Self-Injection Technology and Trends

Modern-day self-injection devices incorporate a number of advanced features which makes them more acceptable to patients, thereby saving on healthcare resources and costs.

By Ian Thompson at Ypsomed

Ian Thompson is Manager, Business Development, at Ypsomed AG, where he has been working for the last 10 years with pharma and biotech partners to develop and bring to market innovative and reliable injection systems for self-administration. Ian has 20 years' experience in the selling and marketing of technical products, the last 14 of which have been spent in the field of medical devices. He has a degree in Biochemistry, a Masters in Biotechnology and an MBA from Henley Management College, UK

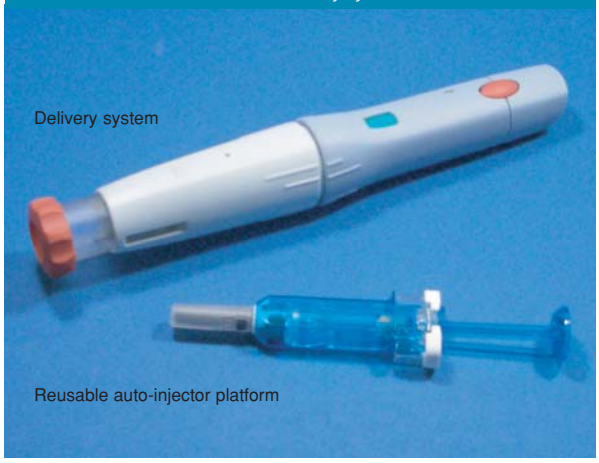
Self-injection technology has come a long way since the first devices were introduced in the early 1980s. Prefilled syringes are becoming more popular for self-injection, and auto-injectors are helping to simplify their use in both existing and new therapeutic areas. This article will review the development of self-injection technology over the years and examine some of the key features incorporated into modern-day devices, as well as possible future developments.

DEVELOPMENT OF THE TECHNOLOGY

The first 'sophisticated' self-injection device became available in 1984, with the launch of the first insulin pen injector. Pen injectors are essentially sophisticated syringes and were developed for the reliable and accurate self-administration of the first wave of biotech molecules, such as insulin and human growth hormone (hGH). Auto-injectors have been on the market as long as pen injectors but, until the 1990s, their use was restricted to emergency situations such as epinephrine for treating anaphylactic shock (EpiPen®). The first prefilled syringe-based reusable auto-injector came in the 1990s with the launch by Glaxo of a self-injectable formulation of its new anti-migraine product Imigran®/Imitrex® (sumatriptan). A disposable auto-injector for a therapeutic protein was first launched in 2005 by Amgen for its erythropoietic protein, Aranesp™ (darbepoetin alfa).

Figure 1: Early auto-injectors – EpiPen® and Imigran®-Pen

Figure 2: Auto-injector designed for SSI's UltraSafe® Passive™ Delivery system



SELF-INJECTION DEVICES

There are various different types of self-injection device available on the market today:

The pen injector is a cartridge-based device designed for the frequent – usually daily – manual injection of hormone replacement therapies. These therapies usually require weight-based dosing or dose titration, and injections are repeated until the cartridge is empty – usually after one to two weeks. The drugs in the multiple

dose cartridges require the use of preservatives, while individual doses are typically 0.5ml or lower in terms of injection volume. Pen injector patients are accustomed to injecting themselves manually with 29-31G pen needles, providing as 'comfortable' an injection as possible.

Auto-injectors, as their name implies, automatically insert the needle and perform the injection (typically spring driven), and are usually designed for use with fillable or prefilled syringes. A key requirement for auto-injection is the need for liquid-stable formulations in a prefilled syringe or cartridge-based drug reservoir.

Reusable auto-injectors have been used since the late 1980s for syringe-based hormone replacement therapies, and are increasingly being used for newer waves of biotech molecules as prefilled formulations became available – for example, β-interferon for treating multiple sclerosis (MS). Some of these drugs are injected daily, but many therapeutics are now injected weekly or less frequently, particularly those for treating autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. Most of these newer drugs do not contain preservative (monodose formulations) and have comparatively large injection volumes of up to 1ml.

The fully disposable auto-injector device is the obvious gold standard for self-injection. Here, the prefilled syringe is already packaged in the auto-injector, providing both ease-of-use and convenience for the patient. All the patient needs to do is remove the rubber needle cap, press the device against the skin and start the injection. The device performs the injection and the needle is automatically covered and made safe, as the device is removed from the injection site. A key prerequisite for these devices is the need for reliability; the injection must be completed every time, with an extremely low risk of failure. Patient feedback with disposable auto-injectors is important; the handling should be intuitive and the device should give visual and audible notification that the injection has been successful.

SCALE OF CONVENIENCE FOR PRE-FILLED SYRINGES

In view of the savings in healthcare costs that can be achieved by expanding the use of self-injection devices, a 'scale of convenience' has been created which includes prefilled syringes, safety syringes and auto-injectors. At the 'least convenient' end of the scale (1) would be a lyophilised drug in a vial, which would then have to be dissolved and drawn up into a syringe prior to injection. At the other end of the scale would be the fully disposable auto-injector which would score a maximum of 10 in terms of convenience (see Table 1).

Table 1: Scale of convenience for self-injection devices

Device	Scale of convenience
Lyophilised formulation	1
Luer syringe	↓
Pre-attached needle syringe	↓
Safety syringe	↓
Reusable auto-injector and safety syringe	↓
Disposable auto-injector	10

A simple prefilled syringe alone can bring much convenience to an injection therapy. This has been well-illustrated recently following the successful launch by Abbott of Humira® (adalimumab) in a prefilled syringe for the treatment of rheumatoid arthritis. But auto-injectors in combination with a prefilled syringe bring an additional level of ease-of-use and safety. For this reason, device companies and pharma partners are developing auto-injector platforms that are compatible with these increasing levels of convenience.

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Table 2: Main therapeutic areas for self-injection devices

Hormone Replacement Therapies
Insulin
Erythropoietin
β-interferon
Follicle stimulating hormone (FSH)
Parathyroid hormone
Heparin
Parkinson's
Autoimmune Diseases
Multiple sclerosis
Psoriasis
Allergies
Irritable bowel disorder
AIDS
Cancer
Emergency Drugs
Migraine
Anaphylactic shock

SAFETY FEATURES AND SAFETY SYRINGES

The operation and safety features of auto-injector devices are being continually improved. Currently, marketed reusable auto-injectors do not have complete needle safety, as they are generally used with standard prefilled syringes with pre-attached needles. However, in the normal clinical environment, it is the need for needle safety which has given rise to new safety syringe and safety delivery system products which are being fitted to prefilled syringes. Increasingly, patients who self-inject are concerned about the risks of needle-stick injuries to friends or family in their midst, and for the easy and safe disposal of the used product. They look for 'safety' – whether it is a syringe or an auto-injector that they are using.

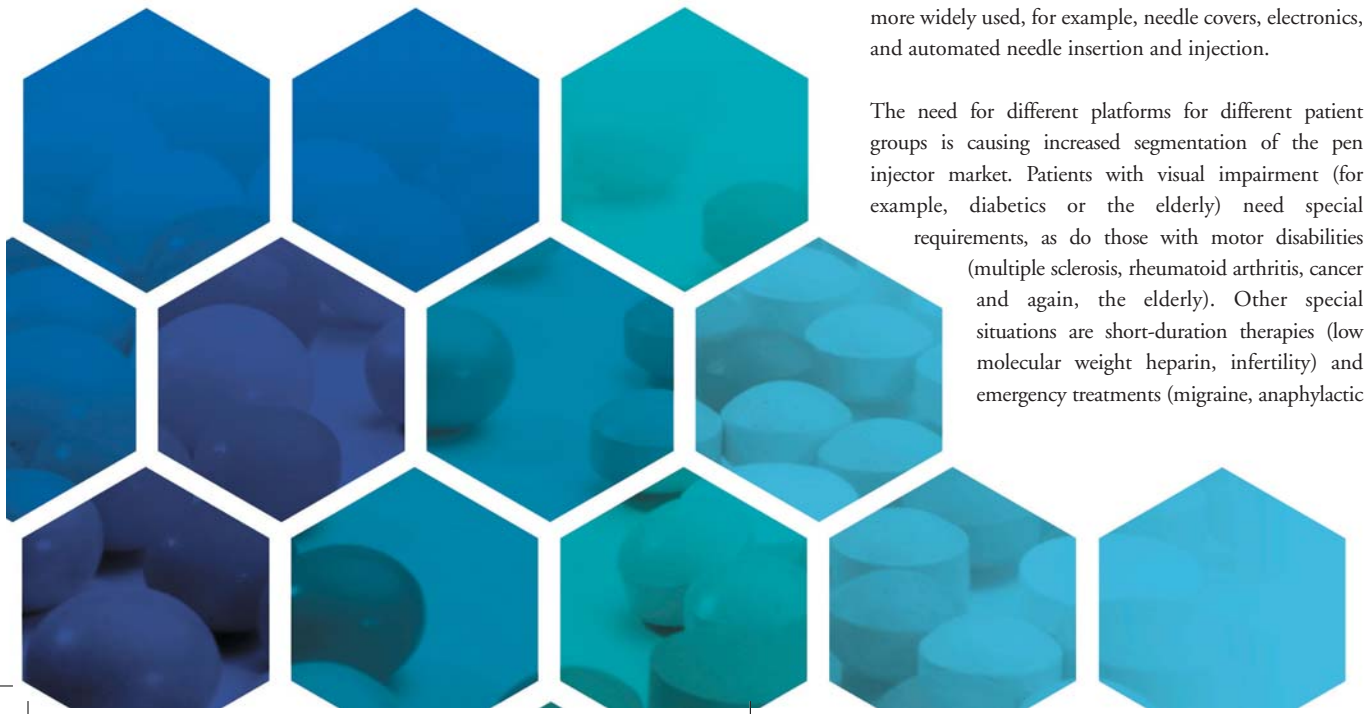
The first generation safety syringe devices were 'active', requiring the user to 'actively' make them safe after injection; by contrast, the newer 'passive' devices automatically provide needle-safety after the injection has been completed. These new passive devices not only provide needle-safety, but are also injection aids, which make it easier to perform injections. The passive devices – with their low activation forces – can also be used in conjunction with new generation reusable auto-injectors. If the patient is still fearful of performing a manual injection with a safety syringe, then a compatible, reusable auto-injector can be made available. This has the advantage that the same safety syringe can be used in both the clinic and home environment with the simple addition of an auto-injector for home care.

MARKET TRENDS

The market for self-injection devices – pens and auto-injectors – continues to show above-average growth as a result of several factors. The surge in biotech-based research means that many more protein therapeutics are reaching the market, driving demand for injectable products as a whole. Also, the increased incidence of diseases such as diabetes and the availability of therapies for previously untreatable conditions are expanding the injectables market. The advanced features of modern-day self-injection devices are making them much more acceptable to patients. If patients can self-administer their medications, then not only is it more convenient for them, it also saves on healthcare resources and costs, making self-injection much more cost-effective.

More recently, the market has been impacted by the introduction of prefilled syringes and auto-injection devices in new therapeutic areas, such as autoimmune diseases. Today, insulin still dominates the market, followed by hGH and newer therapies such as fertility treatment (FSH – follicle stimulating hormone) and osteoporosis (PTH – parathyroid hormone) (see Table 2). Disposable pen systems are generating increased interest, and pen needle safety and handling systems are becoming more widely used, for example, needle covers, electronics, and automated needle insertion and injection.

The need for different platforms for different patient groups is causing increased segmentation of the pen injector market. Patients with visual impairment (for example, diabetics or the elderly) need special requirements, as do those with motor disabilities (multiple sclerosis, rheumatoid arthritis, cancer and again, the elderly). Other special situations are short-duration therapies (low molecular weight heparin, infertility) and emergency treatments (migraine, anaphylactic



Smart Excipients

A new 'smart' excipient has been developed which provides different characteristics depending on the ratio of the main components.

By Oliver Luhn and Bodo Fritzsching at Palatinit GmbH

Oliver Luhn graduated as a Process Engineer from the University of Applied Sciences at Mannheim, Germany, in 1995. After his diploma thesis in the field of agglomeration and tableting at BASF AG, he joined the pharmaceutical supply industry and held positions as Technical Manager and Head of Research and Development at Meggle GmbH, as well as Project Manager, Innovations, at Reckitt Benckiser. In 2003, he joined the Technical Services Department of Palatinit GmbH as Technical Manager, Pharma, and was transferred to the Central Department of Research, Development and Service at Suedzucker AG in 2005. At the department of product development, he heads the Group of Pharmaceutical Technology, and is focusing on the research and development of pharmaceutical excipients.

Bodo Fritzsching graduated as a Nutrition and Equipment Technology Engineer from the University of Applied Sciences at Trier, Germany, in 1992. He subsequently joined Palatinit GmbH, a subsidiary of Suedzucker AG (Mannheim/Ochsenfurt, Germany) as a representative of the Technical Services Department to advise the food and pharmaceutical industry about the properties and applications of isomalt, a polyol derived from sucrose. Between 1992 and 1995, he was in charge of Technical Application Services within Europe. Thereafter, until 1999, he was responsible for the Technical Application Services of NAFTA/North America, supporting Palatinit of America, Inc as Area Manager Technical Services. From 1999 to 2004, Mr Fritzsching became Area Manager, Sales and Technical Services, to develop the company's business in the Middle East and Africa. Since 2004, he has headed up the Pharma Sales Unit of Palatinit GmbH as Sales Manager, Pharma; the Unit is dedicated to the pharmaceutical industry, focusing on the worldwide marketing of galenIQ™.

During the course of tablet formulation, development formulators are challenged to develop robust formulations that can succesfully be scaled up. On the equipment side, different scales of tableting machines are used. In the beginning, small volumes of API often limit trials to lab scale where single punch presses are used that exhibit low compression speeds, whereas in production scale on modern rotary presses the speed increases drastically. On the formulation side, magnesium stearate is often used as a lubricant. It is well known that the concentration of magnesium stearate and blending time can have significant effects on the compaction properties of pharmaceutical powders. Therefore in extreme cases formulations developed in lab scale cannot be reproduced in production.

This article describes a new bulk excipient and presents an evaluation of the effects of tableting speed, magnesium stearate concentration and mixing time on the relationship between compaction pressure and strength of tablets made with the excipient.

A NEW BULK EXCIPIENT

A new multifunctional, non-animal origin excipient range has been developed, galenIQ™ (isomalt Ph Eur, BP, USP29-NF24). Chemically, it is based on hydrogenated isomaltulose (HI) – a disaccharide alcohol belonging to the group of polyols. With physical and chemical modifications, galenIQ™ qualities are tailor-made for pharmaceutical applications – mainly in the field of solid-dosage forms for oral delivery.

The excipient is derived from sucrose in a two-stage production process. First, in an enzymatic transglucosidation, sucrose is converted to the disaccharide 6-0-α-D-glucopyranosyl-fructose (isomaltulose), a significantly more stable reducing compound. In the second step, the hydrogenation of isomaltulose leads to the stereoisomer disaccharide alcohol, 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (1.1-GPM dihydrate) and 6-O-α-D-glucopyranosyl-D-sorbitol (1.6-GPS) in approximately an equimolar mixture. Through an additional special crystallisation process, the ratio between the main components can be varied. As a result, specific qualities can obtained; for example, a higher proportion of 1.6-GPS provides greater solubility. Depending on the quality, the mixture contains approximately 3-5% crystal water, which is bound to the GPM-crystal. In its final state, the excipient is a white, odourless, water-soluble, crystalline substance that complies with the isomalt