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RESEARCH PAPER

Adsorption and Leachable Contamination of Flucloxacillin, Cyclosporin and Amiodarone Following Delivery Through an Intravenous Administration Set

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ABSTRACT

Purpose Interactions between a pharmaceutical drug and its delivery device can result in changes in drug concentration and leachable contamination. Flucloxacillin, amiodarone and cyclosporin were investigated for drug concentration changes and leachable contamination after delivery through an intravenous administration set.

Methods Flucloxacillin, amiodarone and cyclosporin were delivered through an intravenous administration set and the eluate analysed by HPLC-UV and HPLC-MS.

Results The average recovery of flucloxacillin was 99.7% and no leachable compounds were identified. The average recovery of cyclosporin was 96.1%, which contrasts previous findings that have reported up to 50% loss of cyclosporin. This is likely due to the use of DEHP-free administration sets in this study, as adsorption of cyclosporin is linearly related to DEHP content. The average recovery of amiodarone was 91.5%. 5-hydroxymethylfurfural was identified in the amiodarone solution following delivery through the administration set as well as the 5% glucose solution used for delivery.

Conclusions Drug/administration set interactions may modify pharmaceuticals during delivery. In this study, only 90% of the amiodarone was delivered through a generic administration set. Given the growing use of generic administration sets in hospital settings, validation of the suitability of their use is required to ensure patient safety and expected levels of efficacy.

KEY WORDS

Drug Product, Active Pharmaceutical Ingredient, Drug Delivery, adsorption, intravenous

ABBREVIATIONS

ACN	Acetonitrile
API	Active Pharmaceutical Ingredient
DEHP	Diethylhexyl phthalate
EMA	European Medicines Authority
FDA	Food and Drug Administration
HPLC	High-performance liquid chromatography
ICH	International Council for Harmonisation
IV	Intravenous
LC-MS	Liquid chromatography-mass spectroscopy
MP A	Mobile phase A
MP B	Mobile phase B
PVC	Poly(vinyl chloride)
UV	Ultraviolet

INTROUCTION

Intravenous (IV) access and the administration of IV medication is the most common invasive intervention performed in hospitals around the world. It is estimated that 1.2 billion IV devices are used each year (1). A recent international study showed that 75% of hospital patients had an IV device *in situ* (2).

The storage containers and delivery devices for the pharmaceutical drugs delivered intravenously are often considered inert. However, interactions between the Drug Product and the container and/or delivery device have been known to result in adsorption of the Drug Product or undesired compounds being administered to patients (3-9) (reviewed in 10, 11). Compounds that migrate from the container closure system and/or delivery device into the Drug Product during its storage or administration are known as leachables. Despite the development of pharmaceutical drugs being heavily regulated, following guidelines produced by the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and highlighted in the United States Code of Federal Regulations (CFR) and by individual regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Authority (EMA) (12-15), currently there are no formal processes pertaining to leachables relating to generic delivery devices. As a result, quality or safety assessments are rarely undertaken in relation to the use of generic administration sets, which are often used in clinical practice.

To investigate the interactions between the delivery device and the pharmaceutical product, the commonly used pharmaceutical drugs flucloxacillin, cyclosporin and amiodarone were delivered through standard intravenous administration sets adhering to recommended dosage requirements and clinical delivery protocols. These drugs were selected for their chemical diversity and their common use across the globe. Flucloxacillin is a hydrophilic isoxazolyl penicillin used to treat susceptible Gram-positive bacterial infections, particularly *Staphylococcus aureus* (16). Amiodarone is a relatively hydrophobic iodinated benzofuran derivative and a class III antiarrhythmic drug, widely used as an antiarrhythmic agent (17). Cyclosporin is a cyclic undecapeptide

immunosuppressant derived from the fungus *Tolypocladium inflatum* and is frequently used in organ transplantation to prevent and treat graft-vs-host disease (18, 19).

MATERIALS and METHODS

Chemicals and Equipment

Water was purified using an in-house MilliQ Synthesis Quantum EX Cartridge Filter. The following chemical reagents and standards were purchased from Sigma-Aldrich (Castle Hill, NSW 2154): Cyclosporin A standard (Ref: 30024-25MG), Amiodarone hydrochloride standard (Ref: A8423-1G), 99+% benzyl alcohol standard (Ref: 402834-500ML) and 85% Phosphoric acid (Ref: 345245-100ML).

HPLC grade Acetonitrile (ACN, Ref: 015-4) was purchased from Pacific Labs (Blackburn, VIC 3130). Anhydrous glucose (Ref: BSPGL903.500) was purchased from Thermo Fisher (Brendale, QLD 4500).

The pharmaceuticals DBL™ Flucloxacillin Sodium Powder for Injection (Flucloxacillin; Batch Number: 2MF10265; Expiry: April, 2018), Novartis Sandimmun® Concentrate for Infusion (Cyclosporin; Batch Number: S0113; Expiry: January, 2020) and Sanofi Cordarone X® Intravenous (Amiodarone; Batch Number: 5A057 & 5A113; Expiry: June, 2017 & September, 2017) were purchased from CH2 Direct (Lytton, QLD 4178).

The infusion lines utilised in this project were the Alaris® CareFusion 210 cm gravity infusion sets (Ref: 02008382189; Batch Number: 486527; Expiry: August, 2016) and were made from Poly(vinyl chloride) (PVC). The burettes used were the Alaris® CareFusion SmartSite® Add-on Burette Set (Ref: 82113E; Batch Number: 14116315; Expiry: November, 2017); information regarding the construction materials of the burettes are not available. Neither component contained latex or diethylhexyl phthalate (DEHP). The saline bags used were Baxter® Viaflex 1000 ml 0.9% Sodium Chloride Intravenous Infusion bags (Ref: HB1324; Batch Number: S81H8; Expiry: October, 2016). The glucose bags used were Baxter® Viaflex 1000 ml 5% Glucose Intravenous Infusion bags (Ref: AHB0064; Batch Number: W11R4; Expiry: November, 2017). The saline and glucose bags were made from PVC and contained DEHP. The pharmaceuticals were not in contact with the DEHP containing saline and glucose bags, nor did they contact any other plastic

during the experiments. Glass equipment was utilised for preparation and transfer of the drug solutions.

Delivery of pharmaceutical drugs

The delivery apparatus was constructed by attaching the IV line to the burette, and connecting the burette to a normal saline or glucose bag. Flucloxacillin and cyclosporin were delivered through the IV administration set with normal saline (50 ml), while amiodarone was delivered with 5% glucose solution (150 ml). After delivery of the pharmaceutical the burette and IV line were flushed with either normal saline (50 ml) or 5% glucose (150 ml) to remove any residual drug. The eluent from the delivery of the pharmaceutical and the flush was collected in fractions before analysis. Ten fractions were collected and analysed for each of the three pharmaceuticals, as a result the fraction volumes varied from drug to drug. The fraction volumes were 5 ml for flucloxacillin and cyclosporin, and 15 ml for amiodarone. This was completed in triplicate for each pharmaceutical.

The delivery protocol was configured to mimic clinical conditions as closely as was feasible. Clinical delivery protocols for each drug were determined by referring to the manufacturing instructions and clinical guidelines (20-22). Adhering to these dosage requirements 1 g of flucloxacillin was administered through the delivery set over approximately 4 minutes, the line was subsequently flushed with saline over 2 minutes. Approximately 50 mg of cyclosporin was administered through the delivery set over 6 hours and flushed with saline over 2 hours. Approximately 210 mg of amiodarone was administered through the delivery set over 2 hours and flushed with 5% glucose solution over 1 hour. The dosage of amiodarone was scaled to account for the maximum volume of the burettes used in this study.

To determine if the pharmaceutical was adhering to the burette and IV line the procedure was repeated, except the eluted fluid was collected in two fractions, the fluid used to elute the pharmaceutical and the saline or 5% glucose flush.

As amiodarone was observed to adhere to the delivery set a second batch of amiodarone was analysed. The burette and infusion line were also subsequently flushed with 0.0272%

(v/v) H_3PO_4 over 1 hour, methanol over 2 mins and mobile phase A (MP A) over 30 mins in an effort to desorb the drug from the delivery set.

High Performance Liquid Chromatography

The column used for all separations was a Synergi 4µ Fusion - RP 80A (75 × 4.6 mm, 4 µm) with a 1.5 ml / min flow and 20 µL injection volume.

The instrument used for analysis of flucloxacillin and amiodarone samples was a Perkin Elmer Series 200 Autosampler and Pump connected to a Perkin Elmer Flexar PDA Detector. MP A consisted of H_2O / ACN in a 90 / 10 ratio with 0.0272% (v/v) H_3PO_4. MP B consisted of ACN with 0.027% (v/v) H_3PO_4.

The elution program began isocratic for 1 min with 100% MP A, graded to 0% MP A over 10 min, held at 0% MP A for 2 min, graded to 100% MP A over 1 min and held at 100% MP A for 2 min. The photodiode array was set to record at 200, 225, 266 and 330 nm for flucloxacillin and 200, 240, 260 and 330 nm for amiodarone.

Analysis of cyclosporin samples was performed with a Perkin Elmer Flexar uHPLC Autosampler connected to dual Flexar uHPLC pumps with a Flexar column oven set to 60 °C and a Flexar UV/VIS detector. MP A consisted of H_2O / ACN in a 90 / 10 ratio and MP B consisted of ACN. The elution program was the same as previously described except MP A was held at 0% for 3 min instead of 2 min.

Benzyl alcohol and anhydrous glucose standards were also analysed by HPLC with the amiodarone elution program.

Analysis of recovery rate of the Active Pharmaceutical Ingredient (API) for each pharmaceutical was performed with an Agilent 1290 Infinity Autosampler connected to quaternary uHPLC pump with a thermostatted column compartment and a diode array detector, following the same elution programs as described above. Each sample for pharmaceutical recovery rate was analysed by uHPLC in duplicate.

Pharmaceutical Recovery Rate

Calculation of the recovery rate of the pharmaceutical entailed serial dilutions of a standard of each API, which were analysed in triplicate by HPLC. Calibration curves were

constructed from the peak areas of the dilutions and were used to determine the recovery rate of each pharmaceutical after delivery through the administration set. The Limit of Detection (LOD) for Flucloxacillin, Cyclosporin and Amiodarone, were estimated to be 198.8, 75.9 and 46.2 ng/mL, respectively.

Liquid Chromatography - Mass Spectroscopy

After analysis via HPLC-UV, fractions with the highest relative impurity compound concentrations were analysed at the QIMR Berghofer Medical Research Institute by LC-MS for identification of the unknown compounds. The instrument used was an AB Sciex API 3200 LC-MS/MS connected to a Shimadzu SIL-20A Autosampler with dual LC-20AD pumps and a SPD-M20A PDA Detector with a 1.5 ml / min flow and 20 µL injection volume. The ion spray voltage was set at 5500 V. The PDA detector was set to detect wavelengths between 190 and 800 nm. The elution program used for separation was the same as previously described. MP A consisted of H_2O / ACN in a 90 / 10 ratio with 0.1% (v/v) formic acid. MP B consisted of ACN with 0.1% (v/v) formic acid.

For flucloxacillin and amiodarone, the heated nebulizer temperature was set at 550 ºC. Electrospray ionization was performed in the positive ion mode with nitrogen as gas supply 1, gas supply 2 and curtain gas set at 35, 50 and 25 psi. Multiple reaction monitoring mode was used to monitor ions from 50 - 1300 m/z and 200 - 1000 m/z for flucloxacillin and amiodarone, respectively.

For cyclosporin the heated nebulizer temperature was set at 400 ºC. Electrospray ionization was performed in the positive ion mode with nitrogen as gas supply 1, gas supply 2 and curtain gas set at 50, 75 and 20 psi. Multiple reaction monitoring mode was used to monitor ions from 200 - 1500 m/z.

The Limit of Detection (LOD) for Flucloxacillin, Cyclosporin and Amiodarone leachables were estimated to be 1.74, 0.12 and 0.13 mAU, respectively.

Identification and quantitation of 5-Hydroxymethylfurfural

Three compounds were observed in the amiodarone samples, which were not amiodarone. One of the compounds was traced to the 5% glucose solution used to infuse amiodarone.

This compound was identified and subsequently quantified by taking duplicate 2 ml aliquots from three different 5% glucose bags and each placed into a tared test tube so that accurate sample masses could be recorded. Samples were derivatised with O-2,3,4,5,6-(pentafluorobenzyl)hydroxylamine HCl 0.2g/15 ml citrate buffer at pH 4 for 75 minutes prior to the addition of a dilution solvent containing an internal anisole standard. 5-Hydroxymethylfurfural was analysed in duplicate against anisole by HPLC with 263 nm detection (23).

RESULTS

Flucloxacillin

The average recovery of flucloxacillin after delivery through the administration set was 99.7%, which suggested all of the flucloxacillin was successfully delivered. Pharmaceutical recovery rates are displayed in Table I.

After delivery through the administration set, nine compounds that were separate to the flucloxacillin peak were observed. These nine compounds showed mass fragments related to flucloxacillin, mainly the dominant ion at 160 *m/z*, and also possessed UV spectra similar to flucloxacillin. As these compounds were also observed prior to delivery of the flucloxacillin through the administration set it is likely that they are 'related compounds' (e.g. isomers or degradation products) of flucloxacillin or impurities of the manufactured Drug Product, rather than leachables.

Cyclosporin

The average loss of cyclosporin recovered after delivery through the administration set was 3.9%, which suggested the majority of cyclosporin was successfully delivered. After delivery through the administration set, 11 compounds, which were not cyclosporin were found. All of these compounds were observed in the cyclosporin Drug Product prior to delivery through the administration set, which indicates these compounds are excipients, degradation products of cyclosporin or manufacturing related impurities. Nine of these

impurities showed a dominant mass fragment of 307 *m/z*, which is characteristic of the excipient Kolliphor EL (24).

Amiodarone

The average recovery of the first batch of amiodarone (Batch Number: 5A113) after delivery through the administration set was 91.6%. To confirm this result, a second batch of amiodarone (Batch number: 5A057) was analysed, which exhibited an average recovery of 91.3%. The subsequent flushing of the delivery set with acidified water, methanol and MP A did not recover any additional API.

After delivery through the administration set, three compounds, which were not amiodarone were observed (Fig. I). One of the compounds was not observed in the amiodarone Drug Product prior to delivery through the administration set. However, the same compound was identified in the 5% glucose solution used to administer the drug. This contaminant was identified as 5-hydroxymethylfurfural by comparison with a standard and the average concentration was determined to be 3.0 ppm. The remaining two compounds were identified (by retention time, UV spectra and *m/z*) as the excipients benzyl alcohol and Polysorbate 80.

Table I Percentage API recovery after delivery of each pharmaceutical through an administration set

	Flucloxacillin	**Cyclosporin**	**Amiodarone (BN: 5A113)**	**Amiodarone (BN: 5A057)**
Trial 1	99.1%	96.2%	86.8%	90.7%
Trial 2	100.1%	96.2%	94.9%	91.7%
Trial 3	99.9%	96.0%	93.1%	91.4%
Average	99.7%	96.1%	91.6%	91.3%

DISCUSSION

Flucloxacillin

The high recovery rate of flucloxacillin indicates the drug product did not interact substantially with the delivery device. As the flucloxacillin Drug Product does not contain excipients and these nine compounds were observed prior to delivery, they were likely Drug Product manufacturing impurities or degradation products. The mass spectroscopy data supports the hypothesis that the nine compounds were manufacturing impurities, likely 'related compounds', as the impurities also showed the dominant ion fragments characteristic of flucloxacillin.

Cyclosporin

Delivery of cyclosporin through the administration set resulted in a negligible loss of cyclosporin. In contrast, a similar study by Shibata, et al. (25) found 40-50% losses of cyclosporin doses when using PVC infusion sets. They found adsorption of cyclosporin to be linearly related to the PVC's DEHP content. As the infusion sets in this study did not contain DEHP, this would likely account for the comparatively minor loss in cyclosporin recovery observed. Regardless, these findings highlight the need for pharmaceutical-delivery set combinations to be considered from the outset and thoroughly investigated prior to clinical use. The interaction between the materials used to construct different administration sets, and the chemical properties of different drugs can significantly alter the adsorption of the pharmaceutical. More specifically, if limited adsorption has been observed with a particular drug/administration set combination, this result cannot be extrapolated to other drugs or administration sets, as their interaction is difficult to predict. Instances exist where drug adsorption can be of significant clinical relevance.

After delivery through the administration set, 11 compounds, which were not cyclosporin were observed. These compounds were observed in the cyclosporin Drug Product prior to delivery through the administration set, which suggests the compounds are excipients, degradation products of cyclosporin or manufacturing related impurities.

Due to the broad elution pattern of Kolliphor EL, detection of leachable compounds was challenging. However, given the almost complete recovery of cyclosporin in this study, this was not a significant problem. Future investigations exploring the recovery of

cyclosporin, in particular using DEHP containing delivery sets should adopt a HPLC method similar to that detailed by Ciutaru, et al. (26) to mitigate these technical difficulties.

Kolliphor EL, formerly known as Cremophor EL, is a non-ionic surfactant and is used to increase the solubility of the Drug Product in aqueous solutions. The synthesis of Kolliphor EL involves the reaction of castor oil and ethylene oxide in a 1:35 ratio, the resulting product is a mixture of polyethylene glycol ethers, polyethylene glycol esters and polyethylene glycols that have varying molecular weights (27). The observation of multiple Kolliphor EL related peaks during HPLC analysis in this study have previously been documented (28).

Kolliphor EL has been shown to cause neurotoxicity. Rats that were injected with Kolliphor EL at doses equivalent to that likely to be encountered via cyclosporin administration, exhibited axonal swelling, vesicular degeneration and demyelination in the dorsal ganglion neurones (29). Anaphylactoid hypersensitivity has also been observed after infusion of vitamin supplements, which contained Kolliphor EL (30).

Amiodarone

The low recovery rate of amiodarone indicated a substantial proportion of the API was not eluting from the administration set. This finding was replicated with a second batch of amiodarone. Repeated flushing of the delivery set with a variety of solvents did not result in further substantial recovery of amiodarone. It is likely that the amiodarone had adsorbed to the burette/infusion line, and that the adsorption was irreversible or in slow equilibrium. Previous studies by Peters and Hayball (31) and Weir, et al. (32) have reported losses of amiodarone following delivery through administration sets at levels of 4.9% and 18%, respectively. Weir, et al. (32) attributed the loss of amiodarone to the presence of plasticisers in the delivery set as rigid PVC and glass failed to decrease the amiodarone concentration after storage. Importantly, neither of these studies incorporated burettes in their apparatus, which are likely to exacerbate the adsorption effect and would contribute to an increased loss of amiodarone.

HPLC-UV analysis also revealed the presence of 5-hydroxymethylfurfural in the delivered Drug Product and the 5% glucose delivery solution. This impurity is generated

during sterilization of the glucose solution and has been shown to exhibit limited toxicity at the observed concentrations (33).

Benzyl alcohol is a listed excipient of Cordarone and is commonly used as an antibacterial preservative. Benzyl alcohol has been shown to be toxic in high concentrations or when given to high risk patients, such as critically ill neonates. The symptoms of benzyl alcohol poisoning are metabolic acidosis, unremitting gasping respiration, neurologic deterioration, renal failure, convulsions, intraventricular haemorrhage, and cardiovascular collapse (34) and treatment-emergent, drug-related Adverse-Events listed on formal Drug Product labels, which include fever, bradycardia, congestive heart failure, cardiac arrest and nausea (22). Interestingly, Masi, et al. (35) reviewed the potential role of benzyl alcohol in acute amiodarone toxicity following an administration error.

Polysorbate 80 is another listed excipient and is a non-ionic surfactant synthesised via a reaction between sorbitol, fatty acids and ethylene oxide. The resulting product is a mixture of polyoxyethylene sorbitan/isosorbide esters with varying degrees of esterification, varying fatty acid alkyl chain-lengths and varying numbers of ethylene oxide groups (36). The broad elution pattern observed for Polysorbate 80 across a variety of columns and conditions is expected to be caused in part by the large number of structurally similar compounds, which elute in succession (37). The main fatty acid used in the synthesis of Polysorbate 80 is oleic acid, which is fragmented with an ethylene oxide group during mass spectroscopy to give the dominate ion at 309 *m/z*, which was observed during analysis.

CONCLUSION

This study aimed to identify leachable compounds and quantitate adsorption of the pharmaceutical drugs flucloxacillin, cyclosporin, and amiodarone, which resulted from the delivery of the drugs through an administration set that is widely used in clinical practice. Adhering to the standard delivery protocols, flucloxacillin, cyclosporin, and amiodarone were delivered through a commonly used administration set, and the eluted fluid collected in fractions and analysed.

Flucloxacillin did not interact with the delivery set, however several chemically similar compounds, which are believed to be degradation products or isomeric forms of flucloxacillin were observed. These compounds were also observed prior to delivery of flucloxacillin through the administration set and are therefore likely to be impurities of the API or Drug Product.

Recovery rates of cyclosporin showed minor adsorption of the drug to the administration set. This contradicted a previous study that reported losses of up to half of the API following delivery. The lack of DEHP in the administration sets used in this study is expected to account for this discrepancy as adsorption of cyclosporin is linearly related to DEHP content of PVC's. Cyclosporin also showed multiple overlapping elution peaks, which are expected to be caused by the excipient Kolliphor EL. The elution peaks of Kolliphor EL could potentially obscure leachables and future investigations especially with DEHP containing administration sets should adopt an HPLC method similar to that detailed by Ciutaru, et al. (26).

Whilst this study failed to detect any leachable contaminants, recovery of amiodarone was found to be reduced by almost 10% following delivery through an internationally used generic administration set. Clinicians therefore need to be aware that drug delivery through administration sets may result in changes to the amount of API delivered and potentially to the overall composition of the delivered material, possibly compromising patient safety or treatment efficacy. Pharmaceutical companies rigorously assess the quality of APIs and Drug Products and their interactions with delivery systems. However, they cannot control which delivery systems are used in clinical settings. Therefore, it is critical that additional research and quality control is undertaken to investigate interactions between infusion sets and the drug being administered prior to adoption in the clinic.

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