DRUG INFUSION SYSTEMS

SELAHATTIN OZCELIK
Texas A&M University
Kingsville, Texas

INTRODUCTION

An infusion system can be described as the process of delivering fluids and medications in solution to patients by way of an infusion device. Intravenous route is generally used for drug delivery; however, subcutaneous, epidural, and enteral routes are also used for special drug administration (1). Administration of medication into the patient by way of some kind of drug infusion device provides the desired level of medication in the patient and allows direct control over pharmacological variables, such as onset of drug effects and peak serum drug concentrations (1). This type of drug administration has been the choice especially for specific conditions, including the use of antibiotics for severe infection, chemotherapy for malignant conditions, cardiac medication in critical cases, and analgesics for relief of severe pain.

When curing all common medical disorders that justify therapeutic intervention, pharmacological therapy is the preferred and effective method of treatment. Device-based drug delivery systems for the administration of effective pharmacological therapy can be grouped as injection–infusion, transdermal patch-based, and inhalation systems (2). Among the established methods of injection and infusion systems are the needle and jet injection, intravascular, intraspinal, intraoperative site, and intraperitoneal–transperitoneal infusion systems. Major applications of drug infusion are anesthesia delivery, antibiotic–antiviral therapy, nutritional support, pain management, cardiovascular disease therapy, chemotherapy, diabetes management, hydration therapy, bone marrow and organ transplant support therapy, and transfusion therapy (2).

The use of powered infusion devices has grown enormously in the last two decades. Infusion pumps together with an appropriate administration set provide an accurate flow of fluids over a prescribed time period. The simplest devices are the gravity controllers, in which the flow of liquid under the force of gravity is regulated by clamping action. More complex infusion systems include a positive pumping action for infusion (3). Volumetric pumps posses a linear peristaltic pumping mechanism. Syringe pumps work by pushing the plunger of a disposable syringe along at a predetermined rate. The type of pump used depends on the required volume and speed of infusion (3).

Medication errors are a major concern of healthcare professionals and medical institutions and have been reported to contribute to between 7000 and 140,000 deaths only in the United States each year (4–9). The impact of medication errors was found to be more severe in pediatric patients (4). There are a wide variety of reasons for medication errors. Reports suggest that the most significant factor is the user errors; however, the contribution of device-related problems to medical errors cannot be underestimated. Many reports of incidents have also been received involving infusion pumps. These incidents are primarily due to over infusions and may result in patient harm or death (3). In practice, some of the common problems in drug infusion systems originate from syringe pumps. Most of the patient morbidity and mortality, being the most significant among all the problems, has happened when using syringe pumps. Another common problem with drug delivery is venous air embolisms, which can be caused by air ingress due to improper drug delivery technique, damaged equipment and tubing, leaking or loose tubing connectors, or failure to stop delivery prior to complete evacuation of IV bags. Venous air embolisms have been

Encyclopedia of Medical Devices and Instrumentation, Second Edition, edited by John G. Webster

observed in central venous cannulation and pressurized intravenous infusion systems (3).

Today it has been proved that technology is essential in reducing risk in medication delivery. Computerized physician order entry (CPOE) and bar code applications for drug administration are such technologies that are capable of reducing medication errors. Unfortunately, most hospitals have not yet implemented these systems; therefore, many errors that otherwise might be eliminated continue to put patients at risk (10). Computerized intravenous (IV) infusion devices, so-called smart pumps include software that incorporates dosage limits established by the medical institution, warnings when dosage limits are exceeded, configurable settings by patient type, and access to transaction data for quality improvement efforts. Such systems make it possible to provide an additional verification at the point of care to help prevent IV medication errors (11). The Institute for Safe Medication Practices and the Emergency Care Research Institute recognize safety systems for IV medication as vital to reducing medication-related errors (10,12). A couple of examples utilizing a new technology is MEDLEY from Alaris Medical Systems and COLLEAGUE CX by Baxter Healthcare Corporation. These infusion systems allow hospitals to enter various drug infusion protocols into a drug library with predefined dose limits. For example, if a dose is outside the programmed range or clinical parameters, the pump halts or informs the physician by providing an alarm. Some pumps are even capable of integrating patient monitoring and other parameters, such as patient's age or clinical condition. More and more manufacturers are bringing similar devices to market (10).

The aim of this section is to provide a review on drug infusion systems, basic operational principles of pumps used in such systems, new infusion devices that are being developed, and recent developments for the control of infusion devices. With this goal in mind, this section is organized as follows: The section Common Infusion Systems presents most commonly used infusion systems and their operational principles. In the section, New Developments in Drug Infusion Systems, smarter, smaller, reliable, and cost effective new infusion devices, which are currently under development, are reviewed. Since the performance of any automated system highly depends on its controller structure, most recent research work on the control of drug infusion devices is reviewed in the section Recent Advancements in Controller Design for Drug Infusion Systems.

COMMON INFUSION SYSTEMS

Any drug infusion system requires some kind of control unit in which necessary parameters are monitored continuously so that the drug is delivered to the patient in a desired manner. Infusion devices range from very simple mechanical devices based on elastic containers, springs, and flow restrictors to sophisticated microprocessor controlled pumps. The choice of an infusion device depends on both the type of therapy to be applied and patient characteristics. Some IV infusions can safely and effectively be delivered via gravity drip systems, while others require sophisticated microprocessor controlled pumps for more precise control, positive pressure, and greater flow rate range. Traditionally, these devices are used in hospitals for the controlled delivery of drugs and fluids. However, as these devices become smarter with the use of new technology, more and more patients are using them for home therapy.

Therefore, the use of infusion pumps is increasing in the community. To ensure that a patient receives the correct dose, the appropriate infusion device should be chosen for the drug. Syringe pumps are commonly used at low rates of infusion, but may not be suitable for drugs that require constant blood levels (13). It is required that any infusion system be able to reliably deliver the prescribed drug dose–volume to the patient, at pressures that overcome all baseline and intermittent resistance, while causing no harm to the patient. Additive resistances, such as the small bore and kinking potential of connecting tubing, cannula, needles, and patient vessels, make infusion flow difficult. Filters, viscous solutions, and syringe stiction can also adversely affect the infusion flow. Therefore, infusion pumps are required to overcome these resistances and accurately deliver prescribed drugs to patients. These pumps must be capable of delivering infusions at pressures of between 100 and 500 mmHg (2–10 psi or 13.79–68.95 kPa) (13). Ideally, pumps should also reliably detect the infusion pressure and the presence of air in the line close to the patient vessel being infused. Table 1 provides pressure ranges for IV pump pressure settings. Infusion devices can be classified according to their power source as gravity controllers and infusion pumps.

Table 1. Pressure Ranges for IV Pump Pressure Setting[a,b]

Pressure, mmHg	Example	Pressure, psi
2–20	Central venous pressure range	0–0.4
10–30	Peripheral venous pressure range	0.2–0.6
100	Extravasation risk	2
100–150	Systolic arterial pressure range	2–3
75	Gravity pressure of fluid 100 cm above cannulation site	1.5
500	Highest probable pressure required by an infusion pump	10
1000	Maximum modern–Ambulatory pump occlusion pressure setting	20
3000	Common max. pressures form older peristaltic pumps	60

[a]See Ref. 14.
[b]1 mmHg = 1 psi = 6.89 kPa.

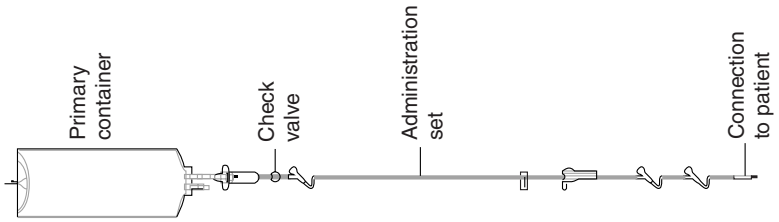

Figure 1. Common gravity drip infusion device.

Gravity Drip Systems

The simplest infusion device is the gravity drip system in which a bag or bottle is hung on a hook of a pole sufficiently high from the level of the patient. Figure 1 shows a typical gravity drip infusion system. The fluid flows by gravitational force down the line and into the catheter. They are quite suitable for lower risk applications, including fluid replacement therapy, provided that the required flow rate is achieved by the delivery pressure of the device (4). Gravity controllers are based on gravity to provide the infusion pressure. Therefore, in order to achieve the desired flow rate, the fluid container is placed sufficiently high above the patient's heart. A drop sensor monitoring the drip rate is attached to the drip chamber of the administration set. The rate of flow in a simple gravity drip system is controlled by a special clamp or valve on the line that can be manually adjusted to permit the prescribed amount of fluid to flow through (usually described in drops per minute).

These devices range in complexity and ease of operation from roller and slide clamps to more sophisticated rotating valves. Compared with slide and roller clamps, rotating valves are less awkward to manipulate and provide a more consistent flow rate. However, even the most sophisticated manual drip valve cannot offer precise flow control, due the viscosity of the solution being infused. Another factor to be taken into account is the second flow control caused by the size of the needle at the end of the line through which the fluid flows into the catheter. The smaller the needle is the slower the maximum rate of flow into the body (15). These types of devices are quite effective in controlling overinfusion; however, control of underinfusion would not be satisfactory due to increased resistance to flow. One way to avoid this problem is to use a drip rate controller with a visible flow status system (14). The pressure available from a bag of saline is equal to the height that the bag is above the patient's heart. Drip rate controller is a type of gravity controller, in which the desired flow rate is set in drops per minute and controlled by occlusion valves powered by electricity. All models of drip controllers have a drop sensor. More advanced models incorporate a flow status system, which gives a visual indication of resistance to flow (4). The required number of drops delivered by gravity controllers is controlled by the drop counting mechanism that is quite accurate. However, the actual amount of volume delivered to patients may vary because of error involved when converting the number of drops to milliliters (mL). Conversion chart values for drops $\cdot$ mL^{-1} are approximate and a small error made for each drop may result in a large difference in the entire volume of drug delivered.

The volume of fluid in a drop depends on several factors, some of which are the fluid's composition, temperature and surface tension, the drip rate set, the size, shape, and condition of the drop-forming orifice (3). Expected nominal volume for a drop is 20 drops $\cdot$ mL^{-1}. This nominal rate can easily be achieved for most simple aqueous solutions of electrolytes, lactates, or dilute sugars. However, due to the viscosity characteristics of parenteral nutrition mixtures, fat soluble vitamins and solutions containing alcohol, the drop volume will be lower than nominal resulting in longer infusion time (3). Naturally, with all fluids, the drop volume decreases as the delivery rate increases. These variations are acceptable for the majority of infusions. However, if the volumetric accuracy is critical, then an infusion pump must be used (3).

There is a standard formula for calculating the flow rate on any type of IV tubing as follows:

$$(V \times df)/t = \text{drops min}^{-1}$$

t = time to be infused (in min); V = volume of solution to be infused; df = drop factor of solution set (drops mL^{-1}); (mL $\times$ drop factor)(min^{-1}) = drops min^{-1}.

If the result of the calculation includes a decimal point, round-off to the nearest.

Electronic controllers provide better accuracy for the regulation of flow by controlling uneven or runaway flow of fluid in a gravity drip system. These electronic devices are equipped with a drop sensor to monitor flow rate and can detect infiltrations and mal-positioning of the catheter or IV tubing by measuring backflow. An alarm sounds when flow rate is altered or when backflow is detected.

The gravity drip is conceptually simple, inexpensive, and requires less equipment than most other infusion systems. In the home setting, however, it has some limitations. First, it is difficult to maintain a constant infusion rate in a gravity drip system due to factors, such as the decreasing volume of fluid in the bag (i.e., the infusion rate will decrease as the bag empties) and changes in the shape of the tubing around the clamp. Consequently, a gravity system may provide insufficient flow control for drugs that require a very slow, very precise, or very long infusion time. Second, errors in using the gravity drip that remain unnoticed can result in serious complications (15). In addition, a gravity drip system may be an inappropriate choice for certain patients due to functional limitations of the patients or their caregivers. Because the IV bag is suspended well above the catheter site in this system, patients with decreased mobility may have difficulty changing the bag. Ambulatory patients on continuous infusion may also find gravity drip frustrating because the system is not easily portable. Despite the drawbacks of this traditional method of IV administration, it does maintain some important functional advantages over more expensive electronic infusion devices discussed below. Because the drugs are

forced into the vein under the pressure of gravity alone, there may be less irritation at the catheter site, especially peripheral catheter sites. Gravity drip systems may also be preferred for patients who are confused by and resistant to learning how to use more complex, computerized drug delivery systems (15).

Infusion Pumps

An electronically controlled device that could deliver constant and precise amounts of fluid over a specified time period was a major technological advance in infusion therapy. Although many therapies can be delivered safely and effectively via gravity drip systems, others require the highly precise and constant flow rate offered by electronic infusion devices (15). For example, intraarterial infusions usually require positive pressure pumps because the back pressure is higher in arteries than in veins (15). Volumetric or syringe pumps are the most common. Other methods include elastomeric, pneumatic, implantable, clockwork, or spring (3). They are used to accurately administer intravascular drugs, fluids, whole blood, and blood products. These pumps can administer up to 2000 mL of fluid (normally from a bag or bottle) at flow rates of 0.1–2000 $mL \cdot h^{-1}$.

Volumetric Pumps. Most volumetric pumps will perform satisfactorily at rates as low as $5\,mL \cdot h^{-1}$. However, these pumps are generally not used for delivering drugs at rates $<1\,mL \cdot h^{-1}$, even though the device can be set to such low rates. The rate is in milliliters per hour ($mL \cdot h^{-1}$) or micrograms per kilogram per hour ($\mu g \cdot kg^{-1} \cdot h^{-1}$) (3).

Most volumetric pumps have the feature of automatic alarm and shut down in case air enters the system, an occlusion is detected, or the reservoir is empty. The device controls the total volume to be infused and provides digital read-out of volume infused. Some of the other features include automatic switching to keep the vein open (KVO) rate at the end of infusion; switch to internal battery operation automatically if the mains supply fails; micro and macro delivery modes; computer interface; operator call alarm; a drop sensor—used for monitoring and alarm purposes (e.g., as an empty container) rather than as a control of the delivery rate; primary and secondary infusion capability; technical memory log for incident analysis. Features, such as air-in-line detection or a mechanism that cannot pump air and comprehensive alarm systems, make IV infusion much safer (3).

Most infusion pumps work by peristaltic action, which is achieved by alternately squeezing and releasing the tube containing the fluid to force the fluid through at a predetermined rate. There are two types of volumetric pumps: peristaltic and dedicated cassette. Peristaltic mechanisms can be further classified as linear peristaltic and rotary peristaltic. Both mechanisms consist of fingers, cams, or rollers that pinch off a section of the set. In linear peristaltic mechanisms as seen in Fig. 2, cams are located on a camshaft. Required volume is delivered to the patient by pinching off each section as the shaft rotates. These mechanisms are commonly used. In rotary peristaltic mechanisms, as seen in Fig. 3, rollers are placed on a

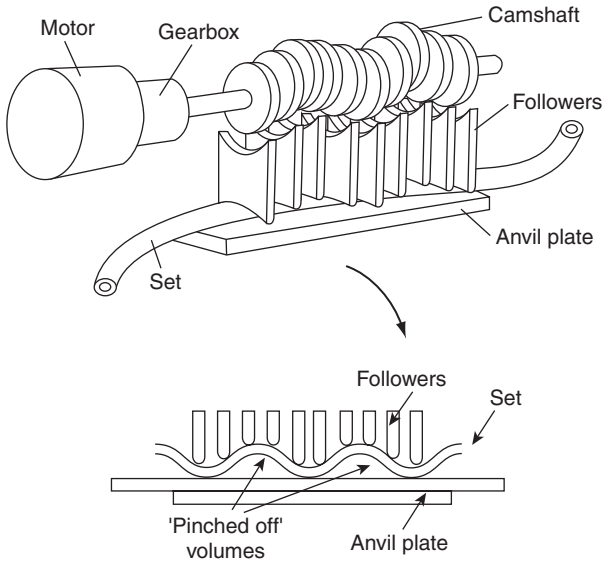

Figure 2. Schematic of a linear peristaltic pump (3) © CROWN COPYRIGHT.

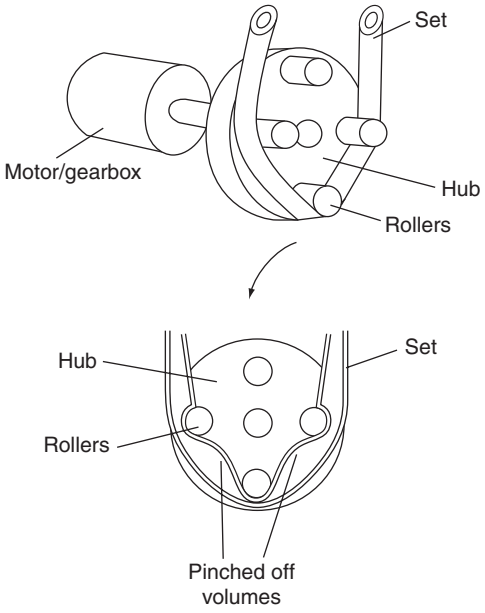

Figure 3. Schematic of a rotary peristaltic pump (3) © CROWN COPYRIGHT.

hub and as it rotates the volume in each pinched off section is delivered to the patient. The volume delivered varies according to the size of the cams, rollers, the tube, and the speed at which they rotate. These mechanisms are usually designed for a particular administration set (3).

Another mechanism used in infusion pumps is the dedicated cassette mechanism. Commonly, these types of pumps consist of a cassette body in which a valve and cylinder are placed, a piston, valve actuator, and a crank mechanism. This type of pump is depicted in Fig. 4. Drug is sucked to the cylinder from a bag or a container as the piston moves down and it is pumped to the patient through

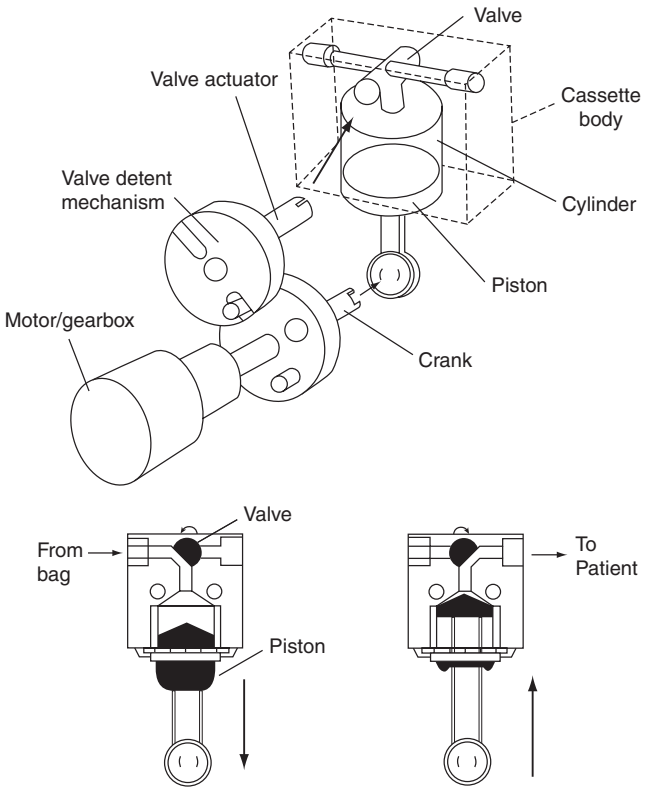

Figure 4. Dedicated cassette set (3) © CROWN COPYRIGHT.

a valve as the piston moves up (3). Although volumetric pumps can develop high pressures, they generally have a preset default value. In determining what pressure level is to be set, one needs to determine the factors of pressure raisers and calculate the needed pressure. However, it is important that the occlusion pressure should be set to the lowest possible value in order to observe early warning of occlusions.

A specific type of infusion set is required when using volumetric infusion pumps in order to achieve satisfactory drug delivery and to detect occlusion pressure. If an infusion set other than the required one is considered to be used, then extra care must be given when configuring the pump for that infusion set. Although using incorrect sets might seem to operate satisfactorily, this may be misleading and the actual performance and accuracy of drug infusion would be far from the desired level. This would lead to severe consequences. Air-in-line detectors use ultrasonic or optics for detecting air bubbles in the line. Air-in-line and occlusion detectors are designed for use with a particular infusion set. Therefore, these detectors may not be working properly if an incorrect set is used. Some other unwanted results are underinfusion due to very small inner-diameter of tube; overinfusion due to tubing material that is not flexible enough; and wear or rupture of tube from pumping action due to tubing material that is not strong enough. It is therefore important to use recommended sets for infusion. Specifications for testing of pumps at maximum flow rates are currently not given by the international standard for infusion devices. Therefore some fall-off in performance at high flow rates should be expected (3).

Most infusion pumps used today are modern, sophisticated versions of one of these two types of pumps. With the development of small, portable pumps with specialized uses for particular types of therapies and adaptations, these pumps are being used commonly by nonprofessionals as part of home therapy. Because computerized pumps can deliver medication at a wide range of dose frequencies and intensities, they broaden the scope of therapies that can be safely and effectively administered at home.

Pumps specifically for the infusion of narcotics to treat cancer-related pain, for example, may have adaptations that provide a low level of ongoing infusion, but also permit patients to dose themselves with bursts of medication when pain becomes intense, up to a preprogrammed number of such extra doses per day. Other pumps, designed for the volume of fluid typical of most antibiotic therapy, can be preprogrammed to deliver infusions at standard intervals (e.g., four times per day), thus enabling patients to sleep undisturbed while receiving therapy. Pumps used for long-term IV nutrition administration, on the other hand, may be designed to administer the large volume of fluid required for the overnight infusions typical of patients receiving this therapy. Infusion pumps currently available range in complexity and sophistication. These pumps can range from very simple, single-medication stationary infusion pumps to fully programmable, ambulatory pumps.

Sophisticated pumps can deliver multiple medications and are equipped with a variety of alarms, bells, and other warning mechanisms. While stationary pumps may be appropriate for patients who are bedridden or whose medications are delivered over shorter periods of time, ambulatory pumps provide greater independence for patients on continuous, frequent, or long-term therapy regimens. Many pumps also have automatic piggyback mechanisms that control secondary infusions at an independent rate, decreasing the nursing time required for multiple infusions (15). Besides these benefits and advancements, infusion pumps do have certain disadvantages. If patients, caregivers, or even health professionals find the level of sophistication of these pumps confusing, the patients' safety could be jeopardized through misuse of equipment. Many patients, and the nurses who instruct and care for them, might prefer simpler models that are easier to operate. Even many hospital nurses are unfamiliar with or unaware of sophisticated features of pumps they use on a regular basis. Highly sophisticated pumps cost more and often require considerably more training for both the health professional and the patient than simpler models. New types of electronic infusion pumps are constantly evolving, widening the menu from which providers must choose and from patients and health professionals must learn to operate.

Syringe Pumps. In this type of pump, drug is pumped forward in the tubing by a syringe-type pushing action. Schematic drawing of a syringe pump is depicted in Fig. 5. The syringe is placed in a housing of the pump, while syringe plunger is attached to a moving carriage. The carriage is attached to the lead screw through a nut,

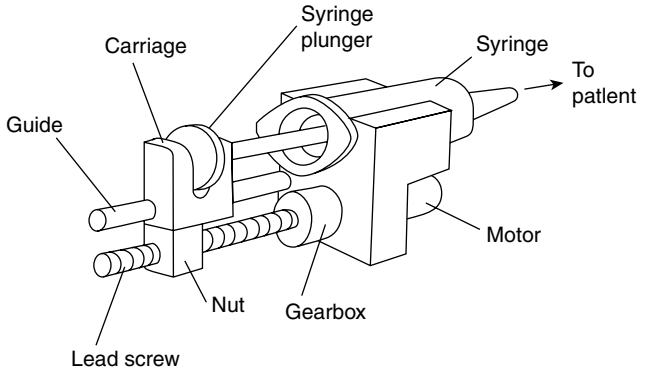

Figure 5. Typical syringe pump (3) © CROWN COPYRIGHT.

and the lead screw is attached to the motor through a gearbox. As the motor rotates, lead screw forces the carriage to slide on the guide, resulting syringe plunger to move forward in the syringe. This forward action delivers the drug to patient and empties the syringe. Controlled rate for the delivery of a drug is ensured by controlling the motor speed and rotation. This controlled rate may be in steps or continuous.

Advanced syringe pumps permit the simultaneous administration of several different therapies at different intervals, with dosages and administration regimens preprogrammed on a microchip that fits in the back of the pump. Syringe pumps can deliver small volumes of drugs at low flow rates. Single-use syringes are inexpensive and mass manufactured items, and are not meant to be highly accurate. When used in a syringe pump at low plunger speeds, the friction between the syringe plunger and the barrel causes a jerking effect and the fluid is delivered as a series of small boluses. The fit between the plunger and the barrel may vary from batch to batch and, consequently, the jerking effect may also vary. This problem is commonly known as stiction. In general, the bigger the syringe and the lower the flow rate, the more pronounced the stiction. Stiction may not be a problem with drugs having a long half-life or that do not require steady blood levels in the short term, such as heparin or insulin. In contrast, the delivery of powerful drugs with short half-life, like catecholamines, at rates under $5\,\mathrm{mL}\cdot\mathrm{h}^{-1}$ from large syringes (>30 mL) is not recommended.

Some currently available peristaltic pumps provide reasonably smooth flows at low delivery rates and should be considered as an alternative. Occasionally, the dimensions of a particular model of disposable syringe may be changed by the manufacturer. As a safe practice, only the syringe recommended by the manufacturer should be used with a syringe pump. These pumps are suitable for lower volume and low flow rate infusions. It is important to note that the actual drug delivered at the beginning of infusion process may be considerably less than the preset value. Due to the backlash, especially at low flow rates, it takes some time for the flow rate to reach steady-state regime.

Syringe pumps vary according to their functionality and so do their features. More advanced and expensive models have many features, including delivery pressure displays and in-line pressure monitoring. In most recent advanced pumps, one can set occlusion alarm pressures to very low values. This feature helps patients to prevent hazards due to occlusions by the alarm signal from the system in shorter times. These advanced pumps may also prevent the delivery pressure rising to unwanted high values. Since these devices are powered externally, placing them approximately at the patient's level will suffice for the pump to work satisfactorily. In fact, if the pump is placed well above patient's level, some draining could result.

Implantable Pumps. Some therapies that require very small drug dosages can be administered by way of totally implantable pumps. Insulin delivery, continuous epidural morphine administration for chronic pain management, and continuous venous antineoplastic therapy infusion for liver cancer patients are some examples where implantable pumps are used. The only service directly related to infusion therapy for these devices is refilling of the pump's reservoir, which may be done weekly or even less frequently in a medical outpatient or home setting (15).

Patient Controlled Analgesia (PCA) Pumps. These pumps are designed specifically for use in PCA. Unlike a general-purpose infusion pump, these pumps allow the patients to deliver the drug on their own by operating a switch or pressure pad connected by a cord to the pump. It is important that free-flow is prevented. These pumps can be connected to a computer or printer and have a memory, where data in terms of usage is stored. This feature allows the clinician to review when, how often, and how much of drug infused by the patient. The PCA pumps are typically syringe pumps, since the required drug to be infused can usually be supplied in a single-use syringe. Some PCA pumps are based on volumetric designs, in which a battery powered volumetric pump has a disposable internal fluid reservoir. The PCA pumps can be disposable (pneumatic and elastomeric) or nondisposable (3). The PCA pumps can be programmed by clinical staff in different ways. Options include loading dose, continuous infusion (basal rate), continuous infusion with bolus on demand, bolus on demand only, with choice of units (mL or $\mu\mathrm{g}\cdot\mathrm{mL}^{-1}$, etc.) and variable lockout time, drug concentration. Once programmed, a key or software code is needed to access control of the pump. In some cases, patients are given limited access in order to change some parameters.

Elastomeric Infusers. Elastomeric infusers are devices that can be used as substitutes for infusion pumps. These infusers consist of disposable containers with inner-elastic bladders that can be filled with the medication. The devices are sold empty and are filled by the pharmacist through a port at the top of the bladder. The drug flows through an opening at the base of the bladder membrane and into the tube leading to the patient. The force of the flow, and thus the rate of infusion, is determined by the elasticity of the bladder and the concentration of the drug, regardless of whether the bladder is above, below, or on level with the IV site. Different drugs and dosages require devices of differing size and bladder membrane composition. Most devices currently on the market are designed for either antibiotic or antineoplastic therapy administration. They can be used

for IV, intraarterial, and subcutaneous administration of drugs.

A patient on a twice-a-day regimen of home IV antibiotics would use two infusers per day, while a patient on continuous antineoplastic therapy might use a single device for several days at a time. Some devices allow patient-controlled administration of bolus doses above and beyond the continuous infusion rate. A disadvantage to the use of these devices for patient-controlled analgesia is the lack of a memory function that can record the frequency of patient-requested bolus doses, like that found in some electronic infusion pumps. Bladder devices are also not appropriate for multiple drug regimens. According to one home infusion provider, the availability of disposable elastomeric infusion devices has increased the feasibility of home-based care for disabled elderly patients. Like sophisticated electronic infusion pumps, these devices can deliver a precise dose over a specific period of time. However, because they are self-contained and much simpler to operate, they may be less confusing for patients who are uncomfortable with high tech equipment. The patient or caregiver need only hook the device to the catheter at dosing time and disconnect and dispose of it when the dose has been completed.

Anesthesia Pumps. These are also syringe-type pumps designed particularly for anesthesia infusion. Operating of these pumps is limited to theaters and high dependency areas. It is possible that the rate and other functions can be adjusted during infusion. Their flow rates are normally much higher than the typical syringe pumps rate. It therefore allows quick delivery in a single operation. These pumps can be interfaced with a computer and have built-in drug libraries. They are embedded with a drug-specific smart card and can be programmed for drug concentration and patient's body weight. The pump is automatically configured for the drug being infused. If the pump is to be used for other applications, automatically built-in features for specific application must be disabled.

Ambulatory Pumps. These pumps are designed so that patients can continue their drug therapy away from the hospital. These pumps allow patients to continue their normal life while treatment is being given. For ease of use and carry they are light and small in size, and are powered by battery. Alarming features of these pumps are not fully provided due to limitation in their size; therefore, their use in therapies in which precise flow is required for critical drugs is not recommended. The main mechanism used in these pumps is the syringe or cassette type.

Therapies that can be administered by ambulatory pumps include analgesia, continuous and PCA, antibiotic or antiviral infusions, chemotherapy, and hormone delivery. Back pressure, temperature of the flow-limiting element, temperature, and viscosity of the fluid are such factors that determine the accuracy of ambulatory pumps. One type of ambulatory pump manufactured by Baxter is given in Fig. 6. Depending on the pumping mechanism used, flow rates can range between 0.01 and 1000 $mL \cdot h^{-1}$. Different models have different features. Flow rates can be set in millimeters per hour or day, milliliters per hour or day. They can also be programmed for different delivery modes (3). Ambulatory pumps are generally powered by electricity. Accuracy and alarming features will be limited if the pump is not powered by electricity. The pumping mechanism is generally the same mechanism used in volumetric and syringe pumps.

Some ambulatory pumps are reusable. They consist of a syringe that is operated by pressurized gas, usually carbon dioxide or a precompressed spring. In the case of a pressurized-gas-operated system, the force generated by the pressurized gas pushes the syringe plunger. As the syringe plunger moves forward, it infuses the drug to the patient. The infusion rate is determined by the pressure of the gas as well as the rate at which pressurized gas is released. When the infusion is completed, syringe and gas cartridges are thrown away and the rest of the device is kept for future use. Infusers and bolus-only analgesia devices controlled by the patient are of disposable devices. They

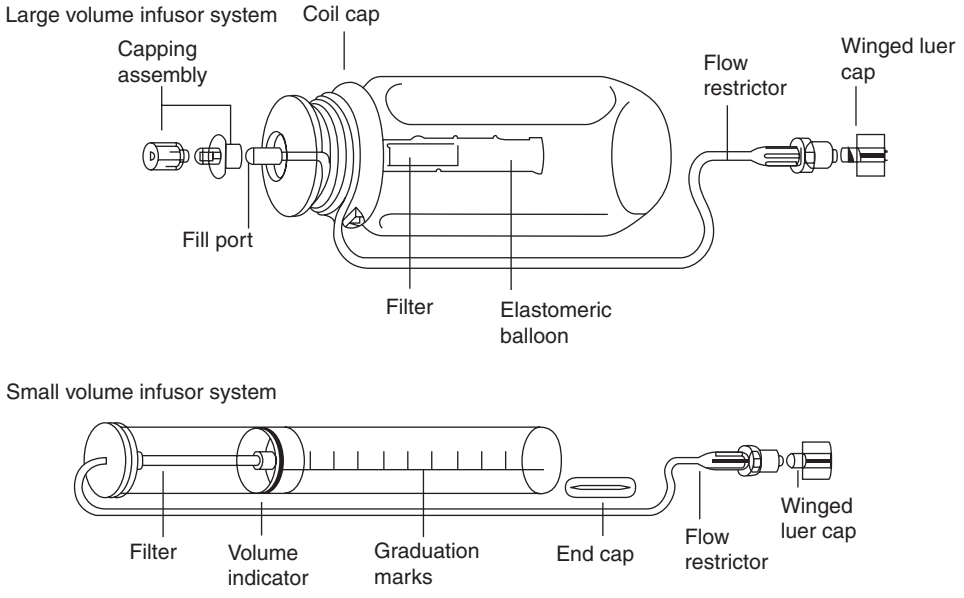

Figure 6. Ambulatory pumps manufactured by Baxter.

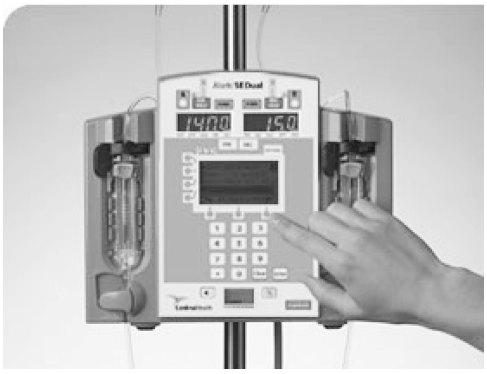

Figure 7. Signature Edition Gold infusion system by ALARIS. A range of infusion programs can be selected to save nursing time and meet sophisticated administration requirements including: Loading Dose, Multi-Dose and Multi-Step.

consist of a calibrated bolus chamber that is filled from an elastomeric reservoir or syringe by a capillary tube (3).

There are a number of companies that manufacture a variety of drug infusion systems. Some of the state-of-the-art products are given in Fig. 7–11. Abbott Laboratories' hospital products business (now Hospira), introduced the Plum A+ IV drug delivery medication management system. This system is an innovative infusion system for electronic control of intravenous medication administration. It is used for standard, piggyback, or concurrent delivery and are suitable for a wide range of medical–surgical and critical care applications

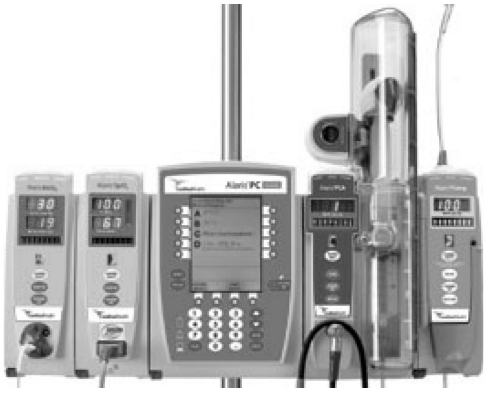

Figure 8. The Medley medication Safety System by ALARIS is a modular point-of-care computer that integrates infusion, patient monitoring and clinical best practice guidelines in a single platform for optimal outcomes.

NEW DEVELOPMENTS IN DRUG INFUSION SYSTEMS

Advances in science and technology result in new materials and devices. These materials and in particular electronic devices allow engineers to develop smarter, better performed, smaller, reliable, and cost-effective products. Therefore, new drug infusion systems are being developed and increasingly used in hospitals as well as in home therapies. Some of these developments are summarized in the following list.

***Automated Syringe-Filling System*:** Stanford Research Institute's (SRI) drug delivery system expertise is to develop a compact, home device for diabetics that would help them fill their insulin syringes accurately. The system needed to handle both long- and fast-acting insulin formulations and needed to be easy to use and reliable for elderly and vision-impaired patients. The SRI developed an automated system that stored both types of insulin, automatically resuspended the long-acting insulin, checked for adequate drug supply, dispensed the proper amount of medication, and kept a dosage record. The system is under test and evaluation (16).

***Disposable Drug Infusion Pump*:** Medical devices and pharmaceutical companies working with SRI to reengineer a disposable drug infusion pump design that reduced the number of parts by 30%, and reduced cost (16).

***Tiny Drug Infusion System*:** A tiny meter in a belt will someday monitor dosages of up to 12 drugs needed around the clock by patients with diabetes, cancer, or acquired immune deficiency syndrome (AIDS). The dime-sized device is being developed by Integrated Sensing Systems Inc. The device will make sure patients are receiving the correct drug in the right volume at the right flow rate. It will hook into a drug controller that attaches to a patient's belt. The controller, $\sim 2.5 \times 1$ in., (6.35×2.54 cm) will deliver drugs from an attached reservoir to the patient. The system, as envisioned, will

Figure 9. Outlook Safety Infusion System with DoseScan and DoseGuard by B|BRAUN technologies helping to ensure that the Right patient receives the Right medication in the Right dose from an authorized clinician at point of care.

Figure 10. The Ipump Pain Management System by BAXTER can be programmed for epidural, IV, or subcutaneous delivery. The PCA doses can be set per hour. Control flow rates can be set in 0.1 $mL \cdot h^{-1}$ increments for maximum flexibility with continuous flow rates up to 90 $mL \cdot h^{-1}$.

Figure 11. This AITECS by EO Systems is a multipurpose syringe pump with flow rates from 1 to 1500 $mL \cdot h^{-1}$, can be used for any nuclear cardiology and nuclear medicine infusion.

simultaneously deliver up to 12 drugs in units as small as nanoliters, or billionths of a liter (17).

***Bar-Coded Infusion System*:** B. Braun Medical has introduced the Horizon Outlook IV Safety Infusion System. Braun notes that the most common source of human error is inaccurate manual programming of intravenous pumps. The Braun infusion system uses bar code technology to ensure the right patient is receiving the right drug in the right dose from an "authorized" clinician. Its patented DoseScan bar code technology creates a primary level of safety, with automated checks and balances that augment the manual procedures in use today. Secondary protection is provided by its DoseGuard software, which notifies clinicians if institution defined dose limits are exceeded (18).

***Coronory Micro-Syringe*:** EndoBionics has created the first micromedical device to inject safely through vessel walls. Using standard interventional procedures, physicians will position the EndoBionics μSyringe (MicroSyringe) in coronary or peripheral vessels. While the μSyringe is closed, the microneedle is hidden and does not injure vessel walls as it is maneuvered into place. When the μSyringe is opened, the microneedle slides through the vessel wall to inject drugs directly to the surrounding tissue. The drugs are deposited around the outside of the vessel and diffuse inward through the vessel layers. The microscopic puncture is so small that it heals almost immediately, limiting trauma and bleeding (19).

***Needleless Injection*:** PowderJect Technologies has developed a technology that could be considered a hybrid of transdermal and parenteral (injection): a needleless injection. The company's device propels powder drugs with a supersonic jet of helium gas. A high pressure ampule of helium within the device is broken open, the gas flows through a cassette that is holding the powder between two membranes. The membranes rupture and the gas stream picks up the particles. The particles are propelled fast enough to penetrate the stratum corneum, the outer layer of the skin. The drug is targeted to the boundary between the epidermis and the dermis. Drugs then dissolve and either reach systemic circulation or exert a local effect. Vaccines can be picked up by antigen-presenting cells in the epidermis or by the lymph system (20).

Alza is another company that is developing technologies to deliver drugs through the skin. One of these technologies, called E-Trans, uses electrical current to deliver drugs across the skin, a process known as iontophoresis. The lead product is for the on-demand delivery of fentanyl, an opioid analgesic used for the treatment of acute pain. When a patient pushes a button on the device, current flows between two electrodes. As current flows, we get a predetermined amount of drug injected into the body. That gives a very reliable way of delivering a particular amount of drug into the body (20).

Alza is also developing what it calls Macroflux technology, which incorporates a thin titanium screen with microprojections to create mechanical pathways for drug transport. It expands the range of drugs amenable to transdermal delivery to include small hydrophilic molecules and macromolecules. It can be incorporated with the E-Trans technology or more traditional transdermal patches. One simple prototype in early exploration involves a Macroflux system where the projections have been coated with the therapeutic agent, such as a macromolecule. After application, the agent is rapidly absorbed into the skin (20).

Elan Pharmaceutical Technologies have a technology known as Medipad worn by the patient on the chest, back, or abdomen. The device is a small, plastic gas-driven pump with an adhesive backing. The adhesive is used to attach the device to the patient's body, and a button is pressed. A needle is deployed, which enters the subcutaneous space and then delivers the drug at a constant rate until the entire content of the reservoir is expended. The first applications for this device will be in chronic pain management and in the delivery of macromolecules that have inherently short biological half-lives (20).

***A Novel Device for Flow Monitoring*:** A novel device for blockage detection in catheters during drug delivery is designed. This device consists of a low cost disposable microfluidic chip and a nondisposable detection unit. The microfluidic chip consists of a microstructured silicon layer bonded between two glass covers using anodic bonding technology. The flow monitoring is performed by a robust light transmission method. The main component of the microfluidic chip is a movable element coupled with a spring to a base. Depending on the drug flow state the element is blocking or vacating an optical path through the chip (21).

***A High Performance Silicon Micropump*:** A new, low cost, high performance silicon micropump has been developed for a disposable drug delivery system (22). It is reported that the pump demonstrated linear and accurate (±5%) pumping characteristics for flow rates up to 2 $mL \cdot h^{-1}$ with intrinsic insensitivity to external conditions. The stroke volume of 160 nL was maintained constant by the implementation of a double limiter acting on the pumping membrane. The chip is a stack of three layers, two Pyrex wafers anodically bonded to the central silicon wafer. The technology is based on the use of Silicon On Insulator (SOI) technology, silicon Deep Reactive Ion Etching (DRIE), and the sacrificial etch of the buried oxide in order to release the structures (22).

***An Implantable Microfabricated Drug Delivery System*:** A fully implantable drug delivery system capable of delivering hundreds of individual doses has been developed by MicroCHIPS (23). This product is intended for the controlled release of potent therapeutic compounds that might otherwise require frequent injections. The device is capable of storing therapeutic drugs in solid, liquid, or gel form. It allows individual storage of discrete doses for multiple-drug regimens. Device monitoring and therapy modification can be achieved via wireless communication with an external controller. Currently, a fully implantable device contains 100 individual doses. A future device intended for human clinical trials will contain 400 doses, enough for a daily release of drug for >1 year (23).

***A Water-Powered Microdrug Delivery System*:** A plastic microdrug delivery system has been designed by utilizing the principle of osmosis without any electrical power consumption. The system has an osmotic microactuator and a polydimethylsiloxane (PDMS) microfluidic cover compartment consisting of a reservoir, a microfluidic channel, and a delivery port. The typical dimension of the microfluidic channel is 1 cm in length with a cross-sectional area of 30–100 μm^2 to minimize the diffusive drug flow while pressure drop remains moderate. Employing the net water flow induced by osmosis, the prototype drug delivery system has a measured constant delivery rate of 0.2 $\mu L \cdot h^{-1}$ for 10 h, with an accumulated delivery volume of 2 μL. Both the delivery rate and volume could be altered by changing the design and process parameters for specific drug delivery applications up to a few years (24).

***Microflow Regulator for Drug Delivery Systems*:** A micromachined flow regulator has been designed to provide a constant liquid flow rate of 1 $mL \cdot h^{-1}$ within a pressure difference of 100–600 mbar (0.01–0.06 kPa). At pressures >600 mbar (0.06 kPa) the device is designed to block the flow, preventing an overdelivery of medicine. One application of this device is the replacement of the flow restrictor in an elastomeric infusion system, which will increase the accuracy and safety of the drug delivery system. This pressure compensating flow regulator is passive; hence it needs no external energy source. The device is small, lightweight, and relatively inexpensive; therefore, it could be used as a disposable unit in a microfluidic system (25).

***Nanoengineered Device for Drug Delivery*:** A high precision device has been developed to yield long-term zero-order release of drugs for therapeutic applications. The device contains nanochannels that were fabricated in between two directly bonded silicon wafers, and therefore poses high mechanical strength. Diffusion through the nanochannels is the rate-limiting step for the release of drugs (26).

***Smartdose by PRO-MED AG*:** This device is a safe, accurate, and simple infusion system. It is a disposable prefilled drug delivery system for enteral or parenteral controlled infusion. SmartDose is equipped with its own source of energy (chemical reaction) to dispense liquid over a specific time with a predetermined administration rate. The administration accuracy and safety is comparable with those of electronic pumps, yet the ease of use is similar to a simple infusion bag. The system is especially convenient for emergency, ambulatory, and homecare therapy, as well as for hospitalized patients (27).

***Biodegradable Polymeric Drug Delivery Systems*:** These systems are increasingly being used for the design of temporary drug delivery systems. As these polymers hydrolyze in the body into low molecular degradation products, which are either metabolized or excreted, biodegradable delivery systems do not have to be removed after completion of release. Poly(DL-lactide-*co*-glycolide) (PLGA) is the most widely investigated biodegradable polyester and is widely used as a carrier polymer in parenteral sustained release formulations, either as microspheres, microparticulates or injectable gels (28).

RECENT ADVANCEMENTS IN CONTROLLER DESIGN FOR DRUG INFUSION SYSTEMS

Closed-loop system control is a technological concept that may be applicable to several aspects of critical care practice. This is a technology in the early stages of evolution and much more research and data are needed before its introduction into usual clinical practice. Furthermore, each specific application and each device for each application are sufficiently different in terms of hardware and computer algorithms (29). Studies have shown that closed-loop infusion systems may have a role in critical care

practice, improve clinical outcomes, eliminate errors due to poor performance of automated infusion devices, and provide precise, error-free drug administration. Some of the most recent works in advanced controller designs are reviewed below:

Huzmezan et al. (30) states that feedback control of drug administration is well suited to anesthetized surgical patients as well as the critically ill patients because of drugs with rapid onset times, short duration of action and small margins of safety are frequently used. The application of an adaptive predictive process control technology to drug administration will assist physicians in avoiding both overdosages and underdosages in their patients. An adaptive controller would avoid overdosing and underdosing by compensating for nonlinear drug responses as well as inter- and intrapatient variation (30).

Linkens has proposed the design of a fuzzy control for patient muscle relaxation (31). With advancements in sensor and instrumentation technology, automated drug infusion systems are also evolving into hierarchical systems. Research in this area has led to a variety of control strategies ranging from simple linear controllers to complex adaptive and rule-based schemes to handle inter- and intrapatient variability in drug responses (31).

For the assessment of depth of anesthesia, an intelligent system has been developed, which utilizes auditory evoked brain potentials, heart rate, and blood pressure measurements (32). Using wavelet analysis, the features within the auditory evoked signals are extracted and then fed to a learning neurofuzzy system, which in turn classifies the depth of anesthesia. In addition, the heart rate and blood pressure signals are used as a second measure based on a rule-based fuzzy logic system. The two measures are then fused to give a final indication of anesthetic depth. This is then fed back to a target controlled infusion (TCI) system for regulating the infusion of the drug Propofol for the maintenance phase of anaesthetic state (32).

A control strategy is developed by Bequette to regulate blood pressure and cardiac output during surgery (33). Adaptation is incorporated through a multiple model predictive control (MMPC) approach. A Bayesian-based estimator recursively updates weighting functions to find the best combination of models that describes the current input–output behavior; this weighted model is used for the output prediction (33).

A robust direct model reference adaptive controller (DMRAC) is developed by Palerm et al. (34) for plants with uncertainty in both the time delay elements and in the transfer function coefficients. The control of hemodynamic variables, particularly mean arterial pressure (MAP) and cardiac output (CO), is a challenging problem. A good controller is difficult to design, due to the complex, nonlinear behavior of the system. Adding to this are the significant changes in dynamics from one patient to another, and even variations in the patient's response to the drugs as his condition evolves (34).

A model predictive control strategy is developed and tested on a nonlinear canine circulatory model for the regulation of hemodynamic variables under critical care conditions (35). Different patient conditions, such as congestive heart failure, postoperative hypertension, and sepsis shock are studied in closed loop simulations. The model predictive controller, which uses a different linear model depending on the patient condition allows constraints to be explicitly enforced. The controller is initially tuned based on a linear plant model, then tested on the nonlinear physiological model; the simulations demonstrate the ability to handle constraints, such as drug dosage specifications, commonly desired by critical care physicians (35).

To evaluate the use of intelligent systems in the improvement of patient care, an agent was developed to regulate ICU patient sedation by Moore et al. in (36). A temporal differencing form of reinforcement learning was used to train the agent in the administration of intravenous propofol in simulated ICU patients. The agent utilized the well-studied Marsh–Schnider pharmacokinetic model to estimate the distribution of drug within the patient. A pharmacodynamic model then estimated drug effect. The agent demonstrated satisfactory control of the simulated patient's consciousness level in static and dynamic set-point conditions. It also satisfactorily demonstrated superior stability and responsiveness when compared to a well-tuned PID controller, which is a method of choice in closed-loop sedation control literature (36).

Advanced model-based controllers that can take into account the model of the patient and constraints on the state of the patient and the drug infusion rates have been developed (32). Delivery of insulin to type 1 diabetics, control of anesthesia, and chemotherapy for cancer patients are typical examples of drug delivery systems. The main objective of a drug delivery system is to provide effective therapy while minimizing the side effects. These controllers are based upon the theory of multiparametric programming. This theory allows an optimal division of the multidimensional space of the state of the patient into a set of regions and each region is characterized by a unique drug infusion law that is an explicit function of the state in the corresponding region. These developments simplify controller implementation and result in tighter control of drug infusion rates and better lifestyle for patients (37).

Parker et al. in (38) discusses closed-loop blood glucose regulation algorithms that use the intravenous route for insulin delivery to insulin-dependent diabetic patients. Classical control methods and advanced algorithms using implicit knowledge or explicit models (empirical, fundamental, or gray-box) of the diabetic patient are examined in (38). Current research on characterizing patient variability is presented, in the context of a model predictive controller able to adjust to changes in patient glucose and insulin sensitivity (38).

Linkens in (39) presents the control of on-line drug infusions to patients in an operating theater for regulating their muscle relaxation according to necessary surgical procedures. It is stated that fuzzy logic control (FLC) offers the advantages of model-free controller design for systems that are dynamically nonlinear, uncertain, and possibly time varying (39).

Rao et al. discusses the design of two different control methodologies for automated regulation of hemodynamic variables in (40). These controllers are designed to regulate

MAP and CO in critical care subjects using inotropic and vasoactive drugs. Both controllers account for inter – and intrapatient variability and handle drug infusion constraints. The first approach is a multiple model predictive controller (MMPC). The algorithm uses a multiple model adaptive approach in a model predictive control framework to account for variability and explicitly handle drug rate constraints. The second approach, a robust direct model reference adaptive controller (DMRAC) is developed for plants with uncertainty in both the time delay elements and in the transfer function coefficients, such as the drug infusion process. The controllers are experimentally evaluated on canines that are pharmacologically altered to exhibit symptoms of hypertension and depressed cardiac output (40).

Bequette (41) discusses the development of an artificial pancreas and current efforts in the control of complex systems. It is stated that advances in continuous glucose sensing, fast-acting insulin analogues, and a mature insulin pump market allow commercial realization of a closed-loop artificial pancreas. Model predictive control is discussed in-depth as an approach that is well suited for a closed-loop artificial pancreas (41).

Target controlled infusion (TCI) systems are discussed by Van Poucke et al. (42). In their work, a novel mathematical algorithm is proposed for controlling the effect site concentration using a TCI device. The algorithm limits the peak plasma concentration, thereby slowing the onset of anesthetic drug effect, but potentially ameliorating side effects. Simulations are used to examine the delay in time to peak effect for fentanyl, alfentanil, sufentanil, remifentanil, and propofol when the peak plasma concentration is limited by the algorithm. Results showed that the plasma overshoot can be reduced by 60% with only $\sim 20\%$ delay in the onset of drug effect (42).

McKinley et al. (43) compares the effectiveness of a new method of closed-loop control of blood pressure with usual manual control. In their work, closed-loop and manual drug administrations were studied. The target and observed MAP and drug infusion rate were recorded electronically. Time taken to achieve initial control; fidelity of control, and average drug dose administered were all measured. Results showed that closed-loop achieved faster initial control and greater fidelity as compared to manual control. There was no difference in average drug dose administered. It was concluded that the new closed-loop system is more effective than the usual manual control in managing acute blood pressure disturbances in the seriously ill patients (43).

The bispectral index (BIS) was used for automatic control of propofol anesthesia, using a proportional-integral-differential control algorithm (44). The performance of the controlled system was measured in patients undergoing minor surgery under propofol and remifentanil anesthesia. Anesthesia was manually induced with target-controlled infusions (TCI) of propofol and remifentanil. After the start of surgery, when anesthesia was clinically adequate, automatic control of the propofol TCI was commenced using the closed-loop system. The system provided adequate operating conditions and stable cardiovascular values in all patients during closed-loop control. The system was able to provide clinically adequate anesthesia in all patients (44).

Brock et al. in (45) presents a study to determine the relative advantage of computer-controlled couch movement versus manual repositioning to correct patient setup error measured using an electronic portal imaging device (EPID). The speed of setup adjustment and accuracy of corrected setup were determined. Computer-controlled setup adjustment was determined to be faster and slightly more accurate than manual correction (45).

Another comparison study between computer and manual control is presented in (46) by Hoeksel et al. They investigated the effects of computer-controlled blood pressures on hemodynamic stability when compared to conventional manual control. Systemic artery blood pressures were managed either by computer or by a well-trained anesthesiologist. Hemodynamic stability was determined from the standard deviation of the MAP samples and from the percentages of time that arterial pressure was hypertensive or hypotensive. The average standard deviation of the MAP samples was smaller for the computer-controlled than for the manually controlled group. The systemic artery pressure was less hypertensive and less hypotensive in the computer-controlled than in the manually controlled group. It was concluded that, compared with manual control, computer control of systemic hypertension significantly improved hemodynamic stability during cardiac surgery (46).

The clinical applicability of administering sodium nitroprusside by a closed-loop titration system compared with a manually adjusted system was evaluated. The MAP was registered and the results were then analyzed. It was reported that the computer-assisted therapy provided better control of MAP, was safe to use, and helped to reduce nursing demands (47).

Chitwood et al. in (48) states that hypertension is common after a cardiac operation and has been treated using manually controlled doses of intravenous sodium nitroprusside. To evaluate the clinical impact of an automated closed-loop administration system on patients after cardiotomy, a prospective trial was conducted. Patients with hypertension were managed by either manual nitroprusside titration or a closed-loop automated titration system. The automated group showed a significant reduction in the number of hypertensive episodes per patient. At the same time, the number of hypotensive episodes per patient was reduced with automated closed-loop titration. Chest tube drainage, percentage of patients receiving transfusion, and total amount transfused were all reduced significantly by the use of an automated titration system (48).

A nonprogrammable and programmable insulin external pump using regular insulin on glycemic stability, the risk of severe hypoglycemia, and metabolic control in type 1 diabetic patients was compared (49). The results of the study suggest that programmable external insulin pumps, although more complex and more expensive than nonprogrammable insulin pumps, significantly reduce fasting glycemia during the day without increasing the risk of severe hypoglycemia and are safer during the night (49).

In Ref. 50, it was argued that continuous improvements in microelectronics, as well as in the development of biomaterials and stable insulin solutions, led to the availability of implantable pumps that are able to infuse insulin by the peritoneal route, in a continuous and programmable way, for several years. These systems represent the most efficient and physiological mode of insulin therapy at the present time. It was demonstrated during clinical trials that intravascular, implantable, glucose sensors using glucose oxidase were able to measure with good accuracy real-time blood glucose for several months. In their study, they performed the first trials of closed-loop insulin delivery according to sensor signal for periods of 48 h in type 1 diabetic patients. This mode of functioning appeared to be feasible and able to establish glucose control closer to physiology than the use of implantable pumps in open loop (50).

Tamborlane et al. (51) states that while treatment of Type 1 diabetes mellitus (T1DM) in children and adolescents is especially difficult, recent technological advances have provided new therapeutic options to clinicians and patients. The urgency to achieve strict diabetes control and the introduction of new and improved insulin pumps have been accompanied by a marked increase in use of continuous subcutaneous insulin infusion (CSII) therapy in youth with diabetes. Results of clinical outcome studies indicate that CSII provides a safe and effective alternative to MDI therapy, even when employed in a regular clinic setting in a large number of children (51).

BIBLIOGRAPHY

1. Draft for Public Comment, Australian/New Zealand Standard. 2005. DR04547.
2. Medtech, Inc., U.S. Markets for Drug and Fluid Delivery Devices. 2001. Report No. RP-485004.
3. Infusion Systems, Medical Devices Agency. 2003. MDA DB 2003(2).
4. Sparks DR, et al. Preventing medication infusion errors and venous air embolisms using a micro-machined specific gravity sensor. Adv Deliv Devices 2004.
5. Kohn L, et al., editors. Report of Institute of Medical Committee on Quality Health Care in America, To err is human: building a safer health system. Washington (D.C.): National Academy Press; 2000.
6. Phillips J, et al. Retrospective analysis of mortalities associated with medication errors. Am J Health-Syst Pharm 2001;58:1831–1841.
7. Gorman R, et al. Prevention of medication errors in the pediatric inpatient setting. Pediatrics 2003;112(2):431–436.
8. Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. BMJ 2003;326:684–696.
9. Parshuram C, et al. Discrepancies between ordered and delivered concentrations of opiate infusions in critical care. Cri Care Med 2003;31(10):2483–2487.
10. Smart infusion pumps join CPOE and bar coding as important ways to prevent medication errors. ISMP Me Safety Alert 2002.
11. Wilson K, Sullivan M. Preventing medication errors with smart infusion technology. Am J Health-Syst Pharm 2004; 61(2):177–183.
12. Steingass SK. Beyond pumps: Smart infusion systems. Nursing Management 2004;35:10–10.
13. Ferrari R, Beech DR. Infusion pumps: guidelines and pitfalls. Aust Prescr 1995;18:49–51.
14. Davis WOM. Types of pumps in use, Infusion devices training tutorial (Online). Available at http://www.ebme.co.uk/arts/art11.htm. 2004.
15. Home drug infusion therapy under medicare. Congress of the United States, Office of Technology Assessment. 1992.
16. Intravenous therapy monitoring and discontinuing, (online) http://www.laras-lair.com/nursing/IVtherapy.pdf. RPN Self Learning Package. SRI International-Medical Development (Online). Available at http://www.sri.com/esd/med_devel/altdrugdel.html. 2005.
17. Infusion device could improve drug delivery (Online). Available at http://www.detnews.com/2004/technology/0402/16/b04-64095.htm. 2005.
18. Braun Medical introduces bar-coded infusion system (Online). Available at http://www.uspharmacist.com. 2002.
19. Endobionics, Inc. (online) http://www.endobionics.com/technology.html. 2005.
20. Henry C. Special delivery. Sci/Technol 2000;78(38):49–65.
21. Richter M, et al. A novel device for low flow monitoring in drug delivery systems. 8th Int Conf New Actuators 2002; 223–226.
22. Maillefer D, et al. A high performance silicon micropump for disposable drug delivery systems. Micro Electro Mechanical Systems (MEMS). The 14th IEEE International Conference on MEMS, 2001; p 413–417.
23. Maloney JM. An implantable microfabricated drug delivery system. Proc IMECE 2003;1–2.
24. Su Y, Lin L. A water-powered micro drug delivery system. IEEE J Microelectromechan Systems 2004;13(1):75–82.
25. Cousseau P, et al. Improved mico-flow regulator for drug delivery systems. IEEE Int Conf MicroElectroMechanical Syst 2001;527–530.
26. Sinha PM, et al. Nanoengineered device for drug delivery application. Inst Phys Publ Nanotechnol 2004;15:S585–S589.
27. Pro-Med AG. SmartDose controlled infusion systems. Business Briefing Pharmatech 2004;1–2.
28. Steendam R. SynBiosys: Biodegradable polymeric drug delivery system. Bus Briefing: Pharma Outsourcing 2005; 59–61.
29. Jastremski M, et al. A model for technology assessment as applied to closed loop infusion systems. Technol Ass Task Force Soc Crit Care Med 1995;23(10):1745–1755.
30. Huzmezan M, Dumont GA, Zikov T, Bibian S. Advances in automatic drug delivery for general anesthesia. Peter Wall Institute Exploratory Workshop, Automation and Robotics: The Key For Computer Integrated Health Care Delivery. University of British Columbia. 2002.
31. Linkens DA. Fuzzy control for patient muscle relaxation. Erudit News Letter. Vol. 2, No. 1 (online). Available at http://www.erudit.de/erudit/newsletters/news_21/page_5.htm, 2003.
32. Linkens DA. An intelligent system for drug delivery in control of anesthesia. Peter Wall Institute Exploratory Workshop, Automation and Robotics: The Key For Computer Integrated Health Care Delivery. University of British Columbia. 2002.
33. Bequette BW. A multiple model approach for adaptation during drug delivery. Peter Wall Institute Exploratory Workshop, Automation and Robotics: The Key For Computer Integrated Health Care Delivery. University of British Columbia. 2002.
34. Palerm C, Bequette BW, Ozcelik S. Robust control of drug infusion with time delays using direct adaptive control: experimental results. Am Control Conf 2000.
35. Rao R, Huang J, Bequette BW, Kaufman H. Control of a non-square drug infusion system-a simulation study. Biotechnol Prog ACS Pub 1999;15(3):556–564.
36. Moore B, Sinzinger E, Quasny T, Pyeatt L. Intelligent control of closed-loop sedation in simulated ICI patients. Am Assoc Artificial Intelligence 2004.

37. Dua V. Explicit model based control for drug delivery systems, CoMPLEX seminar (Online). Available at http://www.ucl. ac.uk/CoMPLEX/dua_abstract.html. 2004.
38. Parker R, Doyle F, Peppas N. The intravenous route to blood glucose control. IEEE Eng Med Bio Mag 2001;20(1):65–71.
39. Linkens DA. Fuzzy control for patient muscle relaxation. Erudit News Letter Vol. 2, No. 1, (Online). Available at http://www.erudit.de/erudit/newsletters/news_21/page_5.htm. 2003.
40. Rao RR, Palerm CC, Aufderheide B, Bequette BW. Automated regulation of hemodynamic variables. IEEE Eng Med Bio Mag 2001;20(1):2438.
41. Bequette BW. A Critical Assessment of Algorithms and Challenges in the Development of a Closed-Loop Artificial Pancreas. Diab Technol Therapeut 2005;7:28–47.
42. Van Poucke GE, Bravo LJB, Shafer SL. Target controlled infusions: targeting the effect site while limiting peak plasma concentration. IEEE Trans Biomed Eng 2004;51:1869–1875.
43. McKinley S, et al. Clinical evaluation of closed loop control of blood pressure in seriously ill patients. Crit Care Med 1991;19(2):166–170.
44. Absalom AR, Kenny GNC. Closed-loop control of propofol anesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery. Br J Anesthesia 2003;90:737–741.
45. Brock KK, McShan DL, Balter JM. A comparison of computer-controlled versus manual on-line patient setup adjustment. J App Clin Med Phys 2002;3(3):241.
46. Hoeksel SAAP, Blom JA. Computre control versus manual control of systemic hypertension during cardiac surgery. Acta Anesthesiol Scand 2001;45:553–557.
47. Bednarski P, et al. Use of a computerized closedloop sodium nitroprusside titration system for antihypertensive treatment after open heart surgery. Crit Care Med 1990;18(10):1061–1065.
48. Chitwood WR, III DMC, Lust RM. Multicenter trial of automated nitroprusside infusion for postoperative hypertension. Ann Thorac Surg 1992;54:517–522.
49. Catargi B et al. A randomized study comparing blood glucose control and risk of severe hypoglycemia achieved by nonprogrammable versus programmable external insulin pumps. Diab Metab 2001;27:323–328.
50. Renard E, Costalat G, Bringer J. From external to implantable insulin pump, can we close the loop? Diab Metab 2002;28(4 Pt. 2):19–25.
51. Tamborlane W, Bonfig W, Boland E. Recent advances in treatment of youth with type 1 diabetes: Better care through technology. Diab Metab 2001;18:864–870.

See also DRUG DELIVERY SYSTEMS; NUTRITION, PARENTERAL.