Developing new drug products is very expensive, especially when formulating new chemical entities (NCEs). Many pharmaceutical companies are turning to FDCs as a way to reduce those development costs. An FDC is a drug product that combines two or more active pharmaceutical ingredients (APIs or drugs) in a single dosage form. FDCs are acceptable only when the dosage of each API meets the...
requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance.

FDCs provide greater convenience and can increase patient compliance because they require patients to take fewer doses [1]. FDCs can be particularly beneficial when used to treat life-threatening diseases such as HIV/AIDS, diabetes, or cardiovascular disease, where a single drug targeting a specific receptor is not considered optimal. For instance, in the case of cardiovascular disease, a combination of antihypertensive and antihyperlipidemic drugs is more beneficial for patients than taking the individual drugs separately because it reduces multiple risk factors without increasing the risk of adverse effects [2]. Similarly, in the case of HIV, an FDC prevents viral drug resistance by decreasing the level of viral replication and raising the barrier to resistance development [3]. An FDC can also improve an API’s bioavailability by combining the API with a drug-metabolizing enzyme inhibitor.

Aside from the approval status of the APIs to be combined, the primary consideration when developing an FDC is the development strategy. Companies typically select APIs for FDC development based on clinical experience and manufacturing feasibility along with the pharmacological mechanisms, biopharmaceutical properties, metabolic pathways, pharmacokinetics, drug-drug interactions, and required doses of the individual APIs [5].

The APIs to be combined should:
• act by different mechanisms;
• have similar pharmacokinetics;
• treat closely related diseases (such as hypertension and hyperlipidemia) or the same disease using different mechanisms (such as antidiuretics and angiotensin converting enzyme inhibitors);
• have minimal drug-drug interaction.

An FDC formulation and development program typically involves a pilot-stage program followed by bioequivalence (BE) studies, which compare the FDC to the constituent drugs co-administered as individual entities. Food-effect bioavailability studies are also required to register the drug product with the FDA. The regulatory requirements may be particularly challenging for FDCs that combine two NCEs. Developing a good strategy and designing appropriate trials to evaluate the formulations, drug-drug interactions, and bioavailability are critical to ensure that the FDC will be stable,
formulation requirements, then the particle size distribution of all the APIs and excipients should be uniform to prevent segregation and provide good flow and content uniformity.

**Multiparticulate/mini-tablet dosage forms.** Multiparticulate or mini-tablet dosage forms are also useful for combining incompatible APIs or excipients or when a formulation requires that the APIs have different release profiles. The most commonly used multiparticulate oral solid dosage form is pelleted and/or powdered material compressed into a tablet or encapsulated into a capsule. A more recent manufacturing trend is to create various mini-tablets with diameters smaller than 3 millimeters (Photo 2), which can then be encapsulated into capsules (Photo 3) depending on the formulation’s requirements.

One of the most common technologies used to create pellets for a multiparticulate FDC is extrusion-spheronization, where the formulation is granulated to prepare a wet mass, which is extruded into cylindrically shaped extrudates. The extrudates are then broken into smaller particles and rounded off to create spheres, which are then dried. Extrusion-spheronization allows for high drug loading and can create pellets with a narrow particle size distribution. The pellets are also durable, making them suitable for film coating for pulsatile drug delivery and combining immediate-release pellets with controlled-release pellets of the same or a different drug. Adjusting the fill weight of the pellets into the capsule allows for dosing flexibility.

Another way of producing a multiparticulate system is by preparing the drug in a solution or suspension and coating it onto readily available sugar pellets. You can then add an additional controlled-release coating to the pellets if required or combine immediate- and extended-release pellets.

**Development challenges and limitations**

Because FDCs contain more than one API, they’re more challenging to develop than single-entity drug products. The challenges are largely related to formulation, dose-ranging, drug-drug interactions, and manufacturing processes. FDC development is also challenging when the APIs’ durations of action differ significantly.

In some cases, drug interaction at the level of pharmacokinetics, efficacy, or safety may limit formulation potential. In other cases, the API dosage becomes too large to administer as a single form. Also, the potential for BE failure is a factor, particularly when the dissolution profiles of the APIs to be combined differ. FDC use may also be limited where the component therapies require dose titration or various dose adjustment patterns because it’s not possible to alter the dosage of one drug in the FDC without altering the dosage of the other drug or drugs [7].
A dose differential between the APIs also poses formulation and processing challenges. For instance, if the dose of one API is low and the dose of the other API is high, each API should be processed individually and combined at the final stage as a bilayer, tablet-in-tablet, or capsule-in-capsule form.

An FDC with three APIs, where API A and API B are low-dose and API C is high-dose with an extended-release profile, presents many formulation challenges. In such a case, you can formulate API A and API B using high-shear granulation and process the high-dose API C by extrusion spherization technology. Then you can apply an extended-release polymer coating only to the API C spheres and compress the blended API A and API B granules and the coated API C spheres into a bilayer tablet.

Other challenges associated with FDCs include:
- Drugs with differing pharmacokinetics create a problem of administration frequency when combined into an FDC.
- FDCs can increase the chances of adverse drug effects and drug interactions compared to single-API dosage forms.
- Determining the cause of an adverse drug reaction can be difficult because the FDC contains more than one API.
- Pharmacists and physicians may overlook the dosage limit of certain APIs in FDCs.

Quality by design

A quality-by-design (QbD) approach is critical when developing an FDC dosage form to meet the FDA’s requirement for a robust formulation and manufacturing process. Although the application of QbD will be similar to the application for a single-API formulation, it will be more complex due to the presence of multiple APIs.

The first and most important step is to define the target product profile (TPP), which describes the use, safety, and efficacy of the product. An in-depth understanding of formulation, excipients, and process is advantageous when defining the TPP and will reduce the amount of experimentation and analytical testing required and, consequently, the manufacturing and testing costs.

The next step is to design the formulation and identify the critical quality attributes (CQA) of the final product that must be controlled to meet the TPP. To achieve the final product's critical quality attributes, it's important to identify and control critical process parameters (CPP). Throughout development, scale-up, and commercialization, establish a control strategy that includes raw-material and API controls (for particle size distribution, moisture, polymorphs, and impurities, among other characteristics), process controls (such as hardness, thickness, friability, tablet weight during compression, inlet temperature, spray rate, and exhaust temperature during tablet coating), and design space around individual or multiple unit operations (such as granulation, compression, coating, encapsulation, and packaging).

It's equally important to monitor these controls and update the process to ensure target product profile. To achieve successful target product profile by QbD approach, it is important to use design of experiment (DOE), risk assessment, and process analytical technology (PAT).

A QbD approach provides several advantages, including:
- negligible chance of batch failure because the batches are manufactured in a design space defined during product development;
- enhanced understanding of the formulation and manufacturing processes;
- the development of a robust process that leads to greater regulatory confidence;
- continuous improvement in the manufacturing process during development, validation, and post-commercialization in a defined design space doesn’t require resubmission to the FDA;
- increased product quality, improved yields, reduced investigations and testing, and lower manufacturing costs;
- guaranteed therapeutic equivalence of each batch of generics manufactured;
- a better, less expensive, and safer drug product.

By using a QbD approach, pharmaceutical companies can develop safe and effective FDCs that optimize the pharmacokinetics, bioavailability, and therapeutic effect of existing approved drug products. This benefits patients, particularly those on long-term management therapies, by reducing the administration burden and improving compliance. This also benefits pharmaceutical companies by extending patents, reducing manufacturing costs compared to single-API drug products, and shortening regulatory approval time and expense compared to NCE development.

References

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