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Review Article

Release kinetics of 3D printed oral solid dosage forms: An overview

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ABSTRACT

Three-dimensional printing (3DP) is one of the most extensively researched methods for producing nano/micro scale biomaterials. This method is typically applied layer by layer. The 3DP method has many advantages over traditional manufacturing methods and ensures that personalized drug design is feasible. Individual dose adjustment provides significant benefits, particularly in some disadvantaged patient groups. Individual release characteristics may be required in these patient groups in addition to dose adjustment. 3DP technology also allows for the adjustment of release kinetics. All of these factors were also increasing interest in 3DP technology in the pharmaceutical industry. The goal of this review is to understand the pharmacological significance of 3DP technology as well as the parameters influencing the release profiles in tablets produced by using technique, and to establish a correlation between them. Within the scope of this review, 79 literature research studies were examined, and it was determined that there is limited data to determine whether there is a correlation between release kinetics and 3DP techniques. When the release profiles obtained by considering the polymer type used in these techniques are evaluated, immediate and rapid release was obtained in studies using PVA + PLA polymers and studies using PVP polymer, immediate release in studies using Kollidon® and Kollicoat® derivatives, and controlled, extended and sustained release was observed in studies using PCL polymer.

Keywords: 3D Printing, Personalized medicine, Release kinetic, Tablet design, Kinetic release model

1. INTRODUCTION

Depending on many factors, the therapeutic efficacy of medications varies. These considerations include drug release profiles, delivery mechanisms, and drug interactions within the body with the external environment. The release profile of drugs can be modified by the use of nano-and micro-size drug carriers in the formulation, such as biodegradable polymers, hydrogels, lipids, and even biological materials (eg, RNA and DNA) [1].

A lot of research has been published in recent years on the controlled release of important therapeutic drugs [2-5]. Researchers have developed many different methods to achieve the desired release of drugs and transport activity inside the body. Some of these methods include modifying the surface properties

of drug particles [6], attaching functional groups to the drug molecule to improve the interactions of drug particles with targeted cells or tissues [7], and extending the half-life of the drug in the body to trick the immune system by coating the drug with special polymers (e.g. polyethylene glycol or PEG). It remains an expensive and difficult method to change these drug molecules (i.e. size, shape, and surface characteristics) [1].

Three-dimensional (3D) printing consists of combining suitable materials to create a 3D object using a series of processes. Generally, this method is done layer by layer [8,9]. In another definition, 3D printing (3DP) refers to any process in which, by fusing layers on top of the material, 3D objects are created in a two-dimensional environment. In this process, a computer is required because 3DP is based on a "Computer-Aided Design" [10-12]. 3DP is also known as 'Additive Manufacturing' (AM). The ISO/ASTM standards describe the process of combining materials produced by layering using 3D model data in contrast to the formative and subtractive production methods [13,14].

The common point of all 3DP techniques called AM is their step-by-step or sequential processing. Compared to previous conventional methods, the manufacturing process based on 3DP techniques has significant advantages and disadvantages. In comparison to traditional methods, **Table 1** discusses some of the advantages and disadvantages of 3DP [8].

The purpose of this review is to understand the pharmacological significance of 3DP technology and one of the most common oral dosage forms obtained using these techniques, the parameters affecting release profiles in tablets.

2. 3D PRINTING TECHNOLOGY

3DP is one of the most studied methods of nano/microscale biomaterial processing. 3DP helps to make a lot of changes to the application scale. Although 3DP technology has shown considerable interest in tissue engineering, implants, and prosthetics, it is also very useful in the micro-manufacturing of drug particles. In addition to minimizing processing time, reducing costs, and being readily available, 3DP often provides high resolution at the stage of drug design [1,15].

New materials are evolving with the use of new applications, and 3DP methods are changing daily. With 3DP, it is possible to significantly minimize or fully eradicate the usage of various machines and facilities. In addition, it only allows custom designs by modifying the 3D model in the program, which during the prototyping process reduces the expense [8].

Table 1. Some advantages and disadvantages of 3DP vs Conventional Manufacturing

Advantages	Disadvantages	Ref.
There is no need for costly machinery for metal smelting plants and for milling pro-cesses	The capacity to generate at low num-bers and speeds	[90]
The ability to create components in a short time with complicated and personalized unconventional structures	Lower surface gloss, accuracy and strength	[91]
The less eco-friendly waste generation and recycling process is	The comparatively few materials that can be processed and reflect the kind of production products	[92]
Cost-effective for low volume and small batch production	The broad restriction on structural di-mensions	[93]

Traditional tablet manufacturing process; current technologies require a variety of unit operations, such as mixing, milling, granulation, drying, compression. In addition, it is necessary to have some costly equipment/tools that require experienced personnel, take a long time and require invest money. All of these make commercially available oral dosage formulations to be costly for the consumer [16]. Apart from these, amid all of these investments, there are so many deficiencies in the production of customized medicines with technologies currently available [17,18].

By allowing individual drugs to be precisely designed, 3DP technology will fill this void. Previous research experiments have shown that to personalize drugs, 3DP can be used [19].

With 3DP technology, which is one of the pharmaceutical technologies through which specific changes can be made, it is unavoidable that doses of the medication's active ingredients should be prepared individually. Dose personalization is not needed for a lot of drugs. But in some other patient groups, in children and particularly in therapies where medications with high toxicity and a limited therapeutic window are used, the individual dose adjustments can offer significant benefits [20]. In addition, the dosage requirements for neonatal, pediatric, and geriatric patients differ considerably from adult dose [21]. In addition, patients with organ dysfunction can need a dosage change to prevent drug toxicity. Although the techniques available in pharmaceutical manufacturing are useful for mass production, 3DP allows for customized, small-scale production. The dosage quantity, geometry, and even the drug release profile can be easily met after customization using 3DP, in line with all these needs. It will also play a vital role in the practice of precision medicine [20,21].

With the approval of Spritam® (levetiracetam), developed using 3DP technology in 2015, by the FDA (U.S. Food and Drug Administration), the use of this technology in the pharmaceutical industry was officially approved for the first time. Spritam®, an anti-epileptic drug developed by Aprecia Pharmaceuticals, is dispersed in the mouth with a very small amount of water in less than 10 seconds, making it very easy to use in the population of disadvantaged patients (eg. pediatric patients, elderly patients) [19-22].

3. 3D PRINTING TECHNIQUES

Inside 3DP technology, there are different approaches. It is possible to group the 3DP methods under five major headings. These include:

- Vat Polymerization,
- Powder Bed Fusion,
- Material Extrusion,
- Material Jetting,
- Direct Energy Deposition.

There are various techniques under each heading. The materials used are different and limited due to the various processes used in 3DP technology used for various purposes. Therefore, only some of them can be utilized in pharmaceutical production [21-23]. In this title, only the techniques that can be used in pharmaceutical applications will be mentioned and detailed.

3.1. Vat Polymerization

The final product of the vat polymerization technique; is obtained by initiating chain reactions in the starting product through various means (UV-light, radiation, electron beam, etc.). Stereolithography (SLA), Digital Light Processing (DLP), 2-Photon Polymerization (2-PP), and Continuous Liquid

Interface Production (CLIP) techniques will be discussed in this section, which comes under the category of vat polymerization and can be used for drug production [21-23].

3.1.1. Stereolithography (SLA)

One of 3DP's key methods, developed in 1986, is SLA [12,24]. In this procedure, by sending UV-light (or electron beams) to a resin layer or a monomer solution, a chain reaction is initiated. By transforming UV-light into a radical form, the monomers used (mainly epoxy-based or acrylic-based) become active. These activated monomers are converted into polymers instantly [8,25]. The resin that is treated with UV light solidifies after polymerization. The remaining component is extracted from the environment using several processes when the printing process is completed [26].

3.1.2. Digital Light Processing (DLP)

This technique is carried out using a photopolymer such as SLA. The difference between these two methods is that the sources of radiation used are distinct. It is a quicker method than the SLA technology [8,27].

3.1.3. 2-Photon Polymerization (2-PP)

2-PP is also referred to as Multiphoton Polymerization. Higher resolution than the SLA system. It is a process that works by polymerizing photo-sensitive material due to the absorption of photons at or above 780-820 nm wavelength and enables micro-and nano-sized printing [8,10,28].

3.1.4. Continuous Liquid Interface Production (CLIP)

It was developed as a new technology for 3DP in 2015. 3D printed models constructed in 2-dimensions are made possible by sending UV-light to liquid resin in the transparent window region. This method based on the photopolymerization process has allowed printing speed and resolution to be improved [29].

3.2. Powder Bed Fusion

The product is obtained after operations on the powder mass, which consists of solid-micro-sized particles on a plane, in the Powder Bed Fusion technique. This section will go over the Selective Laser Sintering (SLS) technique, which is part of the Powder bed fusion technique and can be used for drug production [21,23].

3.2.1. Selective Laser Sintering (SLS)

The most widely used industrial 3DP method is SLS [30,31]. When putting together micro-sized particles in a powder bed to create the finished product, SLS is applied using laser light. In this method [32-35], several different materials, including metals and different thermoplastic materials, are used. In particular, the method enables products with complex geometries to be created [30].

3.3. Material Extrusion

The starting product in the Material Extrusion technique can be semi-solid or solid. This starting product is extruded to produce the final product. This section will go over Fused Deposition Modeling (FDM) and the Pneumatic Extraction / Syringe Extrusion (PE / SE) technique, which can also be used for Material drug production [21,23].

3.3.1. Fused Deposition Modelling (FDM)

The FDM process is based on the thermoplastic polymer's layer-by-layer fusion and solidification by heating to make it semi-solid [12,36,37]. Some

of the advantages are the speed, low cost, and easy processing required by the system [38].

3.3.2. Pneumatic Extrusion / Syringe Extrusion (PE / SE)

For the printing of different semi-solid formulations, such as hydrogels and pastes, the PE / SE method has been developed. A temperature control unit on the syringe system may also control the temperature of the printing material. The temperature regulation of the printing material helps to regulate the material's viscosity and to maintain the material in a semi-solid state that enables the material to be 3D printed [39].

3.4. Material Jetting

In the material jetting technique, it is obtained after the starting product is cured after spraying directly on the surface or after the bonding agent is sprayed on the starting product. Under the main heading of Material Jetting technique, this section will discuss the Material Jetting (MJ) and Binder Jetting (BJ) techniques [21,23].

3.4.1. Material Jetting (MJ)

Among 3DP technologies, MJ allows hard and soft polymer products to be processed in a single process in different colors, with different materials [40]. The material jet allows the modification of the material properties [41]. The photosensitive polymer resin coating is sprayed on the surface by the material jet printer, which releases UV-light into the environment, resulting in the final product [42].

3.4.2. Binder Jetting (BJ)

BJ, one of the 3DP techniques, is based on the concept of spraying a binder solution onto a powder bed [43-45]. The binder solution used in this process must have certain properties. As the average molecular weight and polymer concentration of the solution increase, the viscosity of the binding solution increases, and the substance cannot be printed [46].

4. RELEASE KINETICS AND INFLUENCING PARAMETERS

There are a lot of parameters that affect the kinetics of release. Changing the shape of the particles of the drug first impacts the particles' surface area, causing many changes in their properties [47,48]. If the particle's surface area increases, the particles' size decreases. Reducing the size of the particle increases the particle's surface area and solubility, respectively. It can also be used to improve drug solubility as a safe method [48-51]. Considering the effect on the solubility of the change in particle size, it can be predicted that the change in particle surface area will also have a significant impact on solubility [1].

The drug release profile can also be affected by modifying the 3D shape/structure of the drug particle. A change in the shape of the particle, as mentioned earlier, may cause a change in the surface area that changes the solubility of the drug and as a consequence, changes the kinetics of the release of the drug [52]. As a consequence, a major factor that affects the surface area, drug release kinetics, and therefore its interaction with tissue and cell, is the shift in the particle shape/structure of drugs [1].

Kinetic models used in drug release research have an important role to play in assessing drug release mechanisms. A variety of clinical models have been adopted to specifically define and address the mechanism for the release of drugs for various drugs [53-55]. These clinical models and equations are shown in **Table 2.**

Table 2. Kinetic release model equations.

Model	Equation	Parameters
Zero order	$Q = Q_0 + K_0 t$	K_0 −zero order release constant
First-order	$\frac{dC}{dt} = -K_1 C$	K_1 −first-order release constant C–drug concentration
Higuchi	$Q = K_H t^{0.5}$	K_H–Higuchi constant
Korsmeyer-Peppas	$\frac{Q_t}{Q_\infty} = K_{KP}.t^n$	K_{KP} −constant with structural and geometric information n–indicative release mechanism
Peppas-Sahlin	$Q = K_1.t^m + K_2.t^{2m}$	K_1 −constant indicating Fickian diffusion contribution K_2 −constant indicating case II transport contribution m −purely Fickian diffusion exponent
Weibull	$\log\left[-\ln\left(1-\frac{Q_t}{Q_\infty}\right)\right] = \beta.\log t - \log\alpha$	α −scale parameter β −shape parameter
Hopfenberg	$\frac{Q_t}{Q_\infty} = 1 - \left[1 - \frac{K_{HB}.t}{C_0.a_0}\right]^n$	K_{HB} −erosion rate constant C_0 −initial drug concentration in matrix a_0 −initial radius of the form n −geometry dependent exponent (n=2 for cylindrical forms)
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t$	K_{HC} −constant dependent on the surface-volume relation

Q_0 −initial amount of drug in dosage form, Q_t −amount of drug dissolved in time, Q_∞ −total dissolved drug amount when dosage form exhausted, $^{Q_t}/_{Q_\infty}$ −fraction drug dissolved [54, 55, 72].

5. RELEASE KINETICS ON 3D PRINTED ORAL DOSAGE FORMS

In the studies performed, many different 3DP technologies have been used to produce pharmaceutical dosage forms [56-60]. Using these 3DP methods, parameters such as size, geometry, and surface area of the dosage form may be altered [61-63]. These interventions have made it easy to improve the release properties of the drug. In addition, studies have increased the solubility of active pharmaceutical ingredients with low solubility properties using 3DP technology [64-66]. Interest in the use of 3DP techniques in the pharmaceutical industry is increasing every day due to their unique capabilities [67,68].

Because tablets, which are the most commonly used solid dosage type in the pharmaceutical industry, are easy to use by the consumer, patient compliance is high and their production is cheaper than other dosage forms, it is observed that the studies were mainly based on tablets [19,69,70].

The comparison of oral dosage forms obtained using 3DP technology for various parameters in this compilation analysis is shown in **Table 3**.

Table 3. Comparison in terms of various parameters of oral dosage forms developed using 3DP Technologies

Active Pharmaceutical Ingredient	Dosage Form	Release Profile	Release Kinetic Model	3DP Technique	Polymer	Ref.
4-Aminosalicylic acid	Tablet	Immediate release	N/A	FDM	Kollidon® 12 PF	[80]
Ramipril					Kollidon® VA 64	
4-Aminosalicylic acid	Tablet	Modified release	N/A	FDM	PVA filament	[94]
5-Aminosalicylic acid						
5-Fluorouracil	Patch	Prolonged release	N/A	Syringe extrusion	PLGA	[95]
		Controlled release			PCL	
Amitriptyline HCl	Tablet	Immediate release	N/A	Binder jetting	PVP	[19]
Ascorbic acid	Hydrogel	Controlled Release	N/A	SLA	Poly(ethylene glycol) dimethacrylate	[96]
Aspirin	Tablet	Sustained Release	N/A	SLA	PCL	[97]
Paracetamol					PEGDA	
Aspirin	Tablet	Immediate release	N/A	Syringe extrusion	HPMC	[58]
Atenolol						
Hydrochlorothiazide						
Pravastatin		Sustained release				
Ramipril						
Bicalutamide	Tablet	Combined release (Immediate release and Controlled release)	N/A	FDM	Kollicoat® IR	[81]
					PLA	
					PLA filament	
					PVA filament	
Budesonide	Tablet	Controlled release	N/A	FDM	PVA filament	[98]
		Modified release				
Caffeine	Tablet	N/A	Higuchi	Binder jetting	HPC	[20]
Caffeine	Caplet (DuoCaplet)	Delayed release	N/A	FDM	PVA filament	[15]
Paracetamol		Controlled release				
Calcein	Tablet	Controlled release	N/A	FDM	PVA	[99]
Fluorescein					PLA Filament	
Captopril	Tablet	Rapidly dispersing	N/A	Binder jetting	Mannitol	[87]
Captopril	Tablet	Sustained release	First-order	Syringe extrusion	Cellulose acetate	[71]
Glipizide			Korsmeyer–Pappas		HPMC	
Nifedipin						
Carbamazepine	Scaffold	Sustained release	Zero order	FDM	ABS filament	[100]
Carvedilol	Tablet	Rapid release	N/A	Material jetting	PEGDA	[78]
					PVP	

Table 3. Continued

Active Pharmaceutical Ingredient	Dosage Form	Release Profile	Release Kinetic Model	3DP Technique	Polymer	Ref.
Carvedilol	Tablet	Extended release	Hopfenberg Korsmeyer-Peppas Peppas-Sahlin	FDM	Affinisol™ HPMC HME 15LV Eudragit® E PO HPC HPMC Kollidon® SR	[72]
Catechin	Muco-Adhesive Oral Films	Controlled release	N/A	Syringe extrusion	HPMC	[101]
Cefazolin	Scaffold	Sustained release	N/A	FDM	PCL Gelatin methacrylate	[82]
Cidofovir	Bioadhesive film	Modified release	N/A	Binder jetting	PEG-PCL	[83]
Paclitaxel		Controlled release			PCL	
Ciprofloxacin HCl	Tablet	N/A	Zero order	FDM	PVA	[75]
Copper sulphate (II) pentahydrate Silver nitrate Zinc oxide	Wound dressings (nose and ear)	Controlled release	N/A	FDM	PCL	[84]
Curcumin	Tablet	Controlled release	N/A	FDM	PVA filament	[102]
Deflazacort	Tablet	Prolonged release	N/A	FDM	PCL Eudragit® RL 100 Eudragit® RS 100	[103]
Dexamethasone	Scaffold	Controlled release	N/A	FDM	PCL Poloxamine (Tetronic®)	[104]
Dexamethasone-21-phosphate disodium salt	Scaffold	Prolonged release	N/A	Syringe extrusion	PLGA PVA	[105]
Dipyridamole	Tablet	Sustained release	N/A	Syringe extrusion	HPMC	[106]
Domperidone Ibuprofen	Suppository	N/A	N/A	FDM	PVA filament PEG 400 PEG 6000	[107]
Dronedarone HCl	Tablet	Controlled release	Hixson-Crowell	FDM	PEG PVA filament	[73]
Efavirenz Emtricitabine Tenofovir disoproxil fumarate	Tablet	Controlled release	N/A	Syringe extrusion	Hydroxyethylcellulose ethoxylate	[108]
Fenofibrate	Tablet	Controlled release Tuneable release	N/A	Syringe extrusion	Beeswax	[109]
Fibroblast growth factor-2	Scaffold	Sustained release	N/A	FDM	Calcium Silicate/PCL	[110]
Fluorescein	Tablet	N/A	N/A	FDM	PVA filament	[111]

Table 3. Continued

Active Pharmaceutical Ingredient	Dosage Form	Release Profile	Release Kinetic Model	3DP Technique	Polymer	Ref.
Gentamicin sulfate Methotrexate	Endovascular catheter	Sustained release	N/A	FDM	PLA	[112]
Ginkgolide	Tablet	Controlled release	N/A	Syringe extrusion	HPMC	[113]
Glimepiride Metformin	Tablet	Sustained release	N/A	FDM	PVA Eudragit® RL	[114]
Glipizide	Tablet	Controlled release	Korsmeyer–Peppas	FDM	PVA filament	[76]
Guaifenesin	Tablet	Sustained release	N/A	Syringe extrusion	HPMC Poly(acrylic acid)	[68]
Haloperidol	Tablet	Immediate release	N/A	FDM	Kollidon® VA 64 Kollicoat® IR Affinisol™HPMC HME 15 cP HPMCAS	[61]
Hydrochlorothiazide	Tablet	Immediate release	N/A	FDM	Eudragit® E	[63]
Ibuprofen Riboflavin	Tablet	Delayed release	N/A	SLA	PEGDA PEG 300	[115]
Ibuprofen Paracetamol	Fast-dissolving oral films	Extended release	N/A	FDM	PEO PVA PEG	[116]
Indomethacin	Tablet	N/A	N/A	FDM	PEG HPMCAS	[117]
Indomethacin	Implant	Controlled release	N/A	FDM	PCL	[118]
Indomethacin	Implant	N/A	Higuchi	FDM	Ethylene vinyl acetate	[119]
Insulin	Microneedle	Rapid release	N/A	SLA Binder jetting	Mannitol Xylitol Resin	[88]
Isoniazid Rifampicin B	Implant	Extended release	N/A	FDM	PLA Filament PEO PVA filament	[120]
Lamivudine	Capsule	Delayed release	N/A	FDM	PVA	[121]
Levofloxacin	Implant	Burst release Pulsed release	N/A	Binder jetting	PLA	[122]
Levofloxacin Rifampin Vancomycin	Scaffold	Prolonged release Sustained release	N/A	Syringe extrusion	Gelatin-Glutaraldehyde PVA	[123]
Metformin HCl	Tablet	N/A	N/A	FDM	PVA filament	[124]
Metformin HCl	Capsule	Tunable release	N/A	FDM	PLA Filament PVA filament	[125]
Metronidazole	Tablet	N/A	Zero order	FDM	PVA	[126]
Nitrofurantoin	Implant	Controlled release	N/A	FDM	PLA	[127]

Table 3. Continued

Active Pharmaceutical Ingredient	Dosage Form	Release Profile	Release Kinetic Model	3DP Technique	Polymer	Ref.
Ofloxacin Tetracycline Vancomycin	Implant	Sustained release	N/A	Binder jetting	Dicalcium phosphate anhydrous (monetite, CaHPO4) Hydroxyapatite Dicalcium phosphate dihydrate (brushite, CaHPO4·2H2O)),	[128]
Pantoprazole sodium	Tablet	Immediate release	N/A	FDM	PEG 6000 Kollidon® VA 64 Kollicoat® IR PEO 100,000 PVP Poloxamer 407 PEG 20000	[79]
Paracetamol	Tablet	Controlled release	Zero order First-order	FDM	HPC	[74]
Paracetamol	Tablet	Controlled release	N/A	FDM	PVA filament	[62]
Paracetamol	Tablet	Controlled release	N/A	FDM	HPMC	[129]
Paracetamol	Tablet	Controlled release	N/A	FDM	EC Eudragit® L 100 HPC HPMC Soluplus®	[130]
Paracetamol	Tablet	Controlled release	N/A	FDM	HPMCAS	[131]
Paracetamol	Tablet	Immediate release Modified release	N/A	SLS	Kollicoat® IR Eudragit® L 100 EC	[132]
Prednisolone	Tablet	Extended release	N/A	FDM	PVA filament	[17]
Prednisolone	Implant	Controlled release	N/A	Syringe extrusion	Polydimethylsiloxane	[133]
Progesterone	Biodegradable projectile	Extended release	N/A	FDM	PLA	[134]
Progesterone	Implant	Controlled release	N/A	FDM	PCL PLA	[85]
Propranolol HCl	Orodispersible drug delivery systems	Immediate release	N/A	Binder jetting	HPC	[135]
Propranolol HCl (Indicardin®, 40 mg)	Tablet	Controlled release	N/A	FDM	Cellulose acetate D-Mannitol PEG 6000	[89]

Table 3. Continued

Active Pharmaceutical Ingredient	Dosage Form	Release Profile	Release Kinetic Model	3DP Technique	Polymer	Ref.
Rasagiline mesylate	Orodispersible films / Transparency films	Prolonged release	N/A	Binder jetting	HPMC / Crospovidone	[136]
rhBMP2 (recombined human bone morphogenetic protein-2)	Scaffold	Controlled release / Non-controlled release	N/A	Syringe extrusion	Chitosan	[137]
Riboflavin	Tablet	Controlled release	N/A	FDM	PLA Filament / PVA / PCL	[138]
Rodhamine B	Hydrogel Patches	Controlled release	N/A	Syringe extrusion	Alginic acid sodium salt / Starch	[139]
Ropinirole HCl	Tablet	N/A	Korsmeyer-Peppas	Material jetting	PEGDA	[59]
Salicylic acid	Patches (nose-shape)	N/A	N/A	FDM / SLA	PLA filament / PCL Filament / PEGDA / PEG	[86]
Theophylline	Tablet	Sustained release	Korsmeyer-Peppas	FDM	Eudragit® FS 30 D / HPMC / PLA filament	[77]
Theophylline	Tablet	Extended release	N/A	Syringe extrusion	HPMC	[140]
Thiamine HCl	Tablet	Rapid release	N/A	Binder jetting	PVP	[56]
Vancomycin	Bone graft	N/A	N/A	Syringe extrusion	Sodium alginate	[141]
Warfarin	Tablet	Immediate release	N/A	FDM	Eudragit® E PO	[142]

*N/A: Not Available
**ABS: Acrylonitrile butadiene styrene, EC: Ethylcellulose, HPC: Hydroxypropyl cellulose, HPMC: Hydroxypropyl methylcellulose, HPMCAS: Hydroxypropyl methylcellulose acetate succinate, PCL: Poly-ε-caprolactone, PEG: Polyethylene glycol, PEGDA: Poly(ethylene glycol) diacrylate, PEO: Poly(ethylene oxide), PLA: Polylactic acid, PVA: Polyvinyl alcohol, PVP: Polyvinyl pyrrolidone

6. RESULTS

This review research examined 79 publications in total. When the studies using the release kinetic models in **Table 4** were examined, there was no correlation between the polymer type or print technique and the release kinetic model. Only 15.19% of the 79 studies included release kinetics studies. The kinetics of the active substance's release from the dosage form was not determined in the studies under review, which is believed to be one of the reasons why no correlation could be found.

When the results of the investigations are considered together, no conclusion can be drawn that single release kinetics was obtained in studies using Eudragit® derivatives, PEG, PEGDA, or Cellulose-derived polymers [20,71-74]. However, in research studies PVA and PLA polymers, immediate or rapid release was obtained [73,75-77]. In studies involving PVP polymer, it was found that immediate and rapid release was obtained [19,56,78,79]. Other than Kollidon® SR, the immediate release was observed in studies using Kollidon® and Kollicoat® derivatives [61,72,79-81]. PCL polymer, which provides longer

Table 4. Release kinetic models calculated in studies

3DP Technique	Release Kinetic Model	Polymer	Ref.
Binder jetting	Higuchi	HPC	[20]
FDM	Zero order	ABS filament	[100]
	Hopfenberg	Affinisol™ HPMC HME 15LV	[72]
		Eudragit® E PO	
	Korsmeyer-Peppas	HPC	
		HPMC	
	Peppas-Sahlin	Kollidon® SR	
	Zero order	PVA	[75]
	Hixson-Crowell	PEG	[73]
		PVA filament	
	Korsmeyer-Peppas	PVA filament	[76]
	Higuchi	Ethylene vinyl acetate	[119]
	Zero order	PVA	[126]
	Zero order	HPC	[74]
	First-order		
	Korsmeyer-Peppas	Eudragit® FS 30 D	[77]
		HPMC	
		PLA filament	
Material jetting	Korsmeyer-Peppas	PEGDA	[59]
Syringe extrusion	First-order	Cellulose acetate	[71]
	Korsmeyer-Pappas	HPMC	

*ABS: Acrylonitrile butadiene styrene, HPC: Hydroxypropyl cellulose, HPMC: Hydroxypropyl methylcellulose, PEG: Polyethylene glycol, PEGDA: Poly(ethylene glycol) diacrylate, PVA: Polyvinyl alcohol.

drug release, has been used to achieve prolonged release, controlled release, and sustained release [82-86]. Except for one study, the rapid release was obtained in mannitol studies [87,88]. Mannitol was used in combination with cellulose acetate and PEG in the study, which resulted in controlled release rather than a rapid release [89].

7. CONCLUSION

This study demonstrates the methods, active pharmaceutical agents, polymers, pharmaceutical dosage formulations, and release kinetics used in 79 studies and trials. This research, which we have done, illustrates clearly the benefits of using 3DP techniques in the pharmaceutical industry. It would be very convenient to use it in the development of personalized drugs in the future, considering the advantages of 3DP technologies, such as the ability to modify the dose, to alter the geometry of the dosage shape, to adjust the surface area, to be cheaper and simpler than traditional methods. This is a very convenient technology, especially for vulnerable patients, such as the elderly and children, for the production of drugs at sensitive doses. The parameters needed for production will be better understood and more controllable as the research performed with 3DP technologies increases. Future studies should also establish and define GMP (Good Manufacturing Practice) and QbD (Quality by Design) procedures. The predicted outcome in the future would be that 3DP technology will be used by the pharmaceutical industry and that more approved products will be developed on the market using 3DP technology.

Author contribution

Concept: MSK, EK; Design: MSK, EK; Supervision: MSK; Materials: BK; Data Collection and/or Processing: BK; Analysis and/or Interpretation: BK, MSK, EK; Literature Search: BK; Writing: BK; Critical Reviews: MSK, EK.

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Conflict of interest

The authors declared that there is no conflict of interest.

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