Pelletisation: why multiparticulate drug formulations are on the rise

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Owing to the many benefits they offer both manufacturers and patients, the use of pellets in drug formulation has gained popularity in recent years

With manufacturers beginning to improve their understanding of the uses of multiparticulate products, alongside more research and progressive advancements being made, the future looks bright for pelletisation as a technique in drug development. Here, Dr Beata Vladovicova talks about the wide-ranging advantages of pelletisation, whilst also exploring the use of extrusion-spheronisation to produce these types of drugs. She also discusses the challenges faced in the development of pellets and why some in the industry have yet to explore the use of multi-unit dosage forms (MUDFs).

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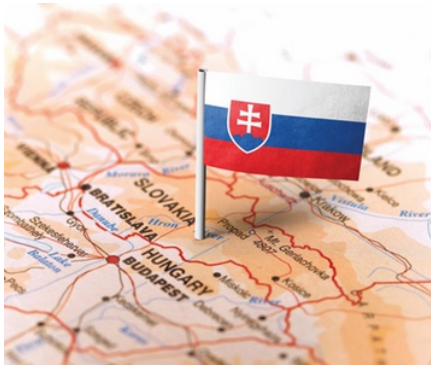

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What are pellets?

MUDFs, otherwise known as pellets, are small, free flowing, spherical particulates that are produced by an assembly process that converts fine powders or grains of bulk substances and excipients into spherical units. They range in size from 0.2–2.0 mm in diameter and are easily formed into tablets and capsules. They are diverse in their abilities, with one key advantage being their capability to produce a multi-drug blend.

What benefits do pellets bring?

The benefits of pelletisation are two-fold as they bring advantages to both manufacturers and patients. Compared with conventional formulations, they show better and a more reproducible pharmacokinetic (PK) performance and provide an alternative for drugs that are otherwise unstable. They also provide a solution for problematic drug-to-drug physiochemical interactions, whereby two drugs cannot be used in conjunction with each other. By having pellets containing different drugs within one capsule or tablet, the two compounds can be released at different times — without the patient having to take more than one dose.

Recently, there have been advancements in pelletisation methods to improve both flexibility and the ability to produce an even higher degree of stability. One highly innovative area is in the development of coating methods, particularly with regards to polymer coating. Polymer coating can now incorporate varying thicknesses of the film to assist in more targeted, moderate, sustained or pulsed release rates.

In terms of manufacturing, there are great advantages to using pellets, varying from offering flexibility when formulating active ingredients into oral dosage forms to the overall finished appearance of the drug. Pellets offer multiple release forms, including controlled release, gastro-resistant and sustained release. They also enable site-specific drug delivery, meaning that the drug will not be released until a certain point in its journey through the body. Pellets can also allow more than one drug strength to be contained in one dose, mitigating the need for formulation or process changes. They can also allow doses to contain high drug capacities without increasing the size of the particles, which could have an adverse effect on patient compliance.

Additional benefits during drug development derive from the low hygroscopicity of pellets, meaning that they do not absorb much moisture from the air. They can also be created to have a uniform shape with a narrow particle size distribution to facilitate coating.

On the patient side, there are also huge therapeutic advantages, particularly when it comes to improving the safety of drugs and ensuring patient compliance. Because pellets can freely disperse throughout the gastrointestinal (GI) tract, it maximises drug absorption and offers an even and predictable distribution of active ingredients. Therefore, pellets can improve drug dissolution, which means higher bioavailabilities and more effective treatment.

These properties mean that pellets are less susceptible to dose dumping than conventional drugs, which results in less risk of adverse side-effects to the patient. They can eliminate the build-up of high local concentrations of bioactive agents that might irritate the patient, as well as reduce peak plasma fluctuations, making the drug more tolerable and less abrasive for patient use. They can also be used to mask the taste of unpalatable drugs for oral consumption.

How are pellets developed?

There are various techniques to prepare pellets, which are grouped by specific criteria. From fluid-bed granulation to spray drying, the success of the pellets will depend on the complicated relationship between the formulation, the equipment and the development and manufacturing process. Currently, the most common and highly discussed technique for creating pellets is extrusion-spheronisation. This technique is a multi-stage process consisting of seven steps that produce pellets from wet granules, converting a pharmaceutical formulation into a spherical product:

- **Dry mixing:** the first stage is to achieve a homogenous powder dispersion.
- **Wet massing:** the second stage creates a wet granulation to produce a plastic mass for extrusion.
- **Extrusion:** the third phase produces rod-shaped particles with a uniform diameter and shape from the wet mass (extrudate).
- **Spheronisation:** the fourth stage involves adding the extrudate to a rotating friction plate; it is then broken into smaller cylinders with a length equal to their diameter, which become rounded by the frictional force.
- **Drying:** enough time must be allowed during the fifth stage for the desired moisture level to be achieved.
- **Screening:** the sixth stage, which is optional, is screening the pellets to achieve a targeted mean size.
- **Coating:** the final stage, which is optional, is adding a supplementary coating for functional or cosmetic reasons.

Using the latest technology, the whole process can be performed in a single closed system. Extrusion-spheronisation has been found to be effective for otherwise poorly soluble active pharmaceutical ingredients (APIs). It is renowned for being a streamlined and efficient pathway to development that offers high throughput and low wastage.

Along with producing pellets of uniform size, the pellets created have a low friability, meaning they are unlikely to chip, crumble or break under compression both during and after the production process.

Challenges presented

Despite the many benefits, there are challenges to overcome when producing pellets. The preparation of pellets is a highly complex and often difficult process. With so many variations in the capabilities of pelleted drugs, each development process needs to be altered to suit the desired outcome. This means that the already complex multiple-step process can become even more complicated. Additionally, when compared with single unit dosage forms (SUDFs), the volume per dose is higher because of the required bulk density; therefore, the amount of coating required will also increase.

As extrusion-spheronisation involves a multi-batch process, it can be labour intensive and often costly. The need for complex and specialised equipment, highly trained employees and the overall technical intricacy means that money and time are intrinsically required. This is driving the outsourcing of drug development to specialist providers.

In summary

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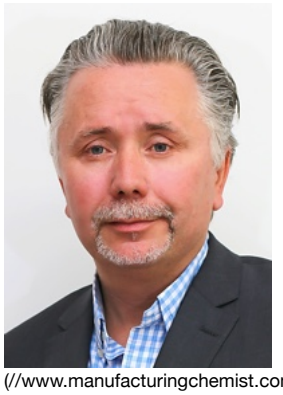

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Pelletisation is a novel process within the pharmaceutical industry that enables the provision of multiparticulate systems. Pellets can provide major benefits to both manufacturers and patients, from enhancing drug delivery to improving safety and boosting patient compliance.

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When it comes to producing pellets, extrusion-spheronisation remains the most popular choice; and, with new advancements, the technique will no doubt bring further possibilities to the formulation of drugs in the future.

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