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3D Printing Zip-Dose Technology in Pharmaceutical – A Review Article

Dhruv Suthar[1], Mayank Bhatt[2*], Ketul Nayak[3]
[1]Master of Pharmacy, Arihant School of Pharmacy, Gandhinagar
[2]Master of Pharmacy, L.J. Institute of Pharmacy, Ahmedabad
[3]Master of Pharmacy, L.M. College of Pharmacy, Ahmedabad

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ABSTRACT:The utilization of 3D printing in the production of pharmaceuticals, known as Zip-Dose technology, is a significant development in the pharmaceutical industry. This technology enables the production of personalized medication, improving medication adherence and overall patient compliance. However, the introduction of this technology poses complex regulatory challenges that must be addressed. This article aims to explore the regulatory implications of 3D printing Zip-Dose technology in the pharmaceutical industry. With the advancement of 3D printing technology, the potential for personalized medicine and on-demand drug manufacturing has increased significantly. Zip-Dose technology, a specific application of 3D printing, enables the production of individualized dosage forms with precise drug dosing and release profiles. This article discusses the regulatory considerations associated with 3D printing Zip-Dose technology, including quality control, validation, intellectual property, and regulatory approval processes. Furthermore, it examines the challenges and opportunities posed by this emerging technology, along with the potential impact on healthcare delivery and patient outcomes. The analysis presented in this article emphasizes the importance of developing appropriate regulatory frameworks to ensure the safe and effective implementation of 3D printing Zip-Dose technology in the pharmaceutical industry.

KEYWORDS: 3D printing, Zip-Dose technology, Pharmaceutical industry, Regulatory implications, personalized medicine.

I. INTRODUCTION

[1]3D Printer pharmaceutical has been subject to publish many articles and patents from academia and small companies. 31 June 2015 U.S. Food and Drug Administration (FDA) approved the New Drug Application (NDA) for spritam (API-levetiracetam), marking the first regulatory approval for a pharmaceutical product that uses 3D printing in the manufacturing process, they are made by zip-Dose technology from Aprecia pharmaceutical, they are also known as a drop of solid, several years of work on the project and improve the machine and product development. In this article, we talk own revolution technology (zip dose technology) and U.S-F.D.A first approved 3D Printer (3DP) spritam product.

II. HISTORY

In the almost 38 years of history of 3DP, many different techniques have been developed and evolved.
[2]The main methods are based on:
• Powder Solidification.
• Liquid Solidification
• Extrusion

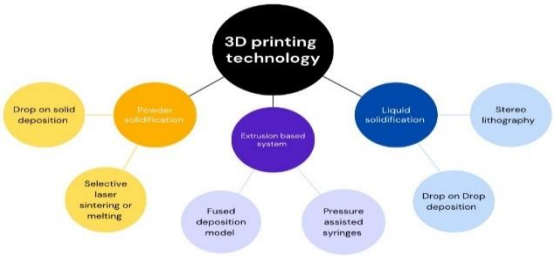

Fig: 1. 3DP method applied for Drug formulation

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powder-liquid 3DP (Zip-Dose technology) is a novel technology that forms objects layer by layer, it was originally developed by the Massachusetts Institute of Technology(MIT) in late 1980 as a prototype technique, and from 1993 to 2003 this work was expanded into the distinct areas of pharmaceutical and tissue engineering. While 3DP technology rights were licensed for a diverse range of industrial fields, the MIT 3DP process & its application in the pharmaceutical industry are exclusively licensed to Aprecia.

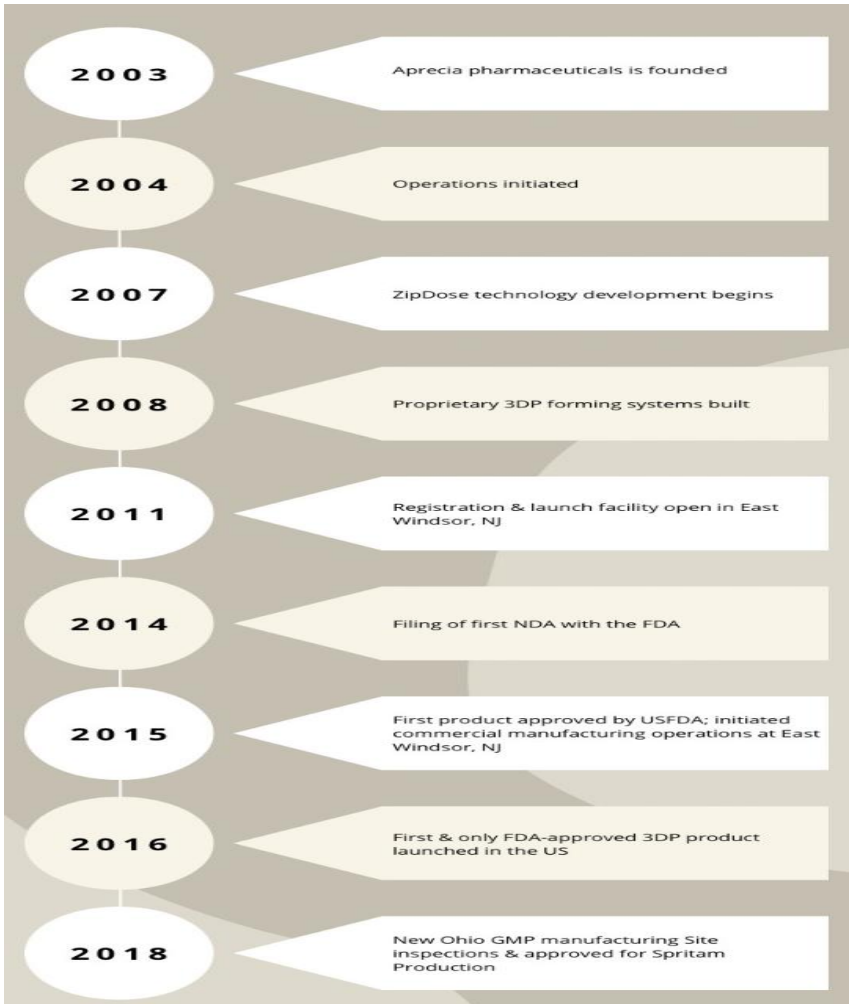

Fig: 2. Aprecia Pharmaceutical history

III. ZIP-DOSE TECHNOLOGY

[3,4] Zip-Dose technology is the band name of aprecia's formulation technology related to orodispesible dosage form by using zip dose technology they made the first product they called SPRITAM, the main point of zip-dose formulation is the ability to load 1000mg and also have the ability to disintegrate in the mouth within seconds. But here we like to ask one question why zip dose technology is required? products designed to disintegrate directly in the mouth are not new, the first orodispersible tablet to get approval from the U.S.FDA was the Zaydis formulation of Claritin, but the ability to do so quickly while also delivering higher doses has remained absent in the marketplace.

[5, 6] Some Previous techniques like freeze-dried and soft compression to make orodispersible dosage form. In freeze-dried to make orodispersible dosage form by dispensing a solution or suspension into empty blister cavities followed by rapid freezing and sublimation of the moisture, leaving behind highly porous dosage forms. Soft compressed forms have limited porosity so we use

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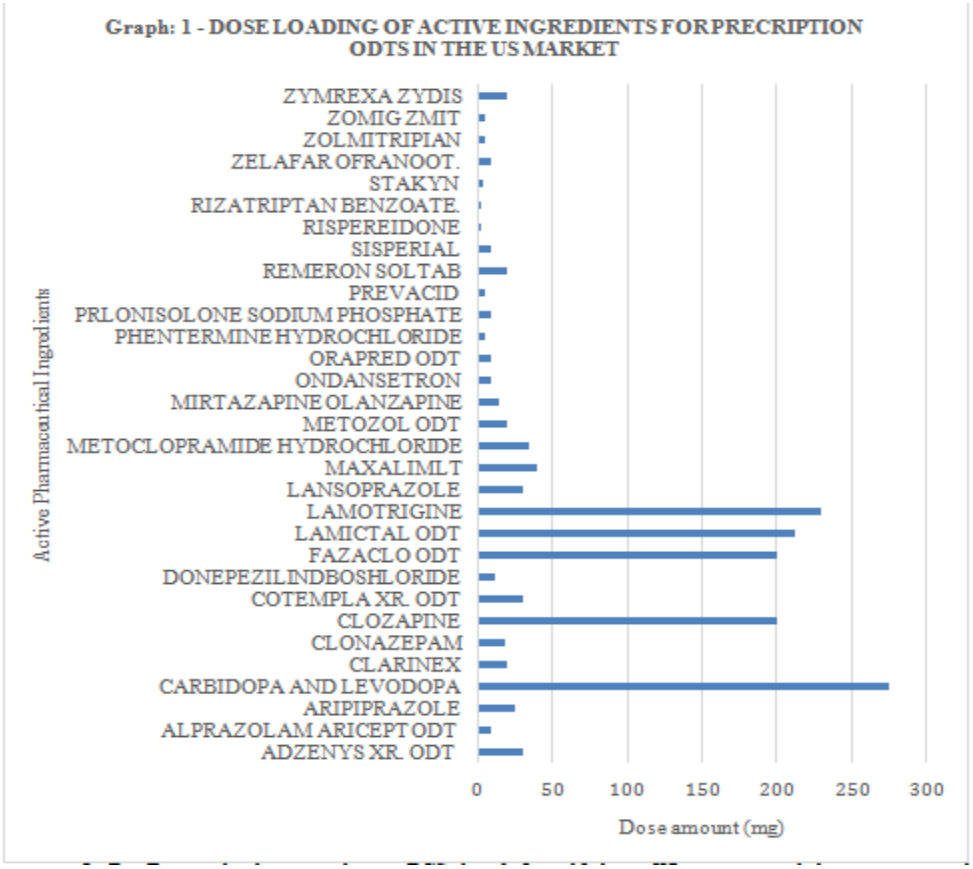
super-disintegration integrands that rapidly disintegrate compared to the conventional compressed tablet.

[7, 8]In the US, the dosage forms made from these processes are generally categorized as orally disintegrating tablets (ODT). these formulations were designed for drug delivery without water, and so both the total mass and API within them tend to be limited FDA also provides a guidance document for ODT formulation, according to the formulation design based on the intended in-mouth disintegration using only saliva and without the use of additional liquid, also requires disintegration in less than 30 seconds. They are tested by using an IP disintegration apparatus or other suitable alternative and recommended that the total mass of each ODT be below about 500mg.

The Bar graph: 1 provides a graphical representation of some current prescription ODT products in the global market. The data is also available in the electronic version of the FDA database/publication, this list also includes the Marketed brand and generic prescription drug products and Over-The-Counter (OTC) products.In the graph maximum product strength is 270mg, now they are compared to the bar graph: 2 ofthe zip-dose technology ODT product strength is improved.

[9] Zip-Dose technology was specifically designed to create formulations that are different from ODT when the product's total mass is more than 500mg, also they are made by Zip-Dose technology so that tablet administration in the mouth with a small sip of liquid (about 10-15 ml) of water. This approach to administration dosage is because some patient is suffering from Sjogren's syndrome disease. In Sjogren's syndrome, the mucous membranes and moisture-secreting glands of your eyes and mouth are usually affected first; resulting in decreased tears and saliva. When the total Dose mass is less than 500mg they are rapid disintegration by a small amount of saliva so not are a sip of liquid and also they are designed on the base.



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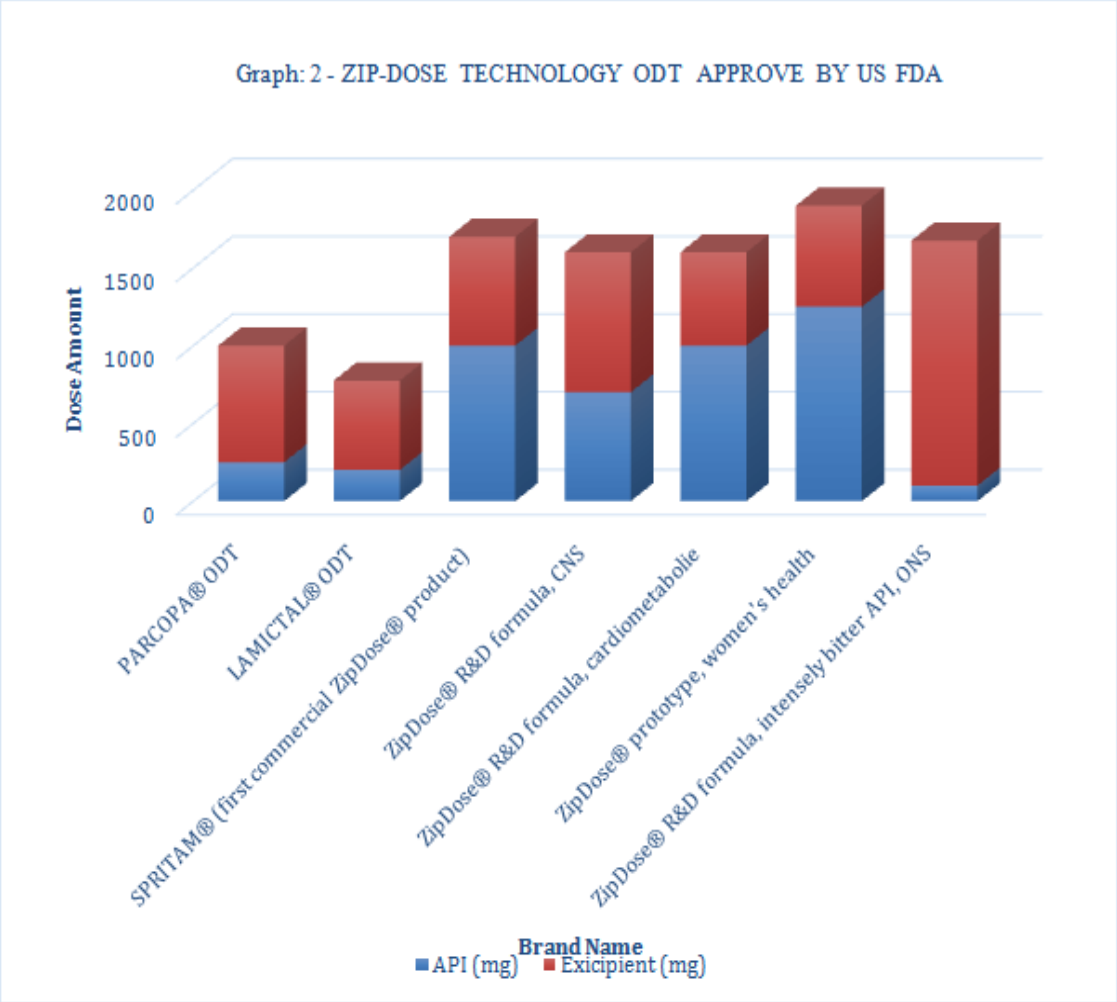
In Zip-Dose technology, we also use BCS class 1, 2, and 3 drugs. When an intensely bitter compound requires physical encapsulation in a hydrophobic material, they are also possible by Zip-Dose technology.Overall zip dose formulation delivers higher amounts of drug and in many instances, the higher connection of drug, when compared to these ODTs.

[10]The fast Disintegration of zip dose formulation depends on which material is used (Drug + Excipients) and the interconnected porous network. The dosage form is taken by a slip of water so the interconnection network quickly loses structural integrity, also in this zip dose theology dosage forms a 'powder-like' character so they void space higher compared to other technology ODT products.

This Zip-Dose technology also prints the symbol or company logo on this Dosage form by the three-dimensional arrangement of a powder particle. Since the structure begins as a thin layer of powder, the particles will have a significant amount of void space between them when limited selective wetting is applied. As more layers of material are added vertically on top of the preceding layers, the wetted zone is bound vertically and horizontally material, creating a 3D symbol on top of the Tablet.

Zip dose dosage forms are usually packaged in unit-dose blisters with crush-resistant cavities and peel-only lids. This design protects porous dosage forms from breaking. That is not suitable for bulking in bottles or highly energetic transfer motions. Normally no need for a special moisture barrier for packaging except for those required by specific active ingredients.



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IV. ZIP-DOSE TECHNOLOGY PROCESS

[11] In Figure: 3 show different element, in this formulation use Raw materials that are the same as a normal convention tablet (Filler, binder, lubricant, designation agent. etc.). In powder blending elements may be prepared by dry blending, dry granulation/wet granulation, or other known technology and also include milling/screening as a need to remove agglomerates. In printing fluid preparation elements suitable binder soluble in a suitable organic solvent.

In the first step, powder blending material thin layers are spread on conveyor belts. Then, they move to print fluid areas, where fluids are sprayed. The overall interaction of printing fluid and powder blend results make a thin layer of dosage form, then this process isrepeated several times and makes powder layer by layer. During each cycle end drying step is conducted to solidify the wet until doses at control temperature, relative humidity, and time.

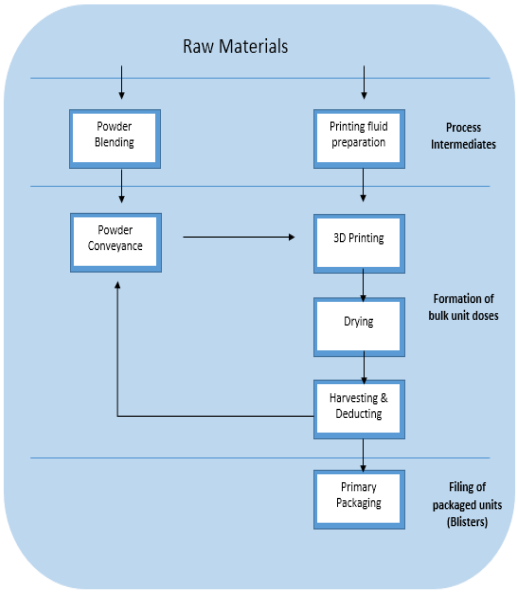

Fig: 3. Process of formulate tablet using 3D printing zip-dose technology

In this technology, liquid binder is sprayedinto powder and makes uniform solid dosage form that reason that technology also called Binder jetting 3D printing technology, also here wetting powder binds horizontally and vertically and makes layer by layer 3D structure that reason it a part of 3D printing.

Finish Dosage forms are collected and unbound powder are removed by using air. The Finished solid dosage form is like a towel tablet. They are shown in Figure: 5.

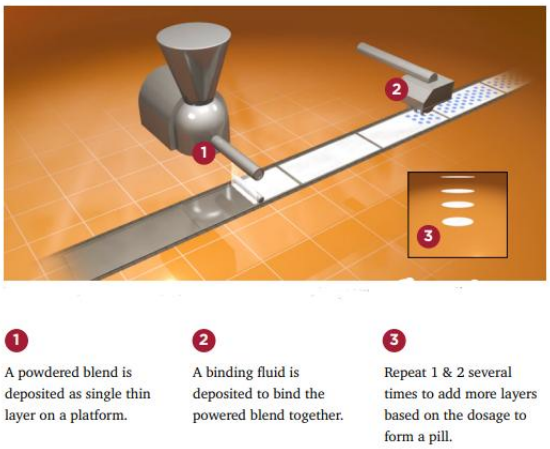

Fig: 4. Zip-dose technology machine process

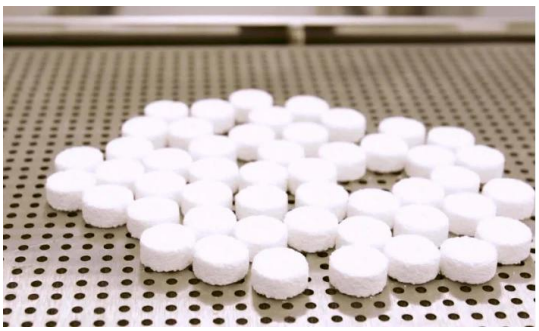

Fig: 5. Photo of dosage forms after harvesting

Every Batch of unit doses will pass out the powder blending, printing, and drying steps together. Those steps are referred to as the 'build-cycle' a batch of the product consisting of several build cycles that are carried out using the same starting material. However, during the process, we can change materials as per your requirements, but before changing materials, check their compatibility with each other and determine their physical and chemical properties.

V. ZIP-DOSE TECHNOLOGY MACHINEDESIGNS

[12] Powder liquid 3D printing (Zip-Dose technology) equipment developed by Aprecia's pharmaceuticals also impoverishes the product in the dosage form. The machine's name is M0 (pronounced "emzero"). That Figure show in Fig: 6.

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Fig: 6. Photo of aprecia`s "M0" 3D printing machine

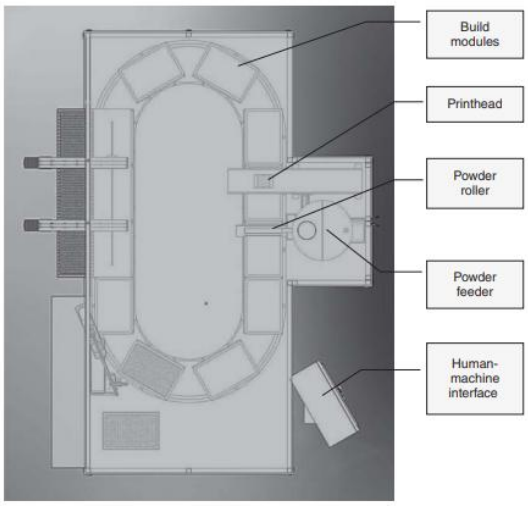

Fig: 7. Top view schematic of aprecia`s "M0" 3d printing machine

M0 machine was designed and built initially as an engineering prototype; they also support cGMP operation in production environments. M0 equipment top view is shown in Figure: 7. that equipment to make the first SPRITAM brand-name product.

VI. APPLICATION OF ZIP-DOSE TECHNOLOGY[13]

•Rapid dispersion at high loads:

Another technology makes ODT's product strength up to 300mg, but Zip Dose technology extends the product strength up to 1000mg and also rapid dispersion in the mouth within a few seconds. For example, spritam (the first commercial zip dose product).

•Taste masking:

A variety of taste masking options is available with powder-liquid 3DP, such as direct masking bitter taste by adding sweeteners and flavouringagents. Taste masking is also possible by drug bind with ion exchange resin.

•Broad application:

3DP zip dose technology to different size and shape ODT make; also in this formulation use two or more API use.

•Flexibility in product development:

This technology allows for an automated process of manufacture. It uses the placement of liquid droplets throughout the structure according to a blueprint for each strength. This approach allows flexibility during product development, particularly to refine the product dimensions and alter the degree of binding or porosity.

VII. CHALLENGES[14]

•Production of the 3D printing pill at Large scale:

Speedis one of the major limitations of 3D printing Zip-Dose technology. For example, when you have to build tablets layer by layer it's a slower process compared to the conventional compression tablet process. Aprecia's accelerated 3D printing process produces 10 - 100 tablets per hour.

•Optimizing pill design & formulas:

Aprecia's team experimented with a variety of medicine-to-filler ratios to determine what was most effective. Yoo says, "As part of the development process, we'd be looking at different types of binding agents and amounts. Because these tablets are supposed to disperse in the patient's mouth, we have to make sure they taste acceptable and are not bitter. If it is a bitter drug, we have to make sure the bitterness is masked out appropriately." The finished pill had to be durable enough to be transported. As well, it had to dissolve quickly in water, but not in the palm. Additionally, for the print head to deposit the binding agent, Aprecia tested several of formulas before arriving at a final version.

•Pre-treatment of powder:

According to some references, all excipients such as a binder, filled, and so on that are used in the formulation must have good flow properties; if the flow properties are not good, the excipient is not spared in the conveyor belt and the powder is not uniform distribute. That is why good

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powder properties are important. Powder pre-treatment is required, which increases processing time and cost.

VIII. FDA APPROVAL

The FDA has been closely monitoring the use of 3D printing technology in the pharmaceutical industry. The agency has acknowledged the potential benefits of the technology but has also raised concerns about its regulatory implications. The FDA has stated that 3D printed pharmaceuticals must meet the same safety and efficacy standards as traditionally manufactured drugs.

Furthermore, the FDA has stated that it will regulate 3D-printed drugs on a case-by-case basis, depending on the specifics of the product. As with all new and innovative technologies, the FDA will need to develop new regulatory frameworks, guidelines, and standards for 3D-printing in the pharmaceutical industry.

IX. CONCLUSION

In conclusion, 3D printing Zip-dose technology in the pharmaceutical industry has the potential to revolutionize drug development and personalized medicine. The technology offers the ability to create custom-designed medication that can be tailored to meet the specific needs of individual patients. But 3D printing Zip-Dose technology is a new field for drug development that reasons are facing a number of problems and challenges. Additionally, it is still challenging to prepare tablets as per FDA regulatory guidelines.

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