INJECTABLE DRUG DELIVERY: DEVICES MEET NEXT-GENERATION FORMULATIONS

Although much effort has been put into making injectable drug delivery a better experience for patients, the problem remains that most devices are unable to deliver the drug to just the targeted organ and not throughout the whole body. Here, Iulia Karlsson, PhD, Regulatory Affairs Specialist at Double Bond Pharmaceutical, discusses a new technology called BeloGal which allows drugs to be delivered in high doses to the right organ and avoids the problems of low water solubility that hamper many modern formulations.

UNMET NEEDS IN DRUG DELIVERY

Today, the vast majority of the world's best-selling drugs require a drug delivery device, no matter whether they are biologics for parenteral delivery, drugs for treatment of asthma requiring an inhaler or chemotherapeutic suspensions delivered intravenously.[1]

The drug delivery industry is focussed on finding ways to enhance the injection experience, i.e. make it more pleasant for the patient, from helpful reminders, self-use devices, connecting to smartphones, making the syringes larger or smaller and containers gentler and smarter. This is a challenge to manage with the increasingly sophisticated drugs that are both unstable and difficult to administer in the right dose.

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However, the industry has largely failed to achieve one very specific and vitally important goal – to deliver the drug exactly to the organ where it is needed, so that the spread and toxicity to healthy organs and tissues is zero or close to that.

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Market for Drug Delivery

The global drug delivery devices market was already valued at more than US$330.0 billion in 2016,[1] and it is expected to grow further to $624.50 billion by 2021 and reach $931.1 billion by 2024, according to a new report by Grand View Research.[2] This growth is equal to CAGR of more than 11% in the forecast period though this is a lower figure compared to some other existing estimations.[3]

What is driving the development of more and more sophisticated drugs and injectable drug delivery systems on the market is a change in the following factors:

- Increased prevalence of chronic diseases such as diabetes and cancer
- Increased understanding about how drug is being taken up and metabolised in the body
- Increased understanding of the heterogeneity of patients and hence the large variety of individual requirements within each given therapy
- Increased understanding of the importance of a controlled release distribution and availability of the drug in the body.

Let us take a closer look at what drug delivery devices today can offer, what they can't and – most importantly – what can be done about it.

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ADVANTAGES & LIMITATIONS OF INJECTABLE DELIVERY DEVICES

Advancements in technological processes have resulted in the generation of improved and enhanced devices, as well as equipment that is tailor-made and specific to different categories of patient care. In addition, technological innovations like dual-injectables have further enhanced the method of drug delivery and the development of the biologics market has led to an increase in the demand for these injectables.

Classification of Injectables Delivery

Injectable drug delivery methods can be divided into two main groups – devices and formulations. Devices and formulations can be used together, so the following delivery device groups and sub-groups have been created:[4]

- Self-injection devices
- Conventional injection devices
- Needle-free injectors
- Auto-injectors
- Pen injectors
- Wearable injectors
- Auto-injector-specific selection factors
- Prefilled syringe devices
- Safety syringes
- Integrated safety syringes
- Patch injectors
- Subcutaneous infusion devices
- Other devices.

The conventional injections subcategory is further classified by material – glass and plastic, by usability – disposable and reusable and by type – fillable and prefilled syringes. The injectable are categorised as conventional drug delivery, novel drug delivery and long-acting injectables.

Advantages of Innovative Injectables

First-generation devices that are still on the market are typically mechanical – functioning only to get the drug into the body. This is still very relevant today, as even novel drugs must be properly administrated, for example, to comatose and subconsious patients. Next-generation parenteral devices are recognised more as the interface between the drug and the patient. They can also offer many features and functions which improve usability, safety, efficacy and compliance, plus many other functions beyond – such as connectivity and even diagnostics.

With the advent of self-injection devices like auto-injectors, pen-injectors and needle-free injectors, the use of injectable drug delivery (IDD) has been made relatively easy allowing patients to administer drugs at home without medical assistance. The increase in the number of diabetic patients globally has allowed the majority of the leading players in this market to launch devices for the administration of insulin with the help of self-injection devices. Thus, the homecare settings segment was the largest grosser in this market in 2015.

Limitations of Injectables

What are the main limitations of injectables? Infections and injuries caused by the needles used in syringes are a major constraint. Contamination arising from previously used injectables and needlestick injuries may cause serious complications needing further remediation and these complications often lead to further hurdles in the management of the disease.

In certain cases other drug delivery methods, such as oral administration, are often preferred over injections as they obviate toxicity implications. In addition, strict regulations can deter the use of IDD forms. Several concerns have been raised in the recent past with respect to the sterility of injectables, which has led to a decline in the number of approved production facilities that manufacture these products and hence the resultant shortage of these drugs in the market.

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Despite many constraints, the market potential for IDD is immense due to the associated advantages and its wide applicability in a range of ailments. Furthermore, the market is also fueled by many major companies that are adapting to the demand of injectables over oral dosages, as oral administration provides a much lower bioavailability compared with intravenous injection, for example, which gives 100% bioavailability with extremely rare exceptions[5,6] (Table 1).

Route	Bioavailability	Characteristics
Intravenous injection (infusion)	100%	Most rapid
Intramuscular injection	75≤100%	Large volume may be injected but painful method
Subcutaneous injection	75≤100%	Smaller volume than IM, may be painful
Oral administration	5≤100%	Convenient, first pass metabolism occurs
Rectal administration	30<100%	Less first pass metabolism than oral route
Inhalation	5<100%	Rapid onset
Transdermal (patch)	80≤100%	Usually slow absorption, lack of first pass metabolism and prolonged duration of action

Table 1: Bioavailability of drugs administered using different routes. (Source: howmed.net)

The next generation of injection devices offer therefore a broad range of upgrades in drug delivery – everything from self-administered injection devices with dose-limiting functions, very ergonomic user-friendly designed wearables to professional systems for instant mix and delivery of complex components allowing for less fluctuations in pharmaceutical ingredient concentration throughout the injection, such as dual-release formulations.

However, they all still have zero ability to restrict the uptake of the drug into healthy organs. The good news is that certain types of formulations can successfully solve this and other problems.

NEXT-GENERATION DRUG DELIVERY FORMULATIONS

New formulations of drugs that are not very water soluble are becoming more prevalent.[7] It has been estimated that 40% of drugs with market approval and nearly 90% of molecules in the pipeline of drug discovery programmes are poorly soluble in aqueous media and/or have very low permeability to allow for their adequate and reproducible absorption from the gastrointestinal tract (GIT) following oral administration.[8]

Various properties which contribute to the poor solubility of drugs include:

- Complex structure
- Size
- High molecular weight
- High lipophilicity
- Compound H-bonding to solvent
- Intramolecular H-bonding
- Intermolecular H-bonding (crystal packing)
- Crystallinity
- Polymorphic forms
- Ionic charge status
- pH
- Salt form.[9]

Formulation scientists try therefore to adopt various strategies to enhance the absorption of the drug molecules.

What Can Formulations Do?

The majority of drug delivery formulations focus on dissolving water-insoluble active pharmaceutical ingredients (APIs) in different ways to improve the drug's solubility, bioavailability in the body and increase loading capacity. Moreover, when an API has a low bioavailability – as is very usual in the case of oral administration – the only way to make the drugs bioavailable in the body is through an intravenous administration. Here, the advantages and breakthroughs in drug delivery devices for intravenous injection are all welcome, but really the absorption and solubility problem must be solved.

Poorly absorbed drugs pose a challenge to formulation scientists to develop suitable dosage forms that can enhance their bioavailability. There are several ways to improve the absorption of the active substance – including lipidic formulations, crystalline solid formulations and amorphous formulations.

One of the most efficient ways for improving the solubility of an API is a micelle formation.[10] Let's take a closer look at what difference it can make in terms of loading capacity using the example of the water-insoluble anticancer paclitaxel, and its three different formulations:

a. Taxol – a mixture of aqueous ethanol and non-ionic surfactant Cremophor-EL – used for dissolving of paclitaxel. Disadvantages in delivery of this drug here is low loading capacity (1:80) and high toxicity of Cremophor-EL.
b. Abraxane – based on use of albumin (HSA) as surfactant. Disadvantages in delivery: medium loading capacity (1:9) and use of HSA (gives risk for cross-infection).
c. Paclical – a semi-natural, non-toxic surfactant is used, finally giving a good loading capacity 1:3.3. Paclical is indicated against ovarian cancer.

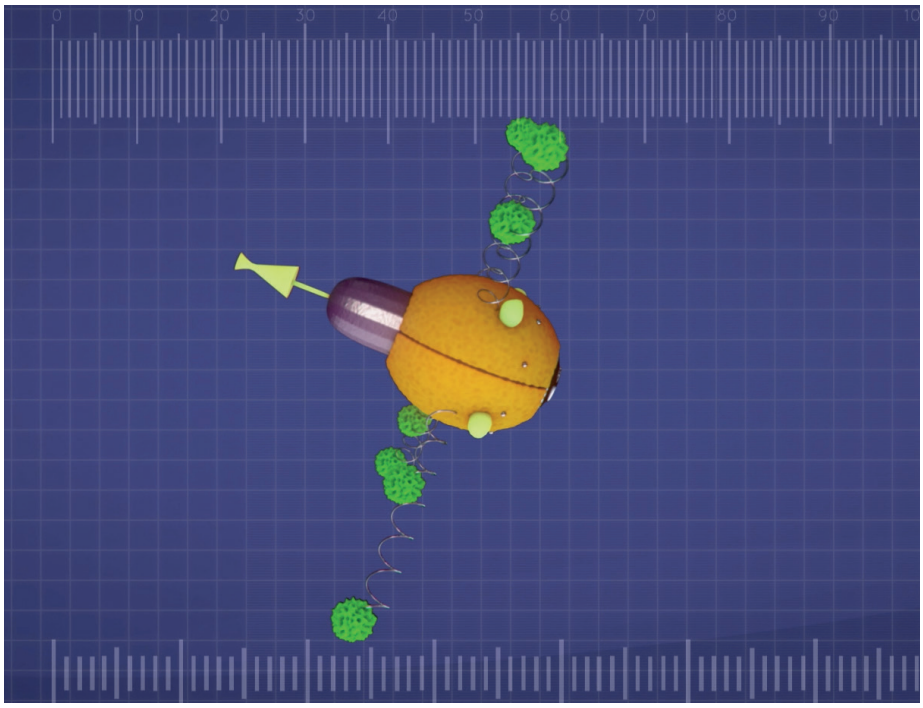

Figure 1: Schematic model of BeloGal formulation package of a water-insoluble API.

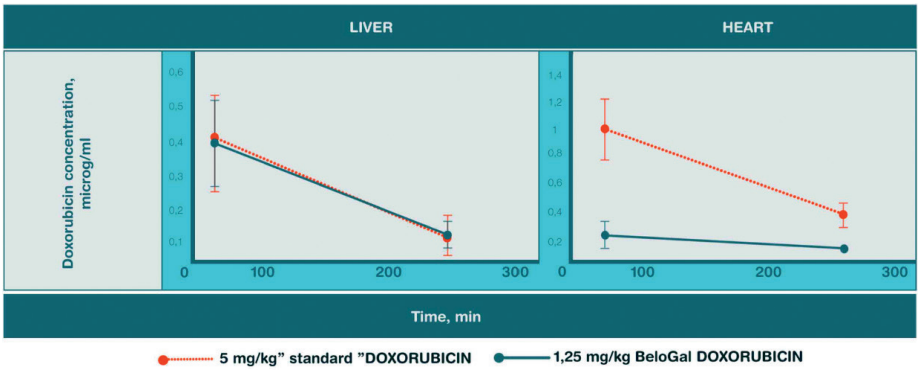

Figure 2: Biodistribution of BeloGal-formulated doxorubicin programmed to target liver specifically: equally high concentrations in the liver (left) using only ¼ of the original dose, and simultaneously 10 times lower concentration in the heart (right) compared with original API (doxorubicin) in rabbit.

Drug delivery formulations based on liposome encapsulation can solve the bioavailability problem by giving a longer plasma circulation time and enhanced target-tissue accumulation. Different APIs are currently being used in this type of formulation: doxorubicin, daunorubicin, cisplatin and vincristine. The main challenge with liposome encapsulation, however, is technical – difficulties of pharmaceutical manufacturing, including quality assurance and cost, in addition to not very pronounced tissue targeting.[11]

BeloGal technology

A very promising solution to virtually all formulation problems of this kind is a new technology called BeloGal. It encapsulates the insoluble API into a biomimetic chemical polymer-based cover[12] (Figure 1) and provides organ-specific targeting of the API to either the liver or lung, avoiding other organs such as the heart (Figure 2). Moreover, the manufacturing process is much simpler compared with other formulation methods and does not involve high costs.

The technology combines the advantages of specific tissue perfusion parameters for the liver or lung with the simplicity of intravenous administration. Furthermore, organ/tissue targeting by the use of self-navigating BeloGal particles significantly widens a therapeutic window, allowing higher doses of the drug to be achieved in the right organ while substantially lowering the spread of the API to healthy organs (Figure 2).

One of the technical advantages of this method is also an easily achieved high-loading capacity. Currently the platform is being used with doxorubicin, and the first drug candidate in the pipeline employing BeloGal technology is SA-033 – indicated against liver cancer and entering clinical trials this year.

It is also possible to use the technology to formulate other APIs to decrease their toxicity and ensure their high therapeutic effects in selected organs. For instance, doxycycline – a well-known antibiotic, can be successfully formulated using BeloGal to be delivered to the lung to combat lung infections.

CONCLUSION

After successful clinical development of the first BeloGal-based drug, the technology is expected to become a gold standard for intravenous delivery of drugs to liver and lung, allowing for an entirely new level of innovation and clinical benefit for both drug delivery and organ-targeting, self-navigating drug formulations.

ABOUT THE AUTHOR

Iulia Karlsson holds a PhD in Medical Biochemistry with a background in human and animal physiology, immunology and infection biology. Iulia is currently working as Regulatory Affairs Specialist and in business development at Double Bond Pharmaceutical in Uppsala, Sweden.

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