Ambulatory devices for prolonged infusion of cancer chemotherapy

One of the key factors in the success or failure of ambulatory chemotherapy is the selection of the ambulatory infusion device. As new devices have entered the market in recent years, the selection process becomes increasingly complex.

For many years it has been recognised that administration of some antineoplastic drugs in prolonged, continuous infusions, as opposed to traditional short infusions or bolus injections, can improve therapeutic response and modify drug-related toxicity [1, 2]. These clinical developments have been combined with technological advances in small, portable infusion devices to enable patients to receive ambulatory chemotherapy by continuous infusion in the community setting [3]. Ambulatory infusion devices may be classified by four main groups (Table 1), although other types of device are available.

Device selection
Many factors influence the selection of infusion devices. These include the volume to be infused, rate of infusion, duration of infusion, accuracy required, patient protection and alarm systems required, patient acceptability (ease of use, size, weight, noise level) and the budget available for both capital and consumable costs. Additional device-specific issues also need to be taken into account, including maintenance and testing costs (electronic devices), and the time taken for pharmacy aseptic units to fill device reservoirs, which can vary considerably between devices.

There is no single device suitable for all applications, and the reader is referred to the specialist literature for a discussion of the key attributes required and evaluation of different devices [4, 5].

A detailed discussion of individual infusion devices is beyond the scope of this short article, but some general guidance on the advantages and disadvantages of the main device categories listed in Table 1 is provided to aid in the selection process [6].

Syringe drivers (example Graseby MS26)
Advantages: Syringe drivers are small, lightweight devices and the range of flow rates achievable (0.06–41 mL/hour for Graseby MS26) makes them ideal for continuous infusion of chemotherapy. These devices use standard Luer lock syringes as the infusion reservoir which significantly reduces consumable costs. Although the flow is pulsatile, the long term accuracy of syringe drivers is usually good. A “Lockbox” is available with some devices to secure the pump and prevent tampering. Capital purchase costs are modest.

Disadvantages: The flow rate of the Graseby MS26 and MS16A syringe drivers is set according to the length of syringe plungers (mm) over a fixed time period. Setting the flow rate in
Table 1: Classification of the main groups of ambulatory infusion pumps

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Examples (manufacturer)</th>
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<tr>
<td>Syringe driver</td>
<td>Uses standard Luer lock syringe (up to 20 mL volume) as drug reservoir, and battery-driven motor to “drive” syringe plunger and infuse drug. The volume delivered over 24 hours can be adjusted within limits. Syringe is disposable, single use.</td>
<td>Graseby MS-26 and MS-16A</td>
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<td>Elastomeric pump</td>
<td>An elastomeric balloon reservoir is filled with drug solution and the elastic properties drive the drug out through a flow restriction device at a constant flow rate. The reservoir may be contained in a rigid protective outer casing. Entire device is disposable, single use.</td>
<td>LV Infusor and SV Infusor (Baxter Healthcare)</td>
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<td>Mechanical pump</td>
<td>Uses a spring mechanism which applies pressure to a PVC drug reservoir contained in a rigid casing. This forces the drug solution through a flow restrictor at a constant rate. A variety of different flow rates and reservoir volumes are available. Reservoir is disposable, single use.</td>
<td>Paragon Infuser (I-Flow Corporation)</td>
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<tr>
<td>Electronic device</td>
<td>Battery powered, usually based on a peristaltic mechanism, featuring an integrated reservoir/cannula which is disposable and normally constructed from PVC. These devices can be very sophisticated with various alarms, programmable flow rates and, in some cases, the capability to download infusion history.</td>
<td>Walkmed 350 (McKinley Medical)</td>
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Electronic device (example Walkmed 350)

Advantages: These versatile and sophisticated pumps offer a

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mL/hour requires a calculation involving syringe length and volume. Confusion between the two Graseby devices can occur because the MS16A device delivers the set travel over one hour, whereas the MS26 delivers the set travel over 24 hours. The alarm and safety systems on these devices are relatively basic, require routine maintenance and are not easy to clean if contaminated with cytotoxic drug infusion. The small reservoir size (syringe) requires frequent changes during long-term infusions.

Elastomeric pumps (example Baxter LV infusor)

Advantages: Light and compact because elastomeric pumps have no battery or motor. No capital costs, the devices are disposable, single use consumables. A wide range of reservoir volumes and flow rates is available (240-272 mL and 1.5, 2, 5, 7, 10 mL/hour, respectively for Baxter LV infusor), and some devices with multiple infusion rates are now available. Most devices include an in-line particulate filter and some also include an air-bubble elimination filter. Accuracy is typically claimed as +/- 10-15%, which is acceptable for most chemotherapy applications. In some devices, the infusion reservoir is protected by a rigid plastic casing. Operation of elastomeric devices is silent.

Disadvantages: Consumable costs are relatively high for these disposable, single-use devices, which can, over a period of time, cost more than the one-off capital purchase and consumable purchases (reservoirs and batteries) associated with electronic devices. Flow rate is influenced by temperature (increase in temperature results in increased flow rate), height of device relative to infusion site, and viscosity of the infusion (confusingly, some devices are calibrated using 5% glucose infusion, others using 0.9% sodium chloride).

Mechanical pumps (example Paragon I-Flow)

Advantages: No motor or electronic components, so no batteries required. Drive mechanism (casing and spring mechanism) is designed for multiple use, so that the infusion reservoir is the only consumable which reduces operating costs compared to elastomeric devices. Nominal reservoir volume is 100 mL with a range of fixed flow rates available from 0.5 to 100 mL/hour. The Paragon Select-A-Flow is available in three variants, so the flow rate can be selected from 0.5-3.5, 1-7, and 2-14 mL/hour in increments of 0.5, 1.0 and 2.0 mL/hour, respectively. The claimed accuracy varies between +/- 10-15%, depending on flow rate, and this is adequate for most chemotherapy regimens. Most spring-powered devices include both particulate and air filters in line. Some devices are fitted with indicators to monitor infusion progress.

Disadvantages: One of the main issues is the weight of mechanical pumps. For example, the unfilled weight of the Paragon device is 260 g, compared to 40-65 g for elastomeric devices. As with elastomeric devices, operating temperature, infusion viscosity and the height of the pump relative to the infusion site can all influence flow rate and infusion accuracy. The non-disposable components can be difficult to clean in the event of a cytotoxic spillage.
wide range of infusion reservoir volumes (typically 50-250 mL) and flow rate range (typically 0.1-20 mL/hour at 0.1 mL/hour increments). Accuracy is typically +/- 5%, and battery capacity allows between 450 and 650 mL to be delivered between battery changes. Most pumps are easy to programme and have either a coded lockout facility or a lockable pump case to prevent tampering. Usually there is an LCD panel providing programme and infusion status. Alarm and safety features are specific to individual devices, but typically include occlusion, air in line, low battery, pump malfunction indicators and systems to prevent the use of non-compatible administration sets. Some devices enable the infusion history to be downloaded to a PC and printed, and others may be programmed with different flow rates over a 24-hour period to facilitate chronotherapy.

Disadvantages: The capital cost of electronic pumps can be very high, and the consumable budget must include provision for batteries and regular maintenance, in addition to infusion reservoirs. However, one reservoir may contain several days' treatment, so overall consumable costs may be favourable. The more sophisticated devices can be bulky and, including the battery, the weight of the unfilled device can range from 350 g upwards. Calculation of battery life and training the patient to replace batteries is a further complication.

Pharmaceutical issues
Pharmaceutical issues to be considered include the filling of the device and infusion-container compatibility and stability issues. Syringe drivers, electronic and mechanical pumps offer the advantage that there is no backpressure during filling. The operating pressure of some elastomeric devices can exceed 500 mmHg, and this must be overcome when filling and inflating the elastomeric reservoir. These issues are of particular significance when large batches are involved causing operators repetitive strain injury and, if automated filling systems are used, the risk of equipment damage. Filling cytotoxic infusions against a backpressure may also increase the risk of aerosol formation and occupational exposure.

Infusion devices should be biocompatible, e.g. ISO 10993-1 compliant, and must also be compatible with the drug infusions they are used to administer. This latter issue is covered in another article, see page 20, Compatibility of anticancer drug solutions with administering devices, by Professor Alain Astier.

The physical and chemical stability of drug infusions in ambulatory devices during storage prior to use, and under in-use conditions, is critical. Device manufacturers can often provide this information and stability reports for specific drug-device combinations are available in the literature [7, 8]. Since ambulatory infusions may be exposed to prolonged refrigerated storage (2-8°C) followed by in-use temperatures of up to 37°C, studies based on the "sequential temperature" design [9] provide the most rigorous validation of stability.

In conclusion, prolonged infusion chemotherapy presents many challenges across the clinical, scientific and technical sectors of pharmacy.

References