Review article

THE IMPACT OF 3D PRINTING ON DRUG FORMULATION AND PERSONALISED MEDICINE

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ABSTRACT

Major advances in the areas of treatment formulation as well as personalized medicine have been generated by the arrival of 3D printing, commonly referred to as additive manufacturing. In contrast with normal pharmaceutical making systems 3-D printing allows you to effectively fabricate intricate drug delivery systems with unique dosages, forms, and structures. This technology creates novel possibilities for targeted therapy by enabling the immediate manufacturing of drugs that adapt to each patient's physiological and therapeutic demands. Multiple pharmaceutical ingredients, also known as APIs, can be included in a single dosage form with regulated release profiles and spatial separation thanks to 3D printing in medication formulation. This ability enhances the effectiveness of medical care, particularly for people who have severe or persistent diseases that call for polypharmacy. Rapid prototyping and the creation of orodispersible, transdermal, or implantable dose forms with improved bioavailability and patient compliance are also made possible by the technique. Because 3D printing allows for the building of prescriptions perfect to a clients genes, way of life, or medical information, personalized medicine benefits incredibly from this technology. For example, special medicines may be better for adolescent and aging populations, who typically necessitate unconventional dosages and formulations. Furthermore, 3D printing aids in the creation of precision treatments, like those used in oncology, where precise dosage is

essential. Furthermore, 3D printing aids in the developing of precision treatments, like those used in oncology, where consistent dosages are crucial for both avoiding side effects and ensuring treatment effectiveness. Nevertheless, its potential, integrating 3D printing into pharmaceutical practice faces with obstacles, including obtaining regulatory approval, standardizing materials and procedures, and securing reproducibility and quality control. However, these problems continue to be solved by current research and technology developments, which is moving the goal of honestly individualized medicine closer to reality. This study analyzes how 3D printing is impacting current drug formulation procedures and how it can completely transform the way that personal medical care is delivered in the future.

KEYWORDS: *Precision drug therapy, Advanced drug delivery system, 3D Printing in pharmaceutical, Innovation in drug, Patient centric formulation design*

1. INTRODUCTION

New concepts for drug design, a deeper knowledge of substance characteristics, technology for production, and procedures that ensure superior medication forms are always encouraged. At every stage of product development, the biological and physical attributes of pharmaceutical ingredients must be recognized and evaluated. Auxiliary contaminants must also be assessed before synthesizing their desired form of administration.

The design and creation of compassionate medicinal goods has got a lot of media coverage over the previous 10 years. The main focus was on creative technologies and level types. Major improvements in individualized healthcare, such as the development of tiny series of tailored doses and devices transformed to each client's biomechanical needs, have been driven by a growing need for bespoke gear and technological advances. 3DP is regarded as the most potent and innovative of the numerous advances launched into the market for pharmaceutical and biomedicine. Process of production is recognised as a versatile instrument for the exact manufacturing industries of a broad spectrum of items. It is a technology applied to the simulation of diseases, tissue and organs a career in engineering and quantity generation.

Among the disciplines of the sciences, the arts, and innovation that is currently developing the fastest is three-dimensional printing, which continues to expand it uses. This technique is one of the additive processing methods where pieces are made from model data while connecting layers of substance, unlike the more common formative and subtractive manufacturing

approaches. Rapid prototyping is the term used to describe a practical methodology (1).

Its benefits include lowering the time and expense of prototyping, making it simple to modify a product at a level that is designed, and enabling the production of small items, Unique goods sets or frameworks that cannot be created using traditional subtractive procedures (2). A game-changing technique, three-dimensional (3D) printing can create unique medications (printlets) with varied drug dosages and goods with several APIs, varying release parameters. (12) In an effort to boost adherence among patients recovering from breast cancer, printing presents a potential alternative for personalised medication called measures, such as variations in concentrations and mixed therapy. Further, 3D printing provides an easy method to produce small-batch medications, which makes it ideal for customized dosages and a way to facilitate clinical studies. There is now an abundance of pharmaceutical 3D printing technologies on hand, but the most for healing complex ones are inkjet printing, binder jetting, fused deposition modelling, direct powder extrusion, and semisolid extrusion. A change in care strategy is envisioned and the first research research evaluating compatibility, care choices and booklet degradation in reality are currently being published even though the use printing at healthcare facilities is still in the beginning stages, with concerns about technological viability and processing time remain to be solved (13) Specific treatments grow more and more favored (14), and this calls for versatile and adaptable manufacturing techniques like three-dimensional (3D) printing (3DP) (15) provides the printlet (3D printed tablet) to be modulated and dosed in real-time to suit the needs of each patient (16). Human and dosage errors are minimized by the medication's-controlled controlled manufacturing process (17). The 3D printer can be seen as a piece of equipment or a tool that aids in automating the production of small batches of individual drugs on a low scale, such as in a hospital setting (16). In contrast to other 3DP procedures, Extrusion of materials is a semi-solid methodology that uses relatively low printing temperatures to deposit a gel or paste (18). Because a drug-containing gel that is pharmaink-based can be prepared easily and simply inside a disposable syringe, it is an affordable device that may be used in a hospital setting (16). Using pre-filled, disposable syringes achieves the crucial criteria for quality set by regulatory bodies. This makes it easy for pharmaceutical manufacturing facilities to produce and fill the syringes in accordance with good manufacturing practice rules
(16). If the right excipients are used, the dosage forms made with SSE can be chewed, which can help with swallowability problems in special populations like children, the elderly, and those with dysphagia. It can also help with treatment adherence (19). Practitioners are left

without the ability to offer their patients entirely personalized medical care in a way that is safe, reasonably priced, and widely available, since the pharmaceutical sector has not yet given in to the pressure of a technological paradigm change. Though it has disadvantages, the 3DP provides pharmacy practice with a fresh way to close the recent patient-centred care gap. Although earlier evaluations have examined the technical uses of 3D printing in the pharmaceutical industry (20), the design, application, and processing of several pharmaceutical products may undergo considerable changes as a result of 3D printers. Conventional manufacturing procedures, although cost-effective, could require strenuous work, and large-scale production may be lengthy. Additionally, the doses in the traditional production process are difficult to adjust to the need of the patient. By personalising the drug for individual patient, printing can revolutionize care through personalized drug and increase patient comfort. To provide the finest medical treatment, this can be accomplished using automated production in therapeutic contexts (42).

2. HISTORY

Pierre A. L. Ciraud detailed the process of using substance and then making each layer solid using a beam of high energy in the early 1970s, which is when the concept of 3DP first emerged. In this situation, it is theoretically possible to prepare objects using meltable materials like metals or polymers. Early in the 1980s, Carl Deckard created a technique known as selective laser sintering for solidifying powder layers using laser beams, and Ross Housholder displayed the concept of binding of sand by different substances in a molding patent process for forming a 3D article. Photo-solidification was the first tech created by Chuck Hull that made it commercially reachable. This method photopolymerized liquid resin using ultraviolet light. Scott Crump submitted a patent technique for fused deposition modelling that prepared objects using thermoplastic matter, near the end of the 1980s. A scientist from MIT named Emanuel Sachs and his colleagues patented in the 1990s. This process involves binding material to link certain powder regions (3).

3. PATIENT CENTRIC THERAPY

The methods used for 3D printing have multiple uses in medicine, such as creating spatial systems for tissue engineering, and in pharmacy to create dose forms like tablets since they can be applied with any kind of material (4). Although extremely personalized medication has been an idea for many years, its relevance has never been as important as it is now. There is a lot of debate on the necessity of creating customized healthcare through patients using

medications responsibly and at the appropriate dosage, as the variety of disorders makes therapeutic intervention challenging. Therapy failures or constraints in therapeutic effectiveness are reasons to alter the amount and type of the active ingredient, especially for specific age groups. The target population and the disease being treated should be taken into consideration while choosing the right dose forms, in addition to the physicochemical characteristics. Although each patient group presents with distinct needs and traits it is majorly encouraged that matter be invented for the pediatric and elderly populations. Tablets tend to be split into two or even four portions in the medical field due to dosage flexibility and variations in swallowing. The literature shows issues with scored pills. Overindulgence or underdosing may result from unequal breaking and mass loss upon division (5). Through dosage and form alterations, such as using orodispersible tablets in place of standard tablets for patients who are active or noncompliant, 3D printing enables the customization of drugs to the consumer's requirement. The scalability of the established item makes it easy to make dose with varying dosages therefore the dosage can be controlled by material calculation taken while the printed object's scaling process, which is already done during the design stage. Making of orphan medications for tiny populations appears to gain greatly from this manufacturing method. One of the main benefits of short series of pharmaceutical products is the affordable cost of producing dosage forms with various doses. (6,7) Unprecedented alternatives for the pharmaceutical or industrial scale research and production of specific medications are presented by 3D printing. Pharmaceutical compounding would reach a completely new level with the spread of 3DP to medical facilities. The quantity of medication given as well as its shape, colour, and taste are key factors in treatment, primarily in young patients together with to the active ingredient's dosage. (8) Furthermore, the taste masking can be done with certain methods of 3-D printing, such as bonded deposition modelling APIs are included in the polymer matrix without the need for additional processing like film coating. Scoutaris et al. made taste mask dosage form with indomethacin in the form of Starmix® Haribo jelly beans using this 3DP process. The dosage forms had rapid API dissolution, reliable information, precision and good consistency. The tablet's form and size have a direct effect on patient acceptability, especially whenever it comes to swallowing issues. Senior citizens additionally need caution when it comes to tablet shape because of problems with swallowing as well as abuse issues. (9) It is possible to create tablets with many active ingredients, each with distinctive features and dissolution profiles, thanks to 3D printing. Therefore, by creating complex medications it might lead to a decrease in the quantity of items that are utilized. (10) The main methods that the additive manufacturing innovation enables precise control over

dissolving behaviour are by using certain soluble or non-soluble excipients and by designing the internal structure and layout of the generated form of administration.

Fluorescein-printed microneedles. To obtain an appropriate mold for the microneedles, an additional etching process was necessary. In the most recent study on microneedles, an inkjet printer was used to coat the microneedles with insulin formulation, and stereolithography was used to create needles of the right size and shape. The authors achieved rapid insulin dissolution in vitro, but what was most notable was the capacity to easily create microneedle patches. (11)

4. Technical methods of 3D printing personalised medicine

A dynamic manufacturing method which permits for quick and easy alteration of the delivery method, product form and dimensions, and the rate of release of drugs to fit each patient's needs and preferences necessary to create a fully PM. The barriers that existing pharmaceutical production methods place on the development of PM can be addressed by 3D print, which is the method of building an object layer by layer in accordance with instructions from computer-aided design (CAD) software. Other industrial industries including agriculture, aviation, and automotive have already embraced 3D printing because of its flexibility, which allows the maker to provide an automate printer make of any feasible specified framework in a large range of component possibilities. However, the potential of printed objects to be produced with high accuracy utilizing biocompatible materials has led to a recent spike in interest in the medical field. (21)

a) HOT MELT EXTRUSION

The method of mixing polymer components at high temperatures in a tank with an oscillating screw is known as "hot-melt extrusion." A polymer may be put to the chamber together with additional excipients and active pharmaceutical ingredients (API). A final amorphous product is formed by molecular level mixing that takes place when the vessel is heated above the monomer's point of breakdown or glass shift range. For other methods, this transform can serve as a drug loaded filament. (22)

b) FUSED DEPOSITION MODELLING

An extrusion nozzle feeds a readymade solid drug-loaded filament that has been heated to the melting point. This filament is mostly made using HME printing. heated fiber is placed on a construction platform and solidify in accordance with the XYZ coordinates provided by the CAD program. Layers of this procedure are continued, increasing upward, until the finished

dosage form is created (23)

c) SEMI-SOLID EXTRUSION

Similar to FDM, SSE uses a nozzle to extrude semi-solid materials like hydrogels or pastes which are then stacked and placed according to CAD specified co-ordinates. It is therefore especially advantageous for usage with thermolabile medications because high temperatures are not necessary (16)

d) VAT PHOTOPOLYMERISATION

A thin coating of liquid photosensitive substance, such as resin is placed on a base inside a vat and exposed to ultraviolet (UV) radiation. Material hardening in a specific shape is made possible by the chemical reaction that takes place within bonds when exposed to UV radiation. After that, the base descends, irradiating each subsequent layer until the last dose form is finished. The two types of vat photographic polymerization processes are stereolithography and electronic optical processing. Although UV light serves as the radiation source for both techniques, their applications differ: DLP use numerous holographic mirrors to instantly solv a complete layer in different locations, whereas SLA use a time-dependent single laser ray that travels to each desired coordinate. (24)

e) INK-JET PRINTING

The idea behind inkjet printing is identical to that of standard office inkjet printers. Instead, inkjet printing ink cartridge include an API solution which is printed onto sheets of various nutritious materials.(25)

f) SELECTIVE LASER SINTERING

To create the shape of the CAD-designed image, SLS uses a laser's heat to fuse a powder layer particle made up of API and other excipient together until the last dosage form is completed the procedure is repeated with fresh powder layers on top. The finished design is revealed after the print is removed and superfluous powder is wiped off. (26) Table 1 provides examples of the advantages each of the aforementioned techniques offers for medical personalization. All methods demonstrated the capacity to produce novel dosage form types that are generally too challenging to accomplish with present pharma processing method mostly in cases of on the spot accumulation like orodispersible films(27), tablet form in syringe (28), gummies (29), and drug contain implantable devices (30). The development of zero order release kinetics was

another noteworthy advantage of personalization.(31) In order to maximize therapeutic result for patients while minimised toxicity rate, CAD software's computational calculations were used to develop a structure that would release consistent quantity of medicine over time. The creation of an solid crystalline dispersion specifically by HME is also very advantageous for customization. When weakly water soluble medications are mixed at the molecular level with molten polymeric material the drug's energy state is greater than that of crystals form which improves its capacity to form solvent and consequently reach at site. The main evidence for this is that 3DP Biopharmaceutical Classification System (BCS) medications have higher bioavailability than traditional dose formulations. (30)(33)

Table 1: 3DP methods

Sr. no	3DP methods	API	Advantage of Customization
1	Hot Melt Extrusion n/Fused Deposition Modelling	Warfarin	Manufactured tablets with warfarin dose determined based on the intended patient result. Warfarin dose ratio was carefully tested to meet the specifications of each patient, as seen in Sprague-Dawley rats throughout pregnancy. (32) Amorphous dispersion that is solid. considerably enhanced solubility and availability of the BSC II class
		Ketoprofen	The disintegrate profile was altered by altering the cover ratio of the internal inner and outer shell. The quickest release of medications happened with the least cover density. Grade according to US Pharmacopoeia (33)

2	Semi-solid Extrusion	Paracetamol ,Ibuprofen phenytoin	Unique the dose type: chewable, drug-loaded components constructed with a soft gelatine-based core. Designed for paediatric use(29) Unique medication form: fast dispersing granules put within a syringe that create an extract for ingesting when drawing the syringe with solution created to make oral medication administration easier for those with difficulty and increase dose effectiveness (28)
3	Vat-photopolymerisation	Paracetamol, caffeine, naproxen, chloramphenicol, prednisolone, and aspirin	Six different drug-containing chambers, each with verified customized release patterns, hold six different drug polypills. Because of the SLA devices' excellent precision, a complex designed polypill containing six drugs may be created in a standard dosage size of about one centimeter in diameter. (34)
4	Ink-jet printing	Propanolol Thiamine hydrochloride	Orodispersible drug delivery systems provide an exclusive level form. designed for uncomplicated oral delivery, especially great for pediatric groups and dysphagic patients (35) Quick drug dispensing was obtained. Since thiamine was suspended, it dissolved well in PVP, enabling manipulation to create a quick breakdown gradient. (36)

5. 3D PRINTING'S VALUE IN SPECIAL MEDICINE

Customizing dose forms for individual is main advantages of 3DP in the pharma company. Depending on the needs of the patients this might be accomplished by creating appropriate dosage forms, altering the amounts, mixing them, or altering the dosage forms' release patterns.

6. DOSE PERSONALISATION

It may be possible to achieve dose flexibility based on patient demands with 3D printing. Pediatric patients whose effective amount varies according on their years of age and their physique are one significant group that requires dose ability. With the help of 3D printers the types of dosage forms listed can be suitably altered to give patients the optimal dosage. This is easily accomplished with formulations by rearranging the quantity of liquid ingredient that is poured onto the film. To customize treatments, ODFs can also undergo form and dimension modifications. (43) To achieve dose flexibility, pill splitting has been done manually or with a splitter in previous years. Since the different characterisation criteria of the divided tablets don't always meet the Pharmacopoeial standards, this has been shown to be useless. In a study conducted by Zheng et al., split tablets were contrasted with 3DP divided pills. It was chosen that the 3D printer divided pills were safer, more accurate, and potentially customizable. (44) Personalized mini-tablets, also known as mini-printlets or 3D printed pellets, have been developed. Additionally, they can be used to mix two distinct medications (45). In order to produce customisation, mini-pellets can also be mixed and encapsulated based on the dosage required (46)

7. MODIFY RELEASE PROFILE

Dosage formulations with various delivery characteristics can be designed to fulfil specific needs and can be produced by 3DP. Changing the forms and geometries of tablets is one way to do this. After fabricating quick-release tablets containing low dose medications, it was determined that reducing the tablet thickness or creating gaps inside it enhanced drug release rates, sometimes achieving full release in five minutes. (47) Khaled et al. created paracetamol pills with different geometries, such as mesh and ring, and contrasted them with solid tablets and one another. While round and solid tablets showed extended release, mesh pills showed immediate release. (48) Another study involved the fabrication of paracetamol pills in the following shapes: square, ladder, disk, and globe. The research discovered that the release of medication from the printlet can be altered by altering its circumference or volume ratio.(49) Using 3DP tablets with unique structure such as a structure of the honey. Different release profiles were obtained by varying the diameters of the honeycomb cells from 0.20 to 1.83 mm. It was driven that various release profile may be obtained by manipulating the dosage form geometries (50).

8. Utilization of 3-DIMENSIONAL PRINTING

- **Solid Dosage Forms**

The only professional 3D printing method currently in use is powder resin jetting. This method was utilized by Aprecia Labs to create the oral dispersible tablet Spritam, which contains 1000 mg of levetiracetam. Instead of using heat to create the tablet, a coating of powder and a liquid glue are employed to help each layer stick to the one before it. Because the dose is printed right into the blisters, there is less need to recycle unprinted powder or harvest dosage forms. An robotic zip dosage assembly machine is used to remove the premade orodispersible tablet base and cover. Because the breakdown period is less than one minute, deglutition and an immediate onset of effect are made possible.(51) Polypills have evolved as a new tailored solid type that attempts to integrate all of the medications that a patient need in a single tablet while customizing the amount and release rate. Drug combinations are commonly used to treat metabolic syndrome, which includes high blood pressure, high blood sugar, and excessive cholesterol levels. However mixed therapy for infectious state and pain are gaining popularity. FDM is now the most used 3D printing process for manufacturing mono- or polypills. The reason of impact in clinical research, given that after processing is not required because no solvents are engaged in the method, and printing solid medication forms have adequate properties in tensile term rate and drug release profile alteration. FDM technology has successfully printed polypills containing two or more medicines. Excipients utilized he dearth of biologic compatibility studies with the resins used for SLA, the use of those methods in clinical practice for the fabrication of polymer material is complicated.

- **DOCTOR ACCEPTABILITY**

Physicians must first comprehend and recognize the effective value of this innovative method in clinical research before 3D printed personalized medication can be made available to the general public. Most medical professionals have a favorable opinion of 3DP uses in pharma sector. In a cross-sectional study 55 Singaporean healthcare professionals were polled, including 33 pharmacists and 22 doctors. (37) Over 60% of medical experts said they would be open to prescribing tablets that were 3D printed. In 2020, Rautamo et al. conduct second research where they conducted interviews with medical professionals, including doctors, regarding the possibility of using 3D printing to manufacture pediatric medications.(38) Many believe that 3D printing can be very helpful in enhancing drug acceptability, creating novel medications on demand in a hospital setting, and giving patient-specific dosage. In order to

reduce polypharmacy and enhance adherence, several physicians also recommended using 3D printing to customize medication combinations and dosages for patients with HIV and organ transplants. Nonetheless, issues with drug interactions, stability, cost, administration, safety, and bioequivalence were also raised. For doctors to alter their present practices and offer 3DP medication goods as part of their treatment these issues must be resolved.

It is important to note that a large number of the worries stemmed from ignorance of the capabilities and operations of this new technology. For instance, 3DP may offer the benefit of avoiding some detrimental drug interactions when it comes to worries regarding medication interactions between a polypill's several active ingredients (37)

- **QUALITY ALONG WITH SAFETY**

The most notable problem with conventional processing is the absence of performance testing procedures that guarantee the consumer is getting safe and appropriately dosed medication. (14)(39)concerns about PMs being 3D printed are common. When a pharmacist is processing on-site, the computerized aspect of 3DP eliminates the possibility of human mistake influencing Quantity estimation and mechanical measurement for people ingredients. This is due to the fact that, without the assistance of a pharmacist, computer algorithms may rapidly and accurately forecast the ultimate print mass and sheets based on the outcome dose. For 3D prints long lasting stability are additional considerations. After a fair amount of time, patients who take any prescription at home have faith that it will continue to work. (40) found that the dosage and dissolution behavior of SSE printed tablets remained constant after five days of storage; however, due to the short duration of this study, it was not possible to draw a valid conclusion about the printlets' stability after this period. The zero-order mechanism of a glue jet printing controlled releasing a stimulant such tablet showed unaltered release kinetics following a month of open container contact to room ambient and normal water content. Other prints with intricate delivery profiles have been evaluated. (41) Techniques for 3D printing PMs' on-site quality control have already been put forth, providing a advantage to PM that traditional compounding has not yet addressed. (35)

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