80/20 ACN/H_2O	94.5	180
6	70	Broken w/sand	20	3	50	2	80/20 ACN/H_2O	96.3	120
7	70	Broken w/sand	20	3	50	2	80/20 ACN/H_2O	64.6	120
8	70	Broken w/sand	20	1	50	6	80/20 ACN/H_2O	94.6	120
9	70	Broken w/sand	20	3	50	1	80/20 ACN/H_2O	64.3	60
10	70	Broken w/sand	20	3	60	1	80/20 ACN/H_2O	91.1	70

is very cumbersome. This is because the instrument forces you to collect individual extractions in separate collection vials. For example, 5 extractions on a sample would require the use of 5 separate collection vials. This is a major drawback of the instrument design, because it impacts the number of samples that can be extracted unattended. For example, extraction of 10 samples with 5 extractions per sample will require the use of 50 collection vials. The ASE 200 system only has capacity to handle 24 collection vials. It was felt that increasing the cell size to 33 mL would help to minimize the number of extractions and increase recovery, due to the greater volume of solvent that could be used. As indicated in Table 4, the use of the larger 33 mL cell did help to reduce the number of extractions needed, but had no dramatic impact on recovery. Although higher recoveries could be obtained by performing multiple extractions on a sample, this was not pursued as the method of choice for the reasons indicated earlier. The optimized ASE method is shown in Table 4 (Method 10), with recoveries of 91.1% ($n = 10$).

3.4. Comparison of the TPW II, MAE, and ASE to the manual sample preparation/extraction method

Table 5 provides a side-by-side comparison of the extraction efficiencies of TPW II, MAE, and ASE to the manual extraction procedure for Compound A. The TPW II provided quantitative recovery of the API from the tablet matrix in the shortest time (30 min) and at room temperature. MAE also provided quantitative recovery of the API from the tablet matrix, however, the extraction time needed was more than doubled that of the TPW II and temperatures above ambient (40 °C) were needed. ASE on the other hand provided the poorest recovery, 91.1%, and required significantly higher extraction temperatures (70 °C). There was no degradation observed in any of the samples extracted above ambient temperatures. The superiority of the TPW II and MAE over ASE is primarily due to agitation. Both the TPW II and MAE allows for the samples to be agitated during the extraction process. This agitation factor is very important for quantitative recovery, especially with SDD formulations in which the HPC polymer can cause gelling of the matrix and trapping of the active, once in contact with solvents. With the TPW II, the tablets are completely homogenized in a very short time. The significant reduction is particle size that is provided by the TPW II, together with its ability to increase interaction between the active and solvent by vortexing the sample are the critical drivers for the shorter extraction times observed. The above, together with the potential to completely automate the extraction and assay process makes the TPW II a superior sample preparation/extraction technique for solid oral dosage forms.

Table 5
Comparison of extraction efficiencies between the optimized TPW, MAE, ASE, and the manual method

Technique	Recovery (%)	Temperature	Total prep time (per tablet) (min)
Manual	100.0	Ambient	330
TPW	101.4	Ambient	30
MAE	100.7	40 °C	70
ASE	91.1	70 °C	70

MAE, like the TPW II, is able to agitate the samples by stirring. Agitation by stirring, in addition to the use of water to help disintegrate the tablet, helps to prevent gelling of the matrix and increases interaction between the active and the extraction solvent. The above process is slower at room temperature and slightly higher temperatures are needed to provide quantitative recovery over shorter time periods. MAE as a sample preparation/extraction technique has two major advantages over the TPW II. Firstly, sample throughput in MAE is higher than the TPW II. The higher sample throughput is due to the fact that in MAE extractions are performed in parallel, while extractions are performed sequentially in the TPW II. In MAE, up to 40 samples can be extracted simultaneously in less than 70 min. However, the same 40 samples would require over 1200 min by the TPW II. Secondly, the ability to increase extraction temperatures in MAE is a potentially powerful tool, which is unavailable in the TPW II. Increasing extraction temperatures decreases solvent viscosity, increasing diffusion and increases analyte/solvent interaction. Additionally, increasing extraction temperatures leads to increased solubility of the analyte in the extraction solvent. One potential drawback of higher extraction temperatures is increase degradation, which has not been observed for Compound A.

Of the three automated extraction techniques, ASE provided the poorest recovery (91.1%). The lower recovery obtained with ASE is due to a combination of factors, most notably the inability to agitate samples in the ASE cells. Addition of extraction solvent to the cell facilitates gelling of the tablet matrix as a result of the presence of HPC polymer. This gelling effect serves to trap the active within the matrix, thus inhibiting the dissolution process. Mixing the crushed tablet with hydromatrix helps to minimize this gelling effect, however, quantitatively recovery was still not possible even at higher temperatures and increased cell volumes. ASE, with its ability to extract samples under elevated temperature conditions, might be better suited for less challenging, non-SDD immediate released formulations. MAE and TPW II on the other hand, because of their ability to agitate samples by stirring or homogenization are well equipped to handle more challenging formulations such as SDDs.

4. Conclusions

The TPW II consistently provided complete recoveries with very short preparation/extraction times (∼30 min) for the extraction of Compound A from a 50 mgA, 15% Spray Dried Dispersion (SDD) tablet IR formulation. MAE required twice the extraction time to provide complete recovery of the API from the same tablet formulation. Of the three non-traditional techniques, ASE consistently provided the lowest recovery of API from the tablet formulation. From a sample throughput perspective, MAE is the most superior technique, since it is capable of performing extractions in parallel (up to 40 samples with the MARSExtractor System). The TPW II has a 100 sample capacity, however, only one tablet can be processed at a time. Both the TPW II and MAE proved to be significantly faster and more efficient than the 5.5 h long manual validated method for Compound A.

References

[1] R.O. Williams III, M.A. Sykora, V. Mahaguna, AAPS *PharmsciTech* 2001; 2 (2) article 8. www.aapspharmsciTech.org.
[2] P. Colombo, R. Bettini, P. Santi, A. De Ascentiis, N.A. Peppas, J. Control. Release 39 (1996) 231–237.
[3] C.K. Choi, M.A. Dong, in: S. Ahuja, M.W. Dong (Eds.), Handbook of Pharmaceutical Analysis by HPLC, 6, 2005, pp. 123–144.
[4] S.M. Han, A. Munro, J. Pharm. Biomed. Anal. 20 (1999) 785–790.
[5] W.F. Shamrock, K. Reilly, D.K. Lloyd, J. Pharm. Biomed. Anal. 21 (2001) 1225–1232.
[6] U. Holler, C. Brodhag, A. Knobel, P. Hofmann, V. Spitzer, J. Pharm. Biomed. Anal. 31 (2003) 151–158.
[7] I. Toro, J.F. Dulsat, J.L. Fabregas, J. Claramunt, J. Pharm. Biomed. Anal. 36 (2004) 57–63.
[8] B.W. Renoe, Am. Lab. 34 (1994) 34–40.
[9] C.S. Eskilsson, E. Bjorklund, J. Chromatogr. A 902 (2000) 227–250.
[10] C.E. Domini, D. Hristozov, B. Almagro, I.P. Roman, S. Prats, A. Canals, in: L.M.L. Nollet (Ed.), Chromatographic Analysis of the Environment, 3rd ed., CRC Press, Boca Raton, 2006 (Chapter 2).
[11] C.S. Eskilsson, E. Bjorklund, L. Mathiasson, L. Karlsson, A. Torstensson, J. Chromatogr. A 840 (1999) 59–70.
[12] S. Labbozzetta, L. Valvo, P. Bertocchi, L. Manna, J. Pharm. Biomed. Anal. 39 (2005) 463–468.
[13] E. Bjorklund, M. Jeremo, L. Mathiasson, L. Karlsson, J.T. Strode III, J. Eriksson, A. Torstensson, J. Liq. Chromatogr. Rel. Technol. 21 (1998) 535–549.
[14] T.H. Hoang, R. Farkas, C. Wells, S. McClintock, M. Di Maso, J. Chromatogr. A 968 (2002) 257–261.
[15] A.M. Abend, L. Chung, D.G. McCollum, W.P. Wuelfing, J. Pharm. Biomed. Anal. 31 (2003) 1177–1183.