The folly of simplicity - trends and potential pitfalls of continuous manufacturing of oral solid dosage forms.

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Editorial

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"Everything should be made as simple as possible, but no simpler"

Attributed to Albert Einstein

Einstein was, in effect, saying that there is danger in oversimplification. This is still true today, and is particularly relevant to pharmaceutical formulation and process design and development. The danger in oversimplification is that there is a greater chance that an unanticipated change in an ingredient can lead to product failure and, ultimately the inability to supply the product to the patient.

Currently there is a lot of interest in continuous manufacturing of drug products. Several continuously manufactured commercial oral solid dosage forms have been authorized for sale in the EU and the US. The attractions of continuous manufacturing can include easier scale-up, increased equipment usage, reduced analytical costs and reduced downtime during a campaign compared to batch manufacturing. However, there are disadvantages as well, including: capital investment, investment in and, validation of Process Analytical Technology (PAT) and, extended cleaning and changeover times between different products.

A trend that has become apparent in oral solid dosage forms is to develop very simple formulations for direct compression consisting of a bulk active drug (API), direct compression binder and a lubricant. The drug and excipient are blended together, followed by blending with the lubricant after which the blend is compacted into tablets. As simple a formulation and processing as possible! Such an approach may work for soluble drugs (many BCS I and BCS III drugs), but will not work for poorly water- soluble drugs (e.g., BCS II and BCS IV drugs) without some form of intermediate processing.

Direct compression has been around for more than 50 years to this author's knowledge, and who has used it successfully on many occasions. Notwithstanding, it is not appropriate for every drug, for example low dose drugs such as, digoxin and warfarin, require a very fine particle size to achieve the requisite blend uniformity.

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Fine powders tend to be cohesive and thus difficult to dry blend to achieve the necessary uniformity of dosage units. It may be possible to form an ordered mix of such drugs with an excipient, but that is no longer simple blending, and possibly the necessary excipient itself may not be directly compressible which adds to the complexity.

For high dose drugs, the suitability of direct compression will depend on the properties of the bulk drug. There will be a percolation threshold above which the compaction properties will become increasingly important. Above this threshold, there is an increasing likelihood that direct compression will not be achievable. Some drugs, such as aspirin do have good compaction properties, but most do not. In general terms, the percolation threshold for such drugs will depend on the particle size distribution of the API; for APIs having a smaller particle size, the percolation threshold could well be lower. In this Author's experience, and based on a range of drugs evaluated over the years, in the absence of any issues with particle size, etc., the percolation threshold is around 20% w/w of the tablet compressed weight. As a rule of thumb, this author would not be confident that a direct compression product could be achieved if the content of the active drug is less than 1% w/w or greater than 20% w/w.

However, let's examine the concept of 'as simple a formulation and processing as possible'. It is attractive in terms of capital outlay (fewer processing steps, less equipment required) and short- term economics (reduced inventory of excipients, etc.) But is it the best approach for the patient in the longer term?

We can illustrate this by means of the following example from more than 20 years ago. There was a tablet product on the market which had been successfully manufactured for a number of years. This was a simple direct compression formulation consisting of the API, microcrystalline cellulose (MCC) and magnesium stearate. There was an unanticipated change of polymorphic form of the API to a more stable, less soluble form, which led to dissolution failures. Despite significant effort, the company was unable to regenerate the original polymorphic form.
So, what to do? Fortunately, there was another higher strength of the same drug on the market which did not exhibit any dissolution failures with the change in polymorphic form of the API. This formulation was not a simple blend of the API, MCC and magnesium stearate. In order to keep the size of the tablet to a manageable size, they had reduced the amount of MCC and added in a super-disintegrant to achieve the required dissolution. The point is that the formulation of the lower strength tablet was too simple. It relied on the disintegrant properties of MCC, which are not exceptional, for the disintegration of the tablet. This was insufficient for the formulation containing the new polymorphic form, whereas the better designed formulation of the higher strength tablet could cope with the changed polymorphic form. In essence, it was a more robust formulation!

This brings me to my point. By designing formulations that are too simple, are we jeopardizing the future reputation of the company and industry, and also the health and safety of patients.