AUTO-INJECTOR DESIGN: MANAGING DRUG TEMPERATURE VARIATIONS

In this article, Jake Cowperthwaite, Partner and Senior Electrical Engineer, Key Tech, Inc, examines the impact of environmental and drug temperature variation on auto-injector performance and describes techniques for managing this variation on modern auto-injectors.

With the increasing prevalence of auto-injection devices, we're entering an age of do-it-yourself therapy and lifesaving. A self-administered drug injection to the thigh, abdomen, or other subcutaneous site (Figure 1) allows patients around the world to take control of their quality of life as well as receive life-saving medications, such as epinephrine.

Injectors may rely on mechanical (spring), electrical (battery) or other (e.g. compressed air) power sources. However, the fundamental architecture and design considerations are common to all injectors.

In recent years, the breadth of features and variety of drugs administered via auto-injectors has grown as pharma companies develop novel drugs, often biologics, which are not suitable for oral administration. This broader spectrum of drugs magnifies traditional auto-injector design challenges and introduces new obstacles. For example, the designer is now faced with managing a wider range of drug viscosities, dose volumes, dispense profiles, and use scenarios.

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UNIQUE TEMPERATURE CHALLENGES

Drug temperature has always been an important consideration in auto-injector design. Figure 2 shows a typical correlation between drug temperature and viscosity, where it is evident that viscosity increases exponentially as temperature is reduced.

Higher viscosity drugs require more energy to dispense when compared with the same configuration at room temperature. As temperature is reduced, either more power must be applied during the injection to maintain the same speed or the dispense duration must be allowed to increase.

Increased Power

For spring-powered injectors, applying more power to compensate for cold temperature is not an option because the pre-loaded spring has a nominal force profile intended to cover all injection temperatures. This design architecture inherently results in a longer dispense duration for colder drugs.

With an electronic injector, applying more power is an option. However, it will increase the size of the battery pack, motor, and gearbox, resulting in a larger device. The size of an auto-injector battery pack is typically based on peak amperage (as opposed to capacity) because injections are relatively short in most cases, making run-time less of a concern. The motor and gearbox must be designed to handle worst case torque conditions in order to avoid stalling or permanent damage. If the expectation is that users will normally inject the drug at room temperature, then this approach results in a larger than desired form factor simply to accommodate a rare use scenario. This is far from ideal in a product space oriented toward compact, portable devices.

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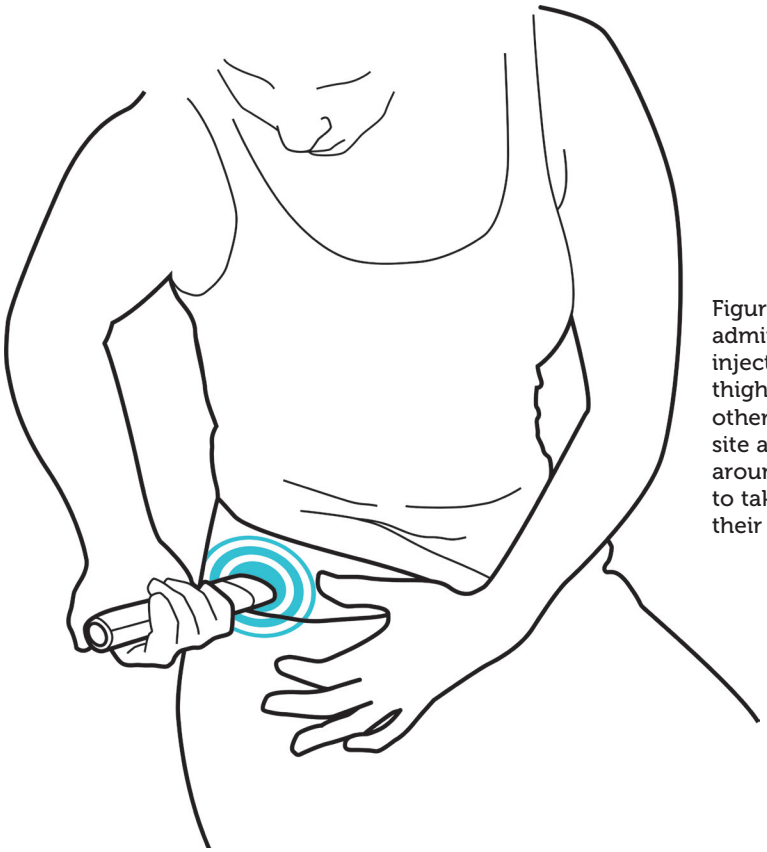

Figure 1: A self-administered drug injection to the thigh, abdomen, or other subcutaneous site allows patients around the world to take control of their quality of life.

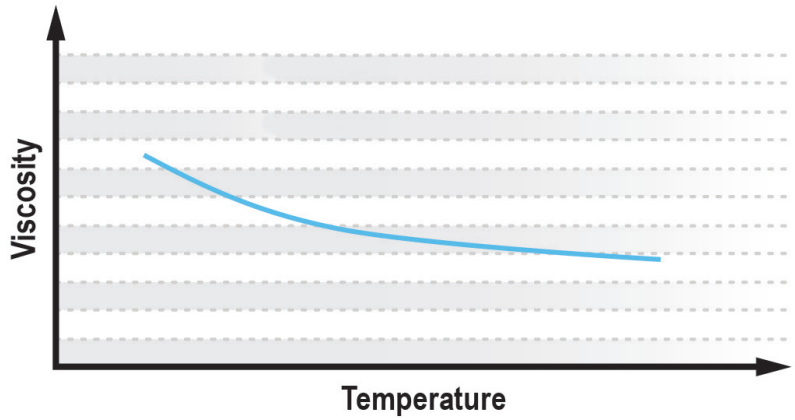

Figure 2: Typical correlation between drug temperature and viscosity.

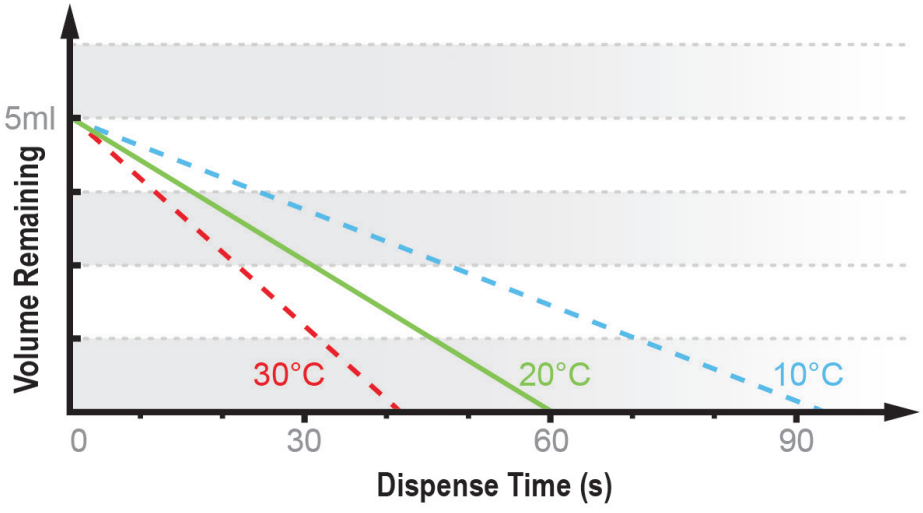

Figure 3: Examples of how dispense time could vary over temperature if the force remains constant.

Longer Injections

Increasing the dispense duration to compensate for cold drugs is also an option with electronic injectors if "smarts" exist to identify the condition. This may include either directly sensing the drug temperature or sensing the drive force and reducing speed to compensate for the increased force. The downside, in addition to longer injections, is that the device must include relatively complex sensors that add size and cost to the device. Figure 3 provides an example of how dipense time could vary over temperature if the force remains constant.

Longer injections can also introduce usability challenges. The user might not notice if a small dispense takes 50% longer because the timescale is very short, but as dose volumes become larger this impact can be significant. For example, a room temperature 1 mL dose that is normally delivered in five seconds might take seven seconds for a cold drug, which would not cause concern. However, auto-injectors designed to handle larger dose volumes with higher viscosity drugs might normally inject for five minutes or more. In these scenarios, the injection time could increase on the order of minutes, causing user confusion and potentially resulting in the needle being pulled away before the dose completes.

When designing for relatively long injections, it makes sense to consider a wearable injector to alleviate the burden of holding the device during administration and mitigate against partial dosing due to user distractions.

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Patient Discomfort

An additional challenge with dispensing cold drugs is user comfort. Evidence suggests that injecting a cold drug may cause more discomfort than a drug at room temperature, presumably because the absorption rate is reduced and the delivered drug has a tendency to pool in the subcutaneous site.

Design Solutions

The obvious solution is to prevent drugs from becoming cold but the reality is that many drugs must be stored between 2-8°C (e.g. in a refrigerator) to maintain efficacy. In fact global sales of drugs requiring cold change storage is growing at a rate nearly double those that do not require cold storage.

Temperature Interlocks

Electronic devices can include interlocks to prevent injecting cold drugs, although sensing drug temperature can be challenging. Electronic injectors are often re-usable and the drug cassette or syringe is inserted prior to use, creating a sensor interface challenge. Contact sensors (e.g thermistors) must be pressed against the exterior of the drug container and the embedded firmware may require a custom algorithm to infer when the drug has adequately warmed. An optical IR sensor can be used in a similar fashion without the need for physical contact, although at a higher cost.

Active Heating

Actively heating the drug in the device prior to injection has been considered, but is unappealing for a variety of reasons. First, rapid active heating of a biologic or other pharmaceutical solution may have unintended consequences that affect efficacy. This option would require extensive stability and pharmacokinetic studies to prove viability. Second, heating drugs requires significant power, particularly at larger volumes. Depending on the drug volume, heating time, and drug properties, the system could consume more energy during heating than for the actual drug delivery, which increases battery size. Finally, accessing the drug with a heating element is a challenge because the drug is typically encapsulated by a glass syringe, which acts as an insulator.

Over-Designing the System

A relatively common approach for managing temperature variation is to overdesign the system components so that the drug can be dispensed at the desired profile even at cold temperatures. This results in conservative design decisions and larger injectors that are capable of handling worst case forces.

Electronic injectors often include a battery "fuel gauge" for checking battery status prior to dispensing to ensure that the entire dose can be completed without interruption. If the designer is forced to assume that the drug could be cold, which requires more energy, the user may be forced to charge their device prematurely even if there is adequate charge for a room temperature dispense.

The needle gauge can also be increased to allow for dispensing higher viscosity drugs with less energy. However, this must be approached with caution because larger needles turn off many patients, resulting in compliance issues and poor product reception.

User Training

Traditional spring-based injectors have relied on the instructions for use and training to mitigate against cold drug injection. Patients are instructed to expose the auto-injector to room temperature for a defined period prior to injection. While this seems reasonable, users may not always have the time or foresight, and instead choose to inject a cold drug while bearing the increased discomfort.

One means to supplement training is to include a temperature sensitive sticker on the auto-injector or drug cassette. In this case the user is instructed to wait until the sticker turns a certain colour before performing an injection. This is a training improvement but it does not prevent users from injecting cold drugs.

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SUMMARY

Environmental and drug temperature variations must be considered during auto-injector design. In particular, the effects of a cold drug temperature can lead to more power consumption, longer injections, and patient discomfort. Techniques for managing temperature variation often result in larger, more expensive devices. The design of temperature management features is crucial as more high viscosity, large dose drugs that require cold storage are developed for use with auto-injectors.

ABOUT KEY TECH

Since 1998, Key Tech has been transforming complex technologies into intuitive medical products. The company designs and develops drug delivery devices, handheld instruments, capital equipment, and consumables using new sensors, wireless, ultrasound, microfluidics, optics and robotics.

Headquartered in Baltimore, MD, US, Key Tech's uniquely personal approach attracts industry leading global companies as well as innovative start-ups. Key Tech scientists, engineers and designers take technologies into new applications, keeping their client and partner pipelines fresh.

ABOUT THE AUTHOR

Jake Cowperthwaite is a Partner and Senior Electrical Engineer who has been at Key Tech since 2004. He has managed a number of large medical and industrial multidisciplinary projects from requirements generation through commercialisation. He has a thorough regulatory understanding and is responsible for streamlining and improving work-processes at Key Tech. His engineering expertise is in the areas of mixed signal design, power electronics, automation, and sensor integration.

Mr Cowperthwaite received a BSEE from the University of Maine (Orono, ME, US) and an MSEE from the University of Maryland (College Park, MD, US) with a concentration in micro-electronics. He is also a registered professional engineer.