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APPLICATION OF 3D PRINTING TECHNOLOGY IN PHARMACEUTICALS

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Abstract:

Three-dimensional printing is a revolutionary technique that uses computer aided design software and programming to create three dimensional objects by placing material on a substrate. 3D printing is an additive layer manufacturing techniques, where consecutive layers of material are deposited or solidified to form a 3D structure. Medicinal substances is configured in three dimensional with computer assisted design module and transformed to a machine legible form which suggests the exterior emerge of the 3D dose form, then it sliced this surface into number of different printable coats and convey these layers to the machine. The different 3D printing techniques has been developing and developed to fabricate novel solid dosage forms, which are among the most well-known and discrete products today. The 3D PRINTING technology has caught the attention of medical devices industry and pharmaceutical industry due to its applications on various platform in health care industry. Even though this technology exists for a long time it is of public interest highly now due to the approval of 3-D printed tablet and other medical devices and also with the advent of USFDA's guidance on technical considerations specific to devices using additive manufacturing which encompasses 3-dimensional (3D) printing has triggered many thoughts about this technology which needs to be considered for successful delivery of intended product. This paper presents regulatory agencies expectations, limitations, problems in establishing such setups for production of drug products, advantages, disadvantages, applications, methods and associated risks involved in manufacturing. It also provides the comprehensive review of the current status of research and development on this platform.

Key words: *Three-dimensional printing, Structure, Print, Laser, Pharmaceuticals, Drugs.*

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INTRODUCTION:

Drug delivery is the technology and formulation developed to efficiently transport a pharmacologically active compound in the body to achieve therapeutic efficiency in a safe manner. The efficiency and safety of a pharmaceutical product can be improved by controlling the release profile which in turn modulates the pharmacokinetics of a drug. The interspecies variability is an obstacle frequently faced in the clinical scenario. Customized medicine and dosing receives increasing attention because of the high chances of undesirable side effects. The probability of adverse reactions is higher in the pediatric and geriatric populations when the bulk manufacturing of pharmaceuticals concentrates on the average population. 3D printing can play a significant role in multiple active ingredient dosage forms, where the formulation can be as a single blend or multi layerprinted tablets with sustained release properties. This reduces the frequency and number of dosage form units consumed by the patient on a daily routine. 3D printing technology has high potential in individualized dosage form concept called the polypill concept [1]. This brings about the possibility of all the drugs required for the therapy into a single dosage form unit. Three dimensional printing technology is a novel rapid prototyping technique in which solid objects are constructed by depositing several layers in sequence. The rapid prototyping involves the construction of physical models using computer-aided design in three dimension. It is also known as additive manufacturing and solid free form fabrication. 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine. It is an effective strategy to overcome some challenges of conventional pharmaceutical unit operations [2].

Regulatory Expectations

Regulatory Expectations (9) US FDA, 2017 issued guidance on Technical Considerations for
Additive Manufactured Medical Devices, this guidance outlines various requirements, like Design and Manufacturing Process Considerations, Device Testing Considerations and labeling. It also suggests the validation of the processes involved to provide high degree of assurance according to the established procedures. In addition documentation must be done to conform to the existing guidelines in the Quality System regulation for device validation. Process validation must be performed to ensure and maintain quality for all devices and components built in a single build cycle, between build cycles, and between machines, where the results of a process (i.e., output specifications) cannot be fully verified by subsequent inspection and test. Software also must be validated for its intended use according to an established protocol [3].

The following examples were suggested in the guidance with respect to powder bed fusion technologies,

- In-process monitoring of parameters such as: temperature at the beam focus, melt pool data,
- Build-space environmental conditions (e.g., temperature, pressure, humidity),
- Power of the energy delivery system (e.g., laser, electron beam, extruder), and
- Status of mechanical elements of the printing system (e.g., recoater, gantry)
- Manual or automated visual inspection with defined acceptance criteria,
- Non-destructive evaluation, and
- Test coupon evaluation Changes to the device, manufacturing process, or process deviations should be identified and analyzed for the potential risks they introduce. Based on this assessment, the change or deviation may trigger the need for revalidation of the process[4].

Advantages of 3D Printed Drug Delivery:

- High drug loading capability compared to conventional dosage forms.
- Accurate and Precise dosing of potent drugs which are administered at small doses for activity.
- Reduced production cost due to less wastage of materials
- Suitable drug delivery for difficult to formulate active ingredients like poor water solubility and narrow therapeutic windows drugs [5].
- Medication can be tailored to a patient in particular based on age, gender, genetic variations, ethnic differences and environment.
- Treatment can be customized to improve patient adherence in case of multi-drug therapy with multiple dosing regimen.
- As immediate and controlled release layers can be incorporated owed to flexible designs, manufacturing method of dosage form and it helps in pick out the best therapeutic regimen for an individual.
- Evades batch-to-batch variations met in bulk manufacturing of conventional dosage forms.
- Manufacture of small batch is feasible and the process can be completed in a single run.
- 3D printers capture minimal space and are affordable [6].

Disadvantages

- Problems related to nozzle are a major challenge as stopping of the print head which affects the final products structure.
- Powder printing clogging is another hurdle[7].
- Possibility of modifying the final structure on to mechanical stress, storage condition adaptions and ink formulations effects.
- Printer related parameters and these effects on printing quality and printercost [8].

PERSONILIZED MEDICINE:

The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications. Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate creating personalized medicines and restrict the ability to create customized dosage forms which are highly complex geometries, novel drug-release profiles, and prolonged stability. Personalized 3Dprinted drugs may particularly benefit for patients who are known to have a pharmacogenetic polymorphism or who use medications with narrow therapeutic indices[9]. Pharmacists may analyze a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose. A Pharmacist then print and dispense the personalized medication via an automated 3D printing system. If necessary, the dose could be adjusted further based on the clinical response. 3D printing also has the ability to produce personalized medicines in entirely new formulations, such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi reservoir printed tablets. Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of health care. Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve the patient compliance [10].

POLYPILL CONCEPT:

The concept of "polypill" refers to a single tablet that includes the combination of various drugs. This concept is highly beneficial for geriatric population, as patients of this age category are prone to multiple disorders and hence multiple therapy. The technology has been realized through the research of Khalid et al, where five different active pharmaceutical ingredients with different release profiles have been formulated in a single 3D dosage form. Three drugs (pravastatin, atenolol, and ramipril). Three-dimensional(3D)extrusion-based printing was used to manufacture the 'polypill' to demonstrate that complex medication regimes can be combined in a single tablet and that it is viable to formulate and 'dial up' this single tablet for the particular needs of an individual were printed in the extended release compartment[11]. The drugs were physically separated by a permeable membrane of hydrophobic cellulose acetate. An immediate release compartment containing aspirin and hydrochlorothiazide was deposited on top of the extended release compartment tablet. The tablets used to provide this concept incorporate an osmotic pump with the drug captopril and sustained release compartments with the drugs nifedipine and glipizide. This combination of medicines could potentially be used to treat diabetics suffering from hypertension. The room temperature extrusion process used to print the formulations used excipients commonly employed in the Pharmaceutical industry [12].

TECHNIQUES IN 3D PRINTING:

3D printing includes a wide variety of manufacturing techniques, which are based on digitally-controlled depositing of materials (layer-by-layer) to create free form geometries[13].

THERMAL INKJET PRINTING:

In thermal inkjet printing, the aqueous ink fluid is converted to vapour form through heat and expands to push the ink drop out of a nozzle. It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating and loading drug eluting stents [14]. It is also an efficient and practical method for producing films a substrate either in the form of Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing, hence it provides a high resolution printing capability. Inkjet printing is also called as 'mask-less' or 'tool-less' approach because the formation of desired structure mainly depends upon the movement of inkjet nozzle or movement of the substrate for an accurate and reproducible formation. It has a low processing cost, rapid processing rates, generation of minimal waste, it gives CAD information in a 'direct write' manner and it process material over large areas with minimal contamination [15].

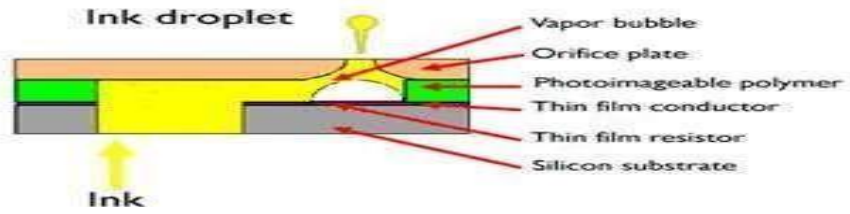


Fig 1: Thermal ink jet printing

FUSED DEPOSITION MODELING (FDM):

Fused deposition modeling (FDM) is the second most important commercial layered manufacturing technique. This process is used to fabricate final products directly without the use of any tooling, die, or molds, which are some of the major constraints of the traditional manufacturing process. This technique has gained popularity due to its short cycle time, highdimensional accuracy, ease of use, and easy integration with different computer-aided design (CAD) software. FDM is an additive manufacturing technology and commonly used for modeling, prototyping, and batch production applications[16]. Fused deposition modeling (FDM) is commonly used technique in 3D printing, in which the materials are soften or melt by heat to create objects during printing, Hence there are several dosage forms. FDM 3D printing helps in manufacturing delayed release printlets without an outer enteric coating, and also provides a personalized dose medicines. FDM 3D printing however, indicates several limitations of the system such as lack of suitable polymers, slow and often incomplete drug release because the drug remain trapped in the polymers and the miscibility of the drug and additives with the polymers used was not evaluated [17].

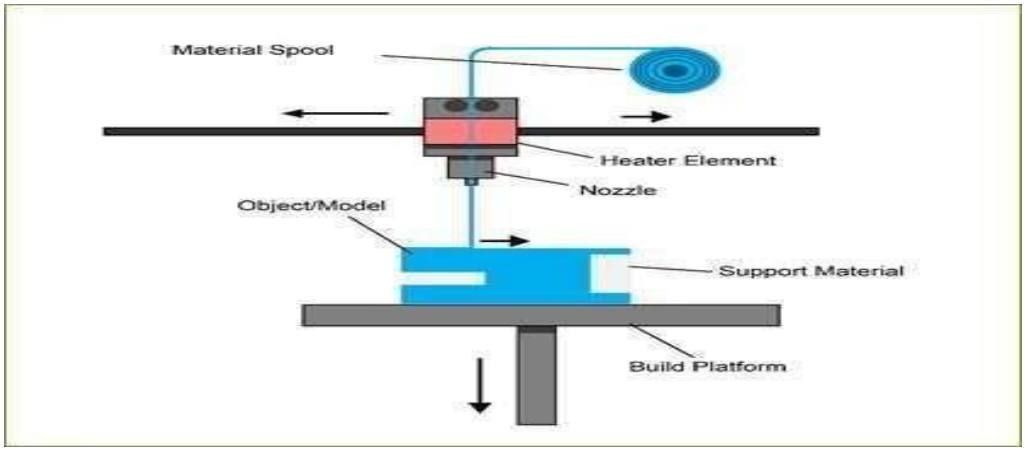


Fig 2: Fused deposition modelling

ZIP DOSE:

Zip dose is the world's first and only FDA-validated, commercial-scale 3DP in new therapeutic areas for drug manufacturers. It has a unique digitally coded layering and zerocompression processes, which is used for formulating a tablet with high dose and rapid disintegration. Hence it helps in overcoming a difficulty in swallowing. It developed with Aprecia's proprietary 3DP [18] manufacturing process, Zip Dose Technology helps patients who need medicines that are easy to take and caregivers—including physicians and nurse practitioners—who want medicines that are easy to administer. By enabling the delivery of high-dose medications in a rapidly disintegrating form, Zip Dose overcomes patient adherence and difficulty swallowing challenges [19].

Spritam (Antiepilipsey drug) is an Orodispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by-layer production system. In which it consists of active ingredients, excipients and a binder liquid to produce a matrix tablet [20].

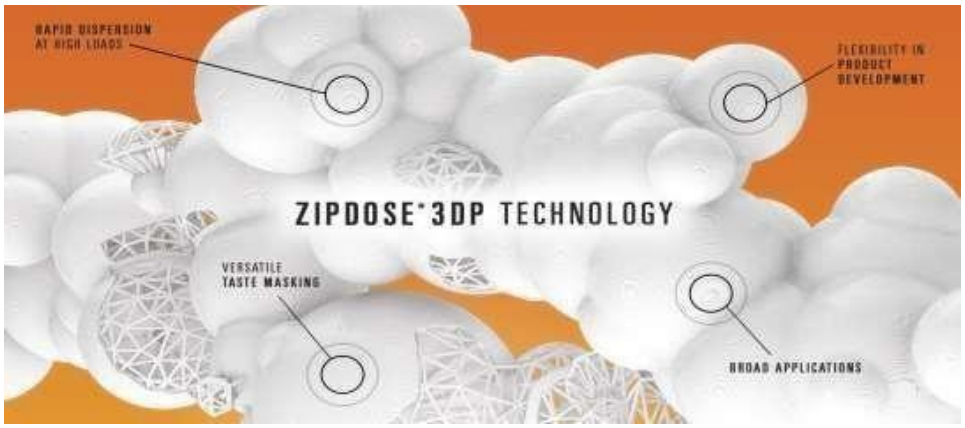
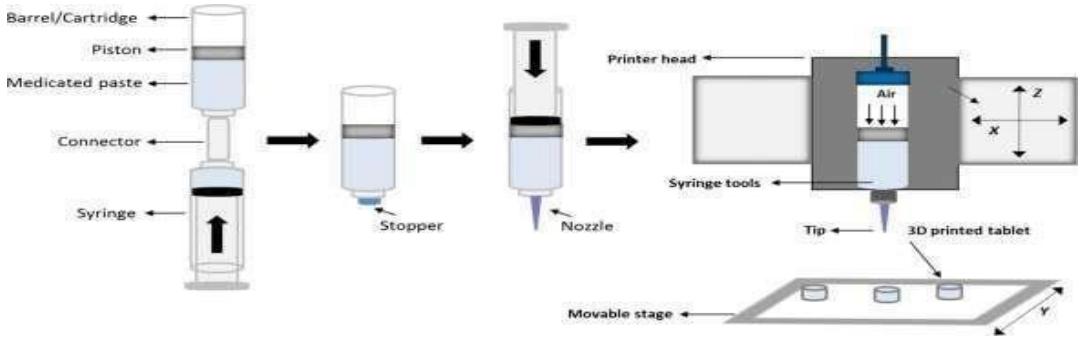


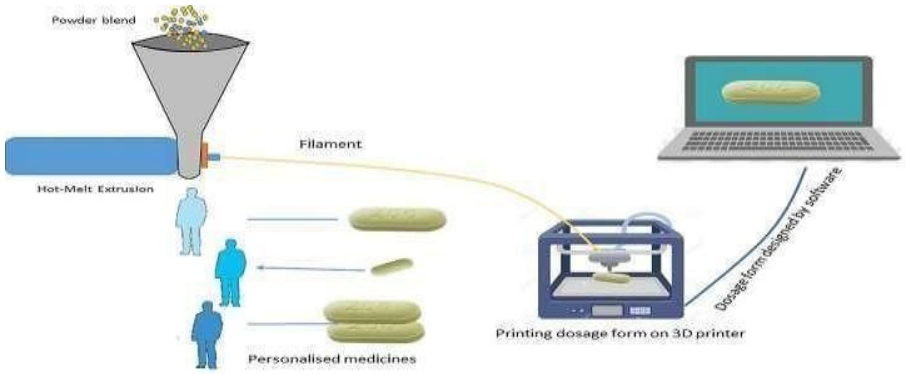
Fig 3: Zip dose 3D printing

Extrusion 3D printing:
According to the ASTM International standards organization, extrusion is an official name given to a specific 3D printing process where material is selectively dispensed through a nozzle or orifice. Extrusion more commonly known as Fused Deposition Modeling Extrusion is the most common and the simplest 3D printing technique. It is used in almost every environment [21]. The main printing material is plastic filament. The filament is heated, and melted in the printing head of the 3D printer. Extrusion is an "additive" technology commonly used for the modeling, prototyping, and production applications[22]. It creates an object by laying down the material in layers; a plastic filament or metal wire is unwound from a coil and supplies material to produce a part. In this technique, material is extruded from the automated nozzle on to the substrate and it does not require any higher support material. It is only used to fabricate tablet containing Guaifenesin as expectorant. The materials that can be extruded are molten polymers, suspensions, semisolids, paste [23].



3D printer:
The 3D printer is a valuable tool which is used to create customized medications with tailored release profiles and the medication is changed as per the patients comfort [24].

HOT MELT EXTRUSION (HME):
Hot melt extrusion (HME) is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending. It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping. In recent years, it has proved that HME can improve the solubility and bioavailability of poorly soluble drugs [25]. HME is used to prepare solid solutions/dispersions for drug delivery systems such as pellets and granules, it can reduce the number of processing steps in dosage form manufacturing and can be automated as a continuous process to give better drug homogeneity, capabilities of sustained, modified, and targeted release [26]. Uniting Hot melt extrusion (HME) with solid freeform fabrication (SFF) such as Fluid deposition method (FDM) offer great chances for designing a wide variety of drug delivery systems by 3D printing technology [27].



STEREOLITHOGRAPHY:

Stereolithography (also known as Stereolithography apparatus, Optical fabrication, Photo-solidification, (or) Resin printing) is a form of 3D printing technology used for creating models, prototypes, patterns, and production parts in a layer by layer fashion using the photochemical processes by which light causes chemical monomers to link together to form polymers[28]. Those polymers are then make up the body of a threedimensional solid. Stereolithography is the technique in which a computer controlled laser beam is used to solidify the liquid polymer or resin, thereby creating a 3D structure.

SLA has some advantages over other types of 3DP, mainly it's remarkable resolution and the avoidance of thermal processes can be detrimental for certain drug molecules [29]

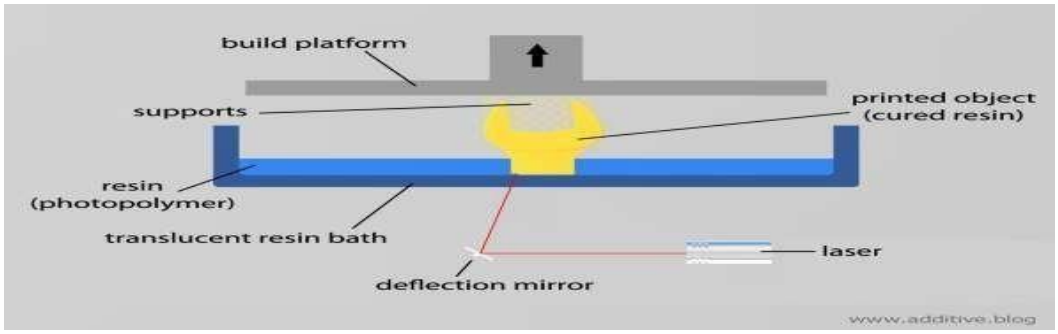


Fig : Stereolithography

SELECTIVE LASER SINTERING:

Selective laser sintering (SLS) is an additive manufacturing (AM) technique that uses a laser as the power source to sinter powdered material (typically nylon or polyamide), aiming the laser automatically at points in the space defined by a 3D model, binding the material together to create a solid structure [30]. For example Paracetamol is an Orodispersible tablets which was prepared by this technique. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects [31]

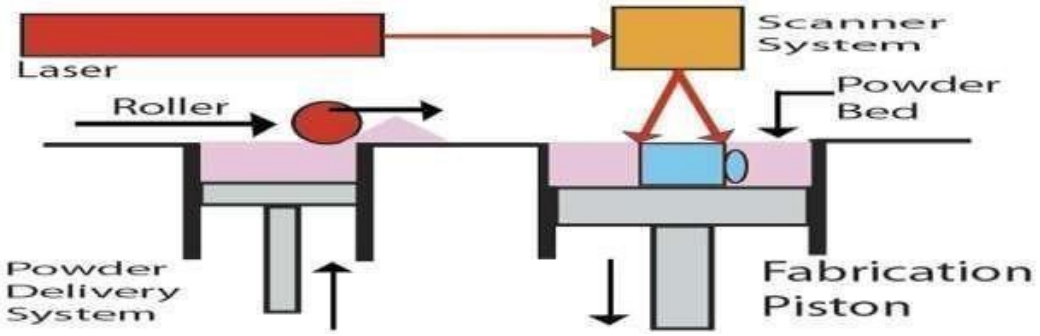


Fig : Selective laser sintering

CHALLENGES IN 3D PRINTING TECHNOLOGY:

- Although proved promising results are there in drug delivery, still under the developing stage.
- Several challenges such as versatile use, appropriate excipient selections, post treatment method to advance the enhancement of 3D printed products and to magnify the application scope in novel drug delivery systems [32].
- The built-in flexibility might be a most important resource of liability from safety point of view for re-designing through 3 Dimensional printing[33].
- The primary parameters are to be modified to improve quality of 3DP such as printing rate, passes, print heads line velocity, printing layers interval time, nozzles and powder layer distance etc [34].

APPLICATIONS OF 3D PRINTING:

- Potential use in improving process, modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, pharmaceuticals.
- It mostly targets on the two potential sites to rise pharmaceutical product development to unexplored areas, manufacturing sophisticated structures for the delivery and personalized medicine.
- In Healthcare industry to create dental implants.
- On fabricating an organized release multi-drug implant for bone tuberculosis remedy.
- Helps in Organ printing, biomaterials and cell-laden materials [35].

Limitations and Challenges of 3d Printing Dosage Forms:

There are a couple of challenges that 3D printing faces which has to be overcome before it is adopted as a widely used manufacturing technique for personalized dosage forms.

Process Challenges Raw material selection:

Printability, thermal conductivity, physicochemical characteristics, Print fluid characteristics and viscoelastic property has to be carefully scrutinized along with safety of the raw materials for human use[36].

Nozzle mechanism:

During 3D printing, nozzle mechanism is used to form the layers of the dosage form. As the printer head stops and restarts during the sequenced layer formation, consistent flow of the printing material is necessary. The common problems faced at this level are clogging of the nozzles in printer head, scraping, binder migration and bleeding and improper powder feeding [37].

- Certain manufacturing process may not be appropriate for thermolabile drugs when printing at high temperatures[38].

RISK ASSESSMENT DURING 3D PRINTING PROCESS:

Risk determination is an important step in 3D printing technology. Mainly it was performed to prevent failure of quality assurance parameters such as assay, content uniformity, appearance, etc.

Risk factors are identified with the process and process variables to conform the quality of product which was manufactured in industries. Risk factors are checked in these conditions

- Software controls should be employed, if a particular printer cannot print a particular pattern.
- Layer thickness variability has to be controlled by real – time layer thickness monitoring[39].

CONCLUSION:

3D printing has become a useful and potential tool for the development of Pharmaceutical sector, leading to personalized technology is emerging as a new horizon for medicine focused on the patients' needs. 3DPrinting technology has the ability to revolutionize the Pharmaceutical manufacturing style and formulation techniques. 3DP technology makes it possible to fabricate highly sophisticated and complex dosage forms of drugs and has enhanced the freedom to control the shape as well as microstructures of dosage forms. Furthermore, 3DP is an innovative and highly promising way for the on-demand manufacturing and dosage form personalization, which may improve the patient compliance and drug effectiveness, reduce the side effects, and resolve the stability issues of drugs with limited shelf-life, and, eventually, lead to the patient-specific health care with on-demand tailored medications.

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Discloure of conflict of interest

The authors have no conflict of interest to declare.

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