APRECIA®
THE 3DP PHARMACEUTICAL COMPANY

The Emerging Possibilities for Oral Solid Dosage Forms Using 3D Printing

While the biologic drug market has shown significant growth over the last decade, oral solid dose forms (OSD) remain the most commonly used method of drug delivery. Patients are more familiar with this traditional and convenient method, which promotes compliance and a better overall patient experience. Yet, there are limitations to OSD that newer technologies may overcome through novel dosage form development. These limitations include, but are not confined to, size, shape, and taste, as well as an inability to combine functionalities, such as rapid disintegration combined with controlled release or pre-gastric absorption.

To address these problems while also keeping pace with advances in patient treatment, pharmaceutical manufacturers must be willing to consider alternative approaches to developing and manufacturing OSD drugs. One such method is 3D printing (3DP), also known as additive manufacturing. 3DP manufacturing enables enhanced drug delivery through novel dosage form options that go beyond the capabilities of conventional manufacturing technologies.

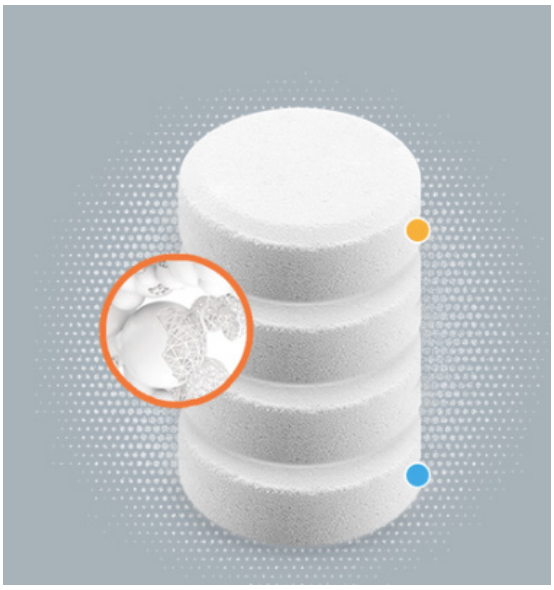
The Functionality Limitations Of Today's Oral Solid Dosages

One major challenge with OSD drugs is that traditional dosage forms limit the functionality possible for administering drugs whose dosages present difficulty for patients to swallow. Current FDA guidance states that, generally, tablet weight should not exceed 500 milligrams.[1] Regulators encourage manufacturers to avoid making high-dose orally disintegrating tablets that are difficult for patients to swallow, unless the combined influence of weight, size, and component solubility are acceptable (specifically the tablet's mouth feel, taste, and disintegration time). Their concern is that "the differences in physical characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors." As a result of this recommendation, the highest strength orally disintegrating tablets (ODT) approved by the FDA is 275 milligrams of active pharmaceutical ingredient (API).

In addition, a national survey recently found that over 40 percent of adults in the general community experience problems swallowing, a condition known as dysphagia.[2] This can have a significant impact on patient compliance, as 14 percent of adults with dysphagia reported that they delay taking their medication because of the issue, with 8 percent of adults skipping a dose altogether. Small and/or dissolvable pills are preferable for those with dysphagia; however, size is dependent on formulation and dosage.

Adherence and dispensing can be especially tricky with pediatric patients, who may not only struggle with swallowing pills but can also be particularly sensitive to any unpleasant taste and/or mouth feel of their medication. Even the shape of a pill is important, as certain shapes fit better through the esophagus. The ability to create varying tablet shapes can help patients with more than one pill in their regimen differentiate

between medications, mitigating the risk of mixing up products. By finding an alternative approach to developing and manufacturing OSD, the industry can address these issues, leading to a positive impact on proper and effective dosing by patients, caregivers, and pharmacists.



Controlling The Performance And Integrity Of Tablets Using 3DP

With traditional tableting machines, compression forces are used and heat produced during manufacturing to form the final tablet, which could impact a pill's molecular structure and, ultimately, its dissolution rate, bioavailability, and overall efficacy. With 3DP, the powder containing the API is dispensed onto a forming area and then moved underneath a print head that deposits a specific pattern of liquid binding fluid to create the shape of the tablet. The build process is complete once the desired number of layers of powder are bound together by the print (binding) fluid. This process can be used to create tablets with varying levels of hardness within the tablet to create desired characteristics, such as a harder outer shell and softer inner core, which aids rapid disintegration. The API may be included in the powder or in the binding fluid, allowing for greater flexibility for either higher or lower drug load. In addition, the process can be used to produce internal channels in a tablet, which is especially beneficial when there are multiple APIs within a tablet, as these channels can control the speed of each API's disintegration while also maintaining tablet integrity. The gentle nature of 3DP manufacturing, i.e., lack of compression forces, lessens the risk of disrupting particles and any coatings (e.g., taste-masking, modified release, etc.) that may have been applied.

Using an aqueous fluid to bind together multiple layers of powder, versus traditional compression tableting, is another advantage to 3DP, as one can create tablets that will rapidly disintegrate on contact with liquid. The ability of 3DP to successfully do this was evidenced in 2015 when the FDA approved Spritam, the first prescription drug manufactured using the 3DP technology, ZipDose. Aprecia Pharmaceuticals, the company that developed ZipDose and Spritam, targeted the epilepsy medication, levetiracetam, to demonstrate the ZipDose value proposition relative to fast-melt formulations. Levetiracetam had four tablet strengths: 250 mgs, 500 mgs, 750 mgs, and 1,000 mgs. Before Spritam, the highest strength of a tablet manufactured with other fast-melt technology platforms was 275 mgs. However, ZipDose technology made it possible to rapidly disintegrate even levetiracetam's highest dose of 1,000 mgs.

The milestone reached with Spritam's approval opened the door to a wide range of therapeutic options a pharma manufacturer could achieve using 3DP for pharmaceuticals. The use of 3DP powder-liquid technology in tablet creation allows for tremendous control over tablet hardness, shape, and size, as well as tablet performance characteristics. Furthermore, 3DP may be particularly useful in the burgeoning market of fixed-dose combination products, where the FDA's current recommendations for tablet size make it difficult to manufacture tablets with multiple APIs. Not only does the rapid disintegration of high dose loads facilitate compliance, but the possibility of putting API in both the powder and the print liquid also offers a unique alternative during formulation. Finally, the capability of 3DP to control tablet hardness and disintegration rates allows manufacturers to consider alternative delivery sites for OSD drugs, such as buccal and sublingual absorption and delivery to the gastrointestinal tract. Looking forward, Aprecia's ZipDose technology and its ability to customize a dose for an individual patient makes it a valuable tool in the future of personalized medicine.

So, while the industry continues to push the boundaries of science and technology, 3DP manufacturing offers the opportunity to address many of the remaining challenges of dosage form design. The various functionalities and opportunities with a 3DP manufacturing process make it a viable option in the evolving landscape of today's pharmaceutical environment. And with competition growing, drug manufacturers must consider new ways to improve patient care while also getting ahead in a market that is changing every day.

1. FDA, Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules Guidance for Industry – https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf
2. Carnaby-Mann, Giselle & Crary, Michael, JAMA Network, Pill Swallowing By Adults With Dysphagia — https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/649710