

Integrated Additive Manufacturing Apparatus and Method

Field of the invention

5 The present disclosure relates to an apparatus for dispensing a composition, and in particular, but not exclusively, to an apparatus for dispensing a pharmaceutical composition to prepare solid pharmaceutical dose forms, for example by additive manufacturing.

Background

10 Additive Manufacturing (AM) is a name used to describe technologies that build 3D objects by printing material layer-upon-layer (i.e. additive) using various materials. AM and 3D printing are commonly used interchangeably, although the former is a broader and all-inclusive term, while the latter specifically involves the creation of objects by building layers of material. Additive manufacturing involves the creation of
15 objects by adding material, which may or may not come in layers.

3D printers are generally operated using a computer-based system which controls the three-dimensional movement of individual parts and also the flow of material creating the desired form. A Fused Filament Fabrication (FFF) printer utilizes this methodology with an incorporated heated printer head, through which the material
20 flows. The material is fed through as a solid filament (having specific dimensional and mechanical properties) and is mobilised as it is heated and melted thus enabling the material to flow through a nozzle. The material exiting the nozzle is deposited in sequential layers onto a surface where it solidifies to create the 3D object.

Recent developments have used FFF printers to create pharmaceutical
25 products such as oral dosage form drugs. However, this technique necessitates pre-preparation of a drug-loaded filament, which requires creating the filament first and then feeding it into the 3D printer, to allow a tablet (or another dose form) to be printed. Early work utilised pre-made filaments being immersed in a drug-solvent solution and deposition of the drug into the filament by infusion. More recent efforts have used Hot
30 Melt Extrusion (HME). Typically, a mixture of polymer and Active Pharmaceutical Ingredient (API) is fed to an extruder, which is then heated, kneaded, conveyed and extruded through a die as a fluid and then cooled to form a solid filament. The filament is fed into a 3D printer, at which point it is re-heated and deposited as a 3D object e.g. into the form of a tablet form. See Zhang et al., Coupling 3D Printing with Hot-Melt

Extrusion to Produce Controlled-Release Tablets, International Journal of Pharmaceutics, vol. 519, pp. 186-197 (2017).

One of the main limitations of such techniques is that the immersion technologies only allow a very small loading of drug into the filament. The HME-based approach (whereby a filament intermediate is created) requires the filament to have very specific properties – and particular dimensional properties (especially diameter) to enable the mechanics of the FFF 3D printer to operate and control deposition rate. Additionally, the filament has to have very specific mechanical properties, for example so that it can be fed through the FFF printer without breaking due to brittle fracture or deforming as a result of being too soft. These disadvantages represent significant limitations in the use of these technologies. The formed filament also needs to have suitable stability properties to enable its use over time.

As a result of these limitations, choice of drug loadings and formulation ingredients (especially polymer) is limited because the final formulation is driven by the constraints encountered during the processing across the basic unit operations. It is a object of the present invention to address or mitigate at least one of the problems associated with the prior art.

Summary

According to a first aspect there is provided a dispensing apparatus configured for dispensing a composition, the dispensing apparatus comprising:

- at least one inlet configured for receiving a composition;
- at least one outlet configured for dispensing the composition;
- at least one directional flow valve located between the at least one inlet and the at least one outlet; and

- at least one regulating module in fluid communication with a respective directional flow valve, wherein the at least one regulating module is configured to control and/or regulate flow of the composition to at least one outlet.

Advantageously, the regulating module may be a volumetric regulating module. By such provision, the regulating module may be capable of controlling and/or regulating flow of the composition to the at least one outlet in a volumetric manner.

According to a second aspect there is provided a dispensing apparatus configured for dispensing a composition, the apparatus comprising:

- at least one inlet configured for receiving a composition;

at least one outlet configured for dispensing the composition;

at least one volumetric regulating module configured to control and/or regulate flow of the composition to at least one outlet in a volumetric manner.

5 The apparatus may further comprise at least one directional flow valve located between the at least one inlet and the at least one outlet. The at least one regulating module may be in fluid communication with a respective directional flow valve.

10 One skilled in the art will understand that the following features are equally applicable to any of the first aspect or second aspect of the present disclosure and are not repeated in each aspect merely for reasons of brevity.

Typically, the at least one inlet may be configured to receive the composition in a fluid state, typically in a liquid and/or molten state.

15 The at least one inlet may be arranged to be in fluid communication with a delivery apparatus configured to deliver the composition. Typically, the delivery apparatus may be configured to deliver the composition in liquid form, e.g. in a molten state or in a solubilised state.

20 The delivery apparatus may comprise or may be a fabrication apparatus, e.g. an apparatus configured to prepare and/or deliver the composition in molten form. The delivery apparatus may comprise or may be an extrusion apparatus, e.g. an extruder. This may be particularly advantageous when the composition is a pharmaceutical composition. For example, this may avoid the need for the pre-preparation of filaments of pharmaceutical composition, which are associated with the limitations discussed above relating to mechanical properties of the filament, filament dimensions, and amounts/concentrations of API in the filament. For example, the present arrangement may allow the printing of various dose forms of pharmaceutical compositions having higher ratios of API to polymer/excipient than previously possible, and/or the use of a wider range of formulation ingredients.

25 Typically, the apparatus may comprise one inlet.

30 The at least one outlet may be configured to dispense the composition in a fluid state, typically in a liquid and/or molten state.

The at least one outlet may be arranged to be in fluid communication with a printing apparatus or part thereof, e.g. a 3D printer or a platform of a 3D printer.

35 Thus, the apparatus may be arranged to be provided between an/the extrusion apparatus and a/the printing apparatus or part thereof.

It will be appreciated that the printing apparatus may be provided in separate parts, such as a printing head or nozzle and a printing platform. In such instance, it will be appreciated that part of the printing apparatus, e.g. printing head and/or nozzle, may be provided within or may be incorporated within the dispensing apparatus.

5 The dispensing apparatus may form part of a system, e.g. an integrated system, comprising:

 at least one delivery apparatus;

 at least one printing apparatus or part thereof; and

 at least one dispensing apparatus provided between the at least one delivery
10 apparatus and the at least one printing apparatus or part thereof.

The system may typically comprise one delivery apparatus, e.g. extrusion apparatus. In such instance, the dispensing apparatus may comprise one inlet.

15 The system may comprise a plurality of delivery apparatuses, e.g. extrusion apparatuses. In such instance, the dispensing apparatus may comprise a plurality of inlets, e.g. each inlet being associated with a respective delivery apparatus, e.g. extrusion apparatus.

20 The system may comprise one printing apparatus or part thereof. In such instance, the dispensing apparatus may comprise one outlet.

 The system may comprise a plurality of printing apparatuses or part thereof. In such instance, there may be provided one or more dispensing apparatuses. The/each dispensing apparatus may comprise one or more outlets. In an embodiment, the/a dispensing apparatus may comprise one outlet associated with and/or in fluid
25 communication with a respective printing apparatus. In another embodiment, the/a dispensing apparatus may comprise a plurality of outlets, each outlet being associated with and/or in fluid communication with a respective printing apparatus.

 The dispensing apparatus may comprise one or more directional flow valves.

30 When the dispensing apparatus comprises one directional flow valve, the dispensing apparatus may typically comprise one inlet in fluid communication with the directional flow valve, and one regulating module in fluid communication with the directional flow valve.

 In such instance, the dispensing apparatus may typically comprise one outlet in
35 fluid communication with the directional flow valve. However, the dispensing apparatus

may alternatively comprise a plurality of outlets in fluid communication with the directional flow valve. Each outlet may be configured to be associated with a respective printing apparatus. In such instance, the dispensing apparatus may be configured to feed several 3D printers simultaneously from a single regulating module, which may be adequate to print pharmaceutical dose forms of low volumes.

When the dispensing apparatus comprises a plurality of directional flow valves, the dispensing apparatus may typically comprise one inlet in fluid communication with the directional flow valve, or may comprise a plurality of inlets, each inlet being in fluid communication with a respective directional flow valve.

When the dispensing apparatus comprises a plurality of directional flow valves, the dispensing apparatus may typically comprise a plurality of outlets, each outlet being in fluid communication with a respective directional flow valve. Each outlet may typically be configured to be associated with a respective printing apparatus. In such instance, the dispensing apparatus may be configured to feed several 3D printers which can be fed independently or in combination with each other, thus allowing the preparation, e.g. 3D printing, of objects, e.g. pharmaceutical dose forms, in a continuous, semi-continuous or batch manner.

For example, in an embodiment, a regulating module may be associated with a respective directional flow valve and a respect inlet configured to be connected to a respective printing apparatus or part thereof. In such instance, each regulating module may be configured to dispense a composition to the respective outlet and its respective printing apparatus, thus allowing a dose form to be printed by printing multiple layers from the printing apparatus.

For example, in another embodiment, a regulating module may be associated with a respective directional flow valve and a respect inlet configured to be connected to a respective printing apparatus or part thereof, but a conveyor system may permit a dose form to be moved from one printing apparatus to another printing apparatus between each layer. Thus, each layer of the dose form may be printed by a particular printing apparatus.

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The dispensing apparatus may comprise one or more regulating modules.

When the dispensing apparatus comprises one regulating module, the dispensing apparatus may typically comprise one directional flow valve in fluid communication with the regulating module.

When the dispensing apparatus comprises a plurality of regulating modules, the dispensing apparatus may typically comprise a plurality of directional flow valves, each regulating module being in fluid communication with a respective directional flow valve.

5 Depending on the number and the configuration of inlet(s), outlet(s), directional flow valve(s), and/or regulating module(s), the composition may be dispensed by the dispensing apparatus in a continuous, semi-continuous or batch manner. Thus, when the dispensing apparatus is associated with one or more printing apparatus, the apparatus and/or system may allow printing, e.g. 3D printing of a composition, e.g.
10 pharmaceutical composition in dosage form, in a continuous, semi-continuous or batch manner.

 The directional flow valve may be provided between an inlet and an outlet. The regulating module, e.g. volumetric regulating module, may be in fluid communication
15 with the/a respective directional flow valve.

 Advantageously, the directional flow valve may be configured to control a flow path of the composition between the/an inlet and the/an outlet.

 The/each directional flow valve may have a plurality of configurations.

 The/each directional flow valve may have at least a first or "feed" configuration
20 and a second or "dispense" configuration.

 The/each directional flow valve may have a first or "feed" configuration configured to allow flow of the composition from the inlet or from a respective inlet to the regulating module or to a respective regulating module. In the first or "feed" configuration, the directional flow valve may allow filling the regulating module or the
25 respective regulating module.

 The/each directional flow valve may have a second or "dispense" configuration configured to allow flow of the composition from the regulating module or from a respective regulating module to the outlet or to a respective outlet. In the second or "dispense" configuration, the directional flow valve may allow the regulating module or
30 from a respective regulating module to dispense the composition to the outlet or to the respective outlet.

 Typically, the first or "feed" configuration and the second or "dispense" configuration may be mutually exclusive. That is, the composition may either flow from the inlet or from a respective inlet to the regulating module or to a respective regulating

module, or flow from the regulating module or from a respective regulating module to the outlet or to a respective outlet.

Alternatively, the first or “feed” configuration and the second or “dispense” configuration may be combinable, e.g. may not be mutually exclusive. That is, the composition may flow from the inlet or from a respective inlet to the regulating module or to a respective regulating module, and may also flow from the regulating module or from a respective regulating module to the outlet or to a respective outlet. In such instance, the dispensing module may be configured to allow flow of the composition from an/the inlet to the regulating module via the directional flow valve, and also flow of the composition from the regulating module to a/the outlet via the directional flow valve.

The/each directional flow valve may optionally have a third or “recirculation” configuration configured to allow flow of the composition from the/an inlet to a recirculation outlet. The recirculation outlet may be configured to be in fluid communication with or be associated with a feeding inlet of the/an extrusion apparatus. By such provision, the composition may be recirculated into the extrusion apparatus, for example when one or more properties of the composition (e.g. pressure, temperature, homogeneity and/or viscosity) are not optimum and/or when filling of the regulation module is not required or desired.

The/each directional flow valve may optionally have a fourth or “discharge” configuration configured to allow flow of the composition from the inlet to a discharge port. The discharge port(s) may be in fluid communication with the inlet conduit and/or with the directional flow valve. By such provision, the composition may be discharged from the dispensing apparatus, for example when one or more properties of the composition (e.g. pressure, temperature, homogeneity and/or viscosity) are not optimum and/or when filling of the regulation module is not required or desired.

The/each directional flow valve may optionally have a fifth or “closed” configuration configured to prevent flow of the composition within the dispensing apparatus. In other words, in the fifth or “closed” configuration, the composition may not flow from the inlet(s) or to the outlet(s).

It will be appreciated that the directional flow valve may have one, two, all, or none of the third configuration, fourth configuration, and fifth configuration, depending on the configuration and requirements of the system.

There may be provided an inlet conduit between the inlet and the/each directional flow valve.

When the dispensing apparatus comprises one inlet and one directional flow valve, there may be provided one inlet conduit between the inlet and the directional flow valve.

5 When the dispensing apparatus comprises one inlet and a plurality of directional flow valves, there may be provided a plurality of inlet conduits, an inlet conduit being between provided between the inlet and a respective directional flow valve.

10 When the dispensing apparatus comprises a plurality of inlets and a plurality of directional flow valves, there may be provided a plurality of inlet conduits, each inlet conduit being between provided between an inlet and a respective directional flow valve.

There may be provided an outlet conduit between the/a directional flow valve and an outlet.

15 When the dispensing apparatus comprises one outlet and one directional flow valve, there may be provided an outlet conduit between the directional flow valve and the outlet.

20 When the dispensing apparatus comprises one directional flow valve and a plurality of outlets, there may be provided a plurality of outlet conduits, an outlet conduit being between provided between the directional flow valve and a respective outlet.

When the dispensing apparatus comprises a plurality of outlets and a plurality of directional flow valves, there may be provided a plurality of outlet conduits, an outlet conduit being between provided between each directional flow valve and a respective outlet.

25 There may be provided a regulation conduit between the/a directional flow valve and the/a regulation module.

30 When the dispensing apparatus comprises one directional flow valve and one regulation module, there may be provided a regulation conduit between the directional flow valve and the regulation module.

When the dispensing apparatus comprises a plurality of directional flow valves and regulation modules, there may be provided a plurality of regulation conduits, a regulation conduit being between provided between each directional flow valve and a respective regulation module.

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Optionally, there may be provided a recirculation conduit between the/an inlet and a/the recirculation outlet or between the/a directional flow valve and a/the recirculation outlet.

5 Optionally, there may be provided a discharge conduit between the/an inlet and a/the discharge port or between the/a directional flow valve and a/the discharge port.

10 The/each directional flow valve may comprise or may be associated with an actuator. The actuator may comprise a powering means, e.g. a motor, and an actuator, e.g. a shaft, allowing the motor to actuate a respective flow valve. The/each directional flow valve may comprise or may be associated with a respective valve control means configured to control actuation of the valve. For example, the valve control means may be configured to actuate a respective motor so as to move a respective flow valve to a desired configuration.

15 The valve control means may be manually controlled, e.g. by a user. Alternatively, or additionally, the valve control means may be automatically controlled, e.g. by a computer, for example based on one or more parameters measured in the dispensing apparatus, such as pressure, temperature, viscosity, piston position, or the like.

20 The/each regulating module may comprise a chamber configured to receive the composition.

The chamber may have a chamber inlet in fluid communication with a respective directional flow valve and/or regulation module conduit.

25 The regulating module may comprise a regulation actuator configured to actuate filling of the chamber with the composition and/or dispensing of the composition from the chamber.

The regulation actuator may comprise or may be a piston or a screw. The regulation actuator may be operated by a motor, e.g. a piston drive motor.

30 The regulation actuator may comprise or may be associated with a respective regulation control means configured to control actuation of the regulating module. For example, the regulation control means may be configured to actuate a motor, e.g. piston drive motor, so as to move a respective actuator, e.g. piston.

35 The regulation control means may be manually controlled, e.g. by a user. Alternatively, or additionally, the regulation control means may be automatically controlled, e.g. by a computer, for example based on one or more parameters

measured in the dispensing apparatus and/or regulation module, such as pressure, temperature, composition homogeneity and/or viscosity, piston position, or the like.

A volume of the chamber may be partially defined by an end of the piston at an end of the chamber opposite the chamber inlet.

5 The dispensing apparatus may comprise one or more sensors.

The dispensing apparatus may comprise one or more pressure sensors. The dispensing apparatus may comprise at least one pressure sensor provided at or near an inlet, e.g. along the/an inlet conduit.

10 The dispensing apparatus may comprise one or more temperature sensors. The dispensing apparatus may comprise at least one temperature sensor provided at or near an inlet, e.g. along the/an inlet conduit.

The dispensing apparatus may comprise at least one temperature sensor provided at or near the regulation module, e.g. along the/a regulation module conduit and/or at or near the/a regulation chamber.

15 The dispensing apparatus may comprise at least one temperature sensor provided at or near an outlet, e.g. along the/an outlet conduit.

The dispensing apparatus may comprise at least one positioning sensor configured to detect the configuration of the regulation module and/or the position of the regulation actuator, for example of a piston within its respective chamber.

20 The dispensing apparatus may comprise and/or may be associated with analytical means, e.g. analytical devices such as Process Analytical Tools (PAT) or spectroscopy devices, to monitor and/or analyse one or more parameters of the composition, such as viscosity, homogeneity, chemical composition, or the like.

25 The valve control means, regulation control means, and/or computer, may be in communication with one or more of the pressure sensors, temperature sensors, positioning sensor and/or analytical means.

The dispensing apparatus may comprise one or more heating elements to control and/or regulate the temperature of the composition within the dispensing apparatus.

30 The regulation module may comprise one or more heating elements to control and/or regulate the temperature of the composition within the regulation module. There may be provided at least one heating element near a respective regulation chamber. In an embodiment, each regulation chamber may be associated with a respective heating element. By such provision, temperature of the composition may be controlled
35 shortly before the composition is dispensed to the outlet.

The regulation module may comprise one or more heat sinks to control and/or regulate the temperature of one or more elements of the regulation module, e.g. of the regulation actuator, e.g. piston and/or motor.

5 The composition may comprise a pharmaceutical composition. The pharmaceutical composition may comprise at least one active pharmaceutical ingredient ("API") and at least one excipient.

The at least one excipient may comprise a binder or any other conventional excipient.

10 The at least one excipient may comprise at least one polymeric component, e.g. a thermoplastic polymer. The at least one excipient may comprise one or more addition polymers.

The at least one excipient may comprise one or more polymers selected from the list consisting of:

- 15 - a random copolymer of N-vinyl-2-pyrrolidone and vinyl acetate (e.g. Plasdone (S630) TM from ASHLAND;
- a methylcellulose type polymer such as hydroxyl-propyl-methyl-cellulose (HPMC), e.g. Affinisol TM from DuPont;
- polyvinyl acetate;
- polyvinyl alcohol;
- 20 - Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer such as Soluplus TM from BASF.

According to a third aspect there is provided a system for manufacturing a solid pharmaceutical dose form, the system comprising:

25 at least one delivery apparatus configured to deliver a pharmaceutical composition;

at least one printing apparatus and/or part thereof; and

at least one dispensing apparatus provided between the at least one delivery apparatus and the at least one printing apparatus or part thereof.

30 Typically, the delivery apparatus may be configured to deliver the composition in liquid form, e.g. in a molten state or in a solubilised state.

The delivery apparatus may comprise or may be a fabrication apparatus, e.g. an apparatus configured to prepare and/or deliver the composition in molten form. The delivery apparatus may comprise or may be an extrusion apparatus, e.g. an extruder.

The least one dispensing apparatus may be an apparatus according to the first aspect or the second aspect. Accordingly, the features described in relation to the dispensing apparatus according to the first aspect or second aspect may apply in relation to the system according to the third aspect, and are not repeated here merely
5 for reasons of brevity.

The at least one extrusion apparatus may comprise at least one hopper configured to receive a material or a mixture of materials. Typically, the composition may be fed to the hopper in solid form, e.g. as a powder, granules, paste or the like.

There may be provided a plurality of hopper, each hopper configured to receive
10 a particular material, e.g. one of the components of the composition. Alternatively, the various components of the composition may be premixed and may be fed into a single hopper.

One or more hoppers may comprise agitation means or mixing means, for example to avoid blockage. One or more hoppers may comprise a control device
15 measuring and/or monitoring an amount, e.g. weight and/or volume of material being fed to the extrusion apparatus, e.g. extruder.

The at least one extrusion apparatus may comprise an extruder, e.g. a melt extruder.

The extruder may comprise at least one funnel configured to receive a/the
20 composition from one or more hoppers.

The at least one funnel may be configured to feed the composition to the extruder.

The extruder may comprise moving means configured to convey the composition within an internal chamber thereof. The moving means may typically
25 comprise one or more screws, e.g. a single screw or twin screws. The moving means may comprise any other suitable arrangement such as a belt or vibration means.

The at least one extrusion apparatus may comprise one or more temperature sensors to measure temperature at one or more locations along the extruder. The at least one extrusion apparatus may comprise one or more heating and/or cooling
30 elements to regulate and/or adjust temperature or the composition within the extruder.

The system may comprise control means, e.g. a control unit, configured to control actuation and/or operation of one or more elements of the system, e.g. at least one delivery apparatus, at least one printing apparatus, and/or at least one dispensing apparatus. The control means may be manually operated. The control means may be
35 manually operated. The control means may comprise a computer.

According to a fourth aspect of the present disclosure there is provided a method of dispensing a composition, the method comprising:

5 receiving a composition from at least one inlet to at least one regulating module via at least one directional flow valve; and

dispensing the composition from the at least one regulating module to at least one outlet via the at least one directional flow valve.

The at least one directional flow valve may be located between the at least one inlet and the at least one outlet.

10 The at least one regulating module may be in fluid communication with a respective directional flow valve.

The method may comprise controlling and/or regulating a flow of the composition to at least one outlet via the regulating module.

15 Advantageously, the regulating module may be a volumetric regulating module. By such provision, the method may comprise controlling and/or regulating flow of the composition to the at least one outlet in a volumetric manner.

The method may comprise using a dispensing apparatus according to a first aspect.

20 According to a fifth aspect of the present disclosure there is provided a method of dispensing a composition, the method comprising:

receiving a composition from at least one inlet to at least one volumetric regulating module; and

25 dispensing the composition from the at least one volumetric regulating module to at least one outlet in a volumetric manner.

The method may comprise receiving the composition from the at least one inlet to the at least one volumetric regulating module via at least one directional flow valve.

30 The method may comprise dispensing the composition from the at least one volumetric regulating module to the at least one outlet via the at least one directional flow valve.

The at least one directional flow valve may be located between the at least one inlet and the at least one outlet.

The method may comprise controlling and/or regulating a flow of the composition to at least one outlet via the volumetric regulating module. By such

provision, the method may comprise controlling and/or regulating flow of the composition to the at least one outlet in a volumetric manner.

The method may comprise using a dispensing apparatus according to a second aspect.

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According to a sixth aspect there is provided a method of manufacturing an object, the method comprising dispensing a composition to a printing apparatus and/or onto a printing platform using a dispensing apparatus according to the first aspect or the second aspect, or a method according to the fourth aspect or the fifth aspect.

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The method may comprise using a system according to the third aspect.

The printing apparatus may comprise or may be a 3D printer or part thereof.

The printing platform may be the printing platform of a 3D printer.

The method may comprise 3D printing the object.

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The composition may comprise a pharmaceutical composition. The pharmaceutical composition may comprise at least one active pharmaceutical ingredient ("API") and at least one excipient.

The at least one excipient may comprise a binder or any other conventional excipient.

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The at least one excipient may comprise at least one polymeric component, e.g. a thermoplastic polymer. The at least one excipient may comprise one or more addition polymers.

The at least one excipient may comprise one or more polymers selected from the list consisting of:

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- a random copolymer of N-vinyl-2-pyrrolidone and vinyl acetate (e.g. Plasdone (S630) TM from ASHLAND;
- a methylcellulose type polymer such as hydroxyl-propyl-methyl-cellulose (HPMC), e.g. Affinisol TM from DuPont;
- polyvinyl acetate;
- polyvinyl alcohol;
- 30 - Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer such as Soluplus TM from BASF.

The method may comprise printing a pharmaceutical composition. Advantageously, the method may comprise printing a pharmaceutical composition in dosage form, e.g. a tablet, pill, or the like.

The method may comprise printing the pharmaceutical composition into/onto an item of packaging such as, but not limited to, blister pack(s), capsule(s), digestible container(s) or the like.

5 The method may comprise feeding the composition to the dispensing apparatus from the/an extrusion apparatus.

According to a seventh aspect of the present disclosure, there is provided an object, the object manufactured using a method according to the sixth aspect.

10 Advantageously, the object may be a pharmaceutical composition in dosage form.

The object, e.g. pharmaceutical dose form, may be provided in an item of packaging, e.g. blister pack(s), capsule(s), digestible container(s) or the like.

15 It will be appreciated that the features described in relation to any aspect may also apply to any other aspect, and are not repeated merely for brevity.

Brief Description of Drawings

Embodiments of the present disclosure will now be given by way of example only, and with reference to the accompanying drawings, which are:

- 20 **Figure 1** a schematic view of a system according to an embodiment;
Figure 2 a cross-sectional view of the dispensing apparatus of the system of Figure 1;
Figure 3 a cross-sectional view of the dispensing apparatus of Figure 2 along line (A-A);
25 **Figure 4** a cross-sectional view of a regulating module of the dispensing apparatus of Figure 2, in a first configuration;
Figure 5 a cross-sectional view of a regulating module of the dispensing apparatus of Figure 2, in a second configuration;
Figure 6 a cross-sectional view of a regulating module of the dispensing
30 apparatus of Figure 2, in a third configuration;
Figure 7 a dispensing apparatus according to another embodiment;
Figure 8 a cross-sectional view of the dispensing apparatus of Figure 7 along line (B-B);
Figure 9 a cross-sectional view of the dispensing apparatus of Figure 7
35 along line (C-C);

- Figure 10** a front view of the printing apparatus of the system of Figure 1;
Figure 11 an elevated side view of the printing apparatus of Figure 10;
Figure 12 a system according to another embodiment including a recirculation unit;
5 **Figure 13** an enlarged view of the recirculation unit of the extruding apparatus of Figure 12.

Detailed Description

10 Referring to **Figure 1** there is shown a system 5 according to a first embodiment. The system 5 includes an extrusion apparatus 100, a 3D printing apparatus 300, and a dispensing apparatus 200 provided between the extrusion apparatus 100 and a printing platform 310 of the printing apparatus 300.

15 The system 5 also includes a control unit 400, e.g. a computer, to receive information from one of more sensors of the system 5, and/or control and/or adjust one or more parameters of the system 5, including temperature, feed rate, pressure, flow valve, regulating module, etc, as will be discussed below in more detail.

20 The extrusion apparatus 100 includes a hopper 112 configured to receive a material or a mixture of materials 110, which in this embodiment is provided in solid form such as powder or granules. The hopper 112 has agitation means (not shown) such as an impeller or vibrating elements so as to improve mixing and also avoid agglomeration and/or blockages.

The hopper 112 is equipped with a measuring device (not shown) which allows measuring and/or monitoring an amount, typically weight, of the material 110 being fed to the extruder 101.

25 The extruder 101 has a funnel 114 configured to receive the material 110 from the hopper 112. The funnel 114 is configured to feed the composition 111 to the extruder 101.

30 The extruder 101 is a melt extruder 101 having moving means 118 configured to convey the composition 111 within an internal chamber thereof. In this embodiment, the moving are in the form of twin screws 118 which are powered by a motor and transmission 116.

The extrusion apparatus 100 has a number of temperature sensors 124 to measure temperature along its length. Temperature sensors 124 may communicate with control unit 400.

The extrusion apparatus 100 also has a number of heating elements 122 and cooling elements 121 to regulate and/or adjust temperature or the composition 111 within the extruder 101, e.g. along its length. The heating/cooling elements 121,122 can be provided in various shapes and sizes such as but not limited to fluid jackets, cartridge heater, ceramic strip heater, or flexible heating elements, and can reach temperatures sufficiently high to transform the materials 110 from a solid to a mobilised fluid state reducing its resistance to motion along the flow path and making the composition 111 suitable for 3D printing. The heating/cooling elements 121,122 may be controlled and/or adjusted by the control unit 400.

It will be appreciated that the precise operating ranges and conditions of the extruding apparatus 100, including for example composition feed rate, rotation speed, and temperature, may vary and may depend on the properties of the materials 110 used, including properties such as melting point(s) of the material(s) 110, melt viscosity and/or rheology of the composition 111, chemical stability of the material(s) 110, etc.

The extrusion apparatus 100 further includes a pump 126 and feeding tube 127 to allow optional feeding of an additive, typically a liquid additive, to the melt zone of the extruder 101. This can allow the incorporation of fluid components such as but not limited to liquid plasticizers.

The extrusion apparatus 100 further includes a vent port 128 which is configured to allow venting of any build up or undesired gases to the external environment.

The composition 111 exists the extruder 101, typically in a molten state, via extruder outlet 129.

Referring to **Figures 2 and 3** there are shown cross-sectional views of the dispensing apparatus 200 of the system 5 of Figure 1.

The dispensing apparatus 200 has an inlet 251 configured to be in fluid communication with the extruder outlet 129. This is particularly advantageous when the composition 111 is a pharmaceutical composition. For example, this may avoid the need for the pre-preparation of filaments of pharmaceutical composition, which are associated with the limitations discussed above relating to mechanical properties of the filament, filament dimensions, and amounts/concentrations of API in the filament. For example, the present arrangement may allow the printing of various dose forms of pharmaceutical compositions having higher ratios of API to polymer/excipient than previously possible, and/or the use of a wider range of formulation ingredients.

The dispensing apparatus 200 also has an outlet 252 configured for dispensing the composition 111, the outlet 252 being in fluid communication with a printing nozzle 252 of printing apparatus 300.

5 The dispensing apparatus 200 includes a directional flow valve 250 located between the inlet 251 and the outlet 252.

The dispensing apparatus 200 defines an inlet conduit 231 between the inlet 251 and the directional flow valve 250.

The dispensing apparatus 200 defines an outlet conduit 232 between the directional flow valve 250 and the outlet 252.

10 The dispensing apparatus 200 includes a regulating module 260 which is in fluid communication with the directional flow valve 250. The dispensing apparatus 200 defines a regulation conduit 233 between the directional flow valve 250 and the regulation module 260 to allow flow of the composition 111 through the regulation conduit 233. The regulating module 260 is configured to control and/or regulate flow
15 of the composition 111 to the outlet 252. The outlet is in fluid communication with a printing nozzle 252.

The directional flow valve 250 is associated with an actuator which in this embodiment includes a motor 255 coupled to a drive shaft 256, allowing the motor 255 to actuate the flow valve 250.

20 The valve actuator 255 is in communication with the control unit 400, such that the control unit 400 is capable of actuating the directional flow valve 250, either or both automatically or manually (e.g. by a user).

The dispensing apparatus includes temperature sensor 242 and pressure sensor 241 to measure and/or monitor temperature and pressure, respectively, of the
25 composition 111. Advantageously, the temperature sensor 242 and pressure sensor 241 are in communication with the control unit 400.

The dispensing apparatus includes a heating element 235 configured to control, maintain and/or adjust the temperature of the composition in the dispensing elements, e.g. in the inlet conduit outlet conduit 231 and/or outlet conduit 232. Advantageously,
30 the heating element 235 is in communication with the control unit 400.

There is provided a discharge port 234 in fluid communication with the inlet conduit 231. The first discharge port 234 may allow the directional flow valve 250 to discharge the composition 111 from the dispensing apparatus 200, for example when one or more properties of the composition 111 (e.g. pressure, temperature, or

viscosity) are not optimum and/or when filling of the regulation module 260 is not required or desired.

There is provided an access port 236 in fluid communication with the directional flow valve 250 and/or flow path 231,232. The access port may allow the use of analytical means, e.g. analytical devices such as Process Analytical Tools (PAT) or spectroscopy devices, to monitor and/or analyse the composition 111.

In use, directional flow valve 250 has a number of configurations to selectively direct flow of the composition 111 within the dispensing apparatus 200.

The directional flow valve 250 has a first or "feed" configuration configured to allow flow of the composition 111 from the inlet 251 to the regulating module 260. In the first or "feed" configuration, the directional flow valve 250 allows filling of the regulating module 260 with the composition 111.

The directional flow valve has a second or "dispense" configuration configured to allow flow of the composition 111 from the regulating module 260 to the outlet 252. In the second or "dispense" configuration, the directional flow valve may 250 allows the regulating module 260 to dispense the composition 111 to the outlet 252.

The first or "feed" configuration and the second or "dispense" configuration are mutually exclusive. That is, the composition 111 may either flow from the inlet 251 to the regulating module 260 or may flow from the regulating module 260 to the outlet 252.

Not shown in the embodiment of Figure 1, but described in the embodiment of Figure 12, the directional flow valve 250 may optionally have a third or "recirculation" configuration configured to allow flow of the composition 111 from the 251 inlet to a recirculation outlet, as will be described later in detail.

In this embodiment, the directional flow valve 250 has a fourth or "discharge" configuration configured to allow flow of the composition 111 from the inlet 251 to a first discharge port 234. By such provision, the composition 111 may be discharged from the dispensing apparatus 200, for example when one or more properties of the composition 111 (e.g. pressure, temperature, or viscosity) are not optimum and/or when filling of the regulation module 260 is not required or desired.

The directional flow valve also has a fifth or "closed" configuration configured to prevent flow of the composition 111 within the dispensing apparatus 250. In other words, in the fifth or "closed" configuration, the composition 111 may not flow from the inlet 251 or to the outlet 252.

The regulating module 260 of the dispensing apparatus 200 of Figures 2 and 3, will now be described in more detail with reference to **Figures 4 to 6**.

As shown in **Figure 4**, the regulating module 260 has a chamber 262 configured to receive the composition 111.

5 The chamber has a chamber inlet 263 in fluid communication with the directional flow valve 250 and the regulation module conduit 233.

The regulating module 260 has a regulation actuator 252 configured to actuate filling of the chamber 262 with the composition 111 and dispensing of the composition 111 from the chamber 262.

10 The regulation actuator 252 includes a motor which drives a piston 270 that reciprocates within the chamber 262. The regulation actuator 252 is associated with and can be controlled and/or operated by the control unit 400, for example in response to one or more parameters measured in the system 5 such as pressure, temperature, viscosity, piston position, or the like.

15 The volume of the chamber 262 is partially defined by an end 274 of the piston 270 at an end of the chamber 262 opposite the chamber inlet 263.

The regulating module has a temperature sensor 266 provided at or near the regulation chamber 262. Advantageously, the temperature sensor 266 is associated with the control unit 400.

20 The regulating module 260 also has a heating element 264 configured to control, regulate and/or adjust the temperature of the composition 111 in the regulation module 260. Advantageously, the heating element 264 is associated with and can be controlled and/or operated by the control unit 400, for example in response to information obtained by the temperature sensor 266.

25 The regulating module 260 also has a cooling element 276 (here in the form of a heat sink). The cooling element 276 may be configured to control, regulate and/or adjust the temperature of the composition 111 in the regulation module 260. Alternatively, or additionally, the cooling element 276 may be configured to prevent the actuator, e.g. motor 252, from overheating, in use. Advantageously, the cooling element 276 is associated with and can be controlled and/or operated by the control unit 400, for example in response to information obtained by the temperature sensor 266.

30 The regulating module 260 includes a positioning sensor 268 configured to detect the position of the piston head 274 within the chamber 262. For example, when the chamber 262 is being filled with composition 111, the positioning sensor 268 may

detect when the piston head reaches its fully retracted position, thus indicating that the chamber 262 is full. Advantageously, the positioning sensor 268 is associated with the control unit 400. When the control unit detects receives a signal from the positioning sensor 268, the control unit 400 may act to cause the actuator 252 to stop moving piston 270.

Referring to **Figure 4**, the regulating module 260 is shown in a first configuration in which the piston 270 is retracted and the chamber 262 is empty.

The directional flow valve 250 is actuated into its first or “feed” configuration configured to allow flow of the composition 111 from the inlet 251 to the chamber 262 of regulating module 260. When the pressure in the chamber has reached a predetermined value, the chamber is considered to be loaded and the regulating module 260 ready to dispense the composition 111 in an accurate volumetric manner, as shown in **Figure 5**.

The directional flow valve 250 is therefore switched to its second or “dispense” configuration (for example by control unit 400) so as to allow flow of the composition 111 from the chamber 262 of the regulating module 260 to the outlet 252 and thus to the printing apparatus 300. During this phase, the actuator 272 acts (for example via a command from control unit 400) to move the piston 270 in the chamber 262 so as to dispense composition 111. When the piston 270 is fully extended and/or when the piston head 270 reaches an inlet end 263 of the chamber 262, the actuator 272 may be stopped, e.g. via a command from control unit 400. The actuator 272 may then be reversed to retract the piston 262 and open the chamber 262, ready to be filled with another load of composition 111 by moving the flow valve 250 to its first or “feed” configuration.

The movement of the piston 270 is accurately controlled by the actuator 272 and control unit 400 to allow control of the exact volumetric displacement of the composition 111 and hence dispensing rate to the outlet 252 (and thus to printing apparatus 300).

In an embodiment, the dispensing apparatus 200 may further include or may be coupled with an analysing device (not shown) configured to monitor at least one parameters of the composition within the dispensing apparatus 200. For example, analysing device may comprise analytical apparatus and/or Process Analytical Tools (PAT), such as but not limited to spectroscopic or physical measurement devices. This may be permitted by using an opening or port such as the access port 236 to enable coupling with or association with the analytical apparatus. Such tools can be used for,

but not limited to, detect homogeneity of the materials in the flow path, materials concentration in a mixture or other species/property identification.

Referring now to **Figures 7 to 9**, there is shown a dispensing apparatus 500 according to another embodiment. The dispensing apparatus 500 is generally similar to the dispensing apparatus 200 of Figures 2 and 3, like parts being denoted by like numerals, incremented by '300'.

As in Figures 2 and 3, the dispensing apparatus 500 of Figures 7 to 9 has an inlet 551 configured to be in fluid communication with the extruder outlet 129. However, in this embodiment, the dispensing apparatus 500 includes four directional flow valves 550, each in fluid communication with the inlet 551 and defining respective inlet conduits 531.

As best shown in **Figure 9**, each directional flow valve 550 is associated with a respective valve actuator 255, such that each directional flow valve 550 can be controlled and/or actuated independently, for example by control unit 400.

As best shown in **Figure 8**, each directional flow valve 550 is associated with a respective outlet 552 and respective outlet conduits 532 between each directional flow valve 550 and a respective outlet 552. Each outlet 552 is in fluid communication with a respective printing nozzle 552.

Each directional flow valve 550 is associated with and is in fluid communication with a respective regulating module 560. Each regulating module 560 operates as described above in relation to Figures 4 to 6.

Each nozzle 552 is configured to be associated with a respective printing platform 310.

The provision of a dispensing apparatus 500 comprising a plurality of directional flow valves 550 and associated regulating modules 560 allows the system to dispense the composition 111 in a continuous, semi-continuous or batch manner. Thus, the dispensing apparatus 500 allows printing, e.g. 3D printing, of the composition 111, e.g. pharmaceutical composition in dosage form, in a continuous, semi-continuous or batch manner.

Referring to **Figures 10 and 11** there are shown a front view and a side view of the printing apparatus 300 of the system 5 of Figure 1.

The printing apparatus 300 includes a printing platform 310. The printing platform 310 is configured to act as support for an object being printed by a printing nozzle (not shown) which is fed by the dispensing apparatus 200,500. The printing platform 310 is capable of moving along the X, Y and Z axis. It has a linear stepper

motor or other conventional drive mechanism 381 to control the z-axis motion. It has a linear stepper motor or other conventional drive mechanism 382 to control the x-axis motion. It also has a linear stepper motor or other conventional drive mechanism 383 to control the y-axis motion. Each motor has a respective suitable switch 384 limiting motion thereof and allowing calculation of relative position and each switch 384 can be controlled by a suitable control means such as computer (not shown).

The temperature of the print platform 310 is controlled by a heater element 385 which is associated with a temperature sensor 386. The temperature of the platform 310 may be maintained by a suitable control system such as a computer associated with the heater element 385 and temperature sensor 386.

The platform 310 receives material 111 deposited on it via a nozzle 552 which is fed by dispensing module 200,500. The weight of the material 111 deposited is determined by suitable weighing means 387 such as load cell(s) or other conventional weighing sensor(s).

In an embodiment, the material 111 deposited onto the print platform 310 may be deposited directly into or onto a suitable receiving container or packaging (not shown) placed onto the print platform 310 such as, but not limited to, blister pack(s), capsule(s), digestible container(s), either using a single or multiple nozzle arrangement and associated dispensing apparatus 200,500.

The platform 310 may be controlled by control unit 400.

In some embodiments, the layers may be set to a thickness in the range of about 0.05 mm – 3 mm, allowing control over the micro to macro structure of the product.

Referring to **Figure 12 and 13** there is shown a system 605 according to another embodiment. The system 605 of Figures 12 and 13 is generally similar to the system 5 of Figure 1, like parts denoted by like numerals, but incremented by '400' in respect of the dispensing apparatus 600.

In this embodiment, the system includes a recirculation unit 690 configured to allow recirculating of the composition 111 from the inlet 651 of the dispensing apparatus 600 to the extruder 101.

In this system 605, the directional flow valve 650 has a "recirculation" configured to allow flow of the composition 111 from the inlet 651 to a recirculation outlet 659. The recirculation outlet 659 is configured to be in fluid communication with or be associated with a flow path 691 of the recirculation unit 690. The flow path 691 of

the recirculation unit 690 is in fluid communication with a recirculation inlet 119 of the extruder 101.

By such provision, the composition 111 may be recirculated into the extruder 101, for example when one or more properties of the composition (e.g. pressure, temperature, or viscosity) are not optimum and/or when filling of the regulation module 660 is not required or desired.

The temperature within the recirculation unit 690 maintained by a temperature control/heating element 692 and associated temperature sensor 694. The temperature control/heating element 692 and associated temperature sensor 694 may be in communication with control unit 400.

A suitable port 696 can be used to purge material 111 from the recirculation unit 690 and/or may be used to connect peripheral devices such as analytical devices, e.g. PAT and/or spectroscopy equipment.

15 **Examples**

The following examples are exemplary embodiments illustrating the preparation of various compositions in oral solid dose form.

The pharmaceutical dose forms were prepared using a system similar to the system of Figure 1 described above.

20

Example 1. Preparation of a Plasdane S630- Acetaminophen formulation

The particular formulation of components in this example is typically *not* suitable for printing using existing fused filament fabrication (FFF 3DP) methods, due to the limitations discussing in the background section above. In particular, Plasdane and Plasdane-Acetaminophen mixtures post extrusion are too brittle in nature to enable them to be used in existing FFF processes which require good control over filament dimensions and appropriate mechanical properties (e.g. flexural modulus). Additionally, on exiting the die of an HME process, the rheology of plasdane and plasdane acetaminophen formulations provides a challenge in control of dimensions of the extrudate by conventional means. (See for example - Prasad *et al.* "Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol™ 15LV filaments for fused filament fabrication (FFF) 3D printing." Additive Manufacturing, Volume 29, October 2019, which outlines these dimensional and mechanical limitations).

35

(1A) PREPARATION OF SYSTEM

A powder mixture of acetaminophen and Plasdane™ (N-vinyl-2-pyrrolidone and vinyl acetate from Ashland) was prepared (offline) in a suitable powder mixer. The powder blend 110 was loaded to the material hopper 112. The feed rate was controlled by measuring a loss in weight of the material in the hopper 112. The feed rate was set to 0.1kg/hr.

The staged heating elements 122 of the melt extruding apparatus 100 were set to 20°C at the funnel inlet 114 and suitable temperature profile to raise the temperature of the materials 111 conveyed along the length of the extruder 101 from the feed funnel 114 to 180°C at a discharge end 129 thereof.

The screw 118 speed set point was set to 100 rpm (using controller of drive motor (118)).

The print platform 610 of the printing apparatus 300 was set to 90°C and monitored/controlled by temperature sensor 386.

Using CAD software, an oral solid dose form was drawn (in this case an 8 mm diameter by 3 mm tall cylindrical tablet shape) and a G-code file was generated to control the X-Y-Z motion of the printer platform 310 and the deposition rate/motion of the piston 270 of the regulating module 260 during the printing of the composition 111. It will be appreciated that singular or multiple dose forms can be drawn in CAD software and laid out spatially to generate a suitable 3D print G-code for multiple object printing, as is known in the field.

The piston 270 was set to its retracted position as shown in Figure 4, i.e. the chamber 262 is in the open or "fill" position as shown in Figure 2C and the heating element 264 was set to 180°C to maintain the temperature of the composition 111 in the regulating module 260.

The directional flow valve 260 was set to its first of "feed" configuration to allow the composition 111 to flow from the extruder outlet 129 to the chamber 262 of the regulating module 260.

(1B) CHARGING OF THE REGULATING MODULE

The extruder module screws 118 were rotated at 100 rpm. The powder feed mixture 110 was charged to the system hopper 112 at 0.1 kg/hr. This feeding was continued so the material 110 was conveyed and passed through the extruder 110 towards the dispensing apparatus 200. As the composition 111 is conveyed, it melts and mixes due to the temperature rise it experiences from the heater elements 122 of

the extrusion apparatus 100. This was continued until the pressure in the dispensing apparatus 200 reaches 20 bar indicating that the chamber 262 of the regulating module 206 is filled with the Plasdane-Acetaminophen composition.

5 The feeding of the materials 110 into the extruder 101 and the rotation of the extruder screws 118 was then paused.

(1C) PRINTING OF DOSE FORMS

10 The operation of the print phase was commenced by activation of the G-code which controls the X-Y-Z motion of the print platform 310 via motors 381,382,383 and materials deposition via motor 272 of regulating module 270 to dispense the composition 111 from the chamber 262.

15 Simultaneously, the directional flow valve 250 is set to its second or "dispense" configuration to create the flow path for the composition from chamber 262 to nozzle 252. The composition 111 is then printed by deposition of additive layers governed by the G-code. As the deposition commences the deposited composition 111 is solidified as it cools to form the oral solid dose form(s). Printed dose form weights are confirmed by weight sensor 387. The oral solid dose forms were then recovered from the print platform 310.

20 Utilising the above steps singular and multiple dose forms were printed by repetition of the operation of the print phase and/or by use of suitable G-code generated from a CAD drawing of a multiple of dose forms to generate a multiple object print as described above. This may depend upon the number of dose forms required (e.g. a single or small number of units for testing versus a large number of units for production).

25

(1D) EXTENSION OF DEPOSITION AND PRINTING FOR PRODUCTION AND REFILLING THE REGULATING MODULE

30 When larger numbers of oral solid dose forms were being printed (beyond the materials holding capacity of the chamber 262, the following additional steps were taken.

35 As the chamber 262 empties as the full volume of the composition 111 is dispensed from the module 260, the limit switch 268 is activated. This causes the control unit 400 to command printing to be paused. At this point the directional flow valve 250 was actuated to position it to its first or "feed" configuration to allow flow of the composition 111 from the extruder outlet 129 to the regulation chamber 262.

The extrusion module screws 118 and the feeder module 112 were restarted and the piston 270 retracted back to enable the chamber 262 to be refilled with the composition 111. As previously, the filling is continued until the pressure in the chamber 262 reached 20 bar to indicate that the chamber 262 was full. The extruder screws 118 and feeding module 112 were then paused as above.

The directional flow valve 250 was actuated to move it to its second or "dispense" configuration to allow flow of the composition from the chamber 262 to the nozzle 252. At this point printing was resumed as described above in paragraph 1C. This cycle can be repeated as required until sufficient dosage forms are produced.

It should be appreciated that the specific conditions of temperature control across the system 5, rotational speed of the screws 118 within the extruder 101 and other operational parameters are subject to optimisation of operation, which may depend in particular to the specific composition 111 being used.

Within the above example, variants of the Plasdene-Acetaminophen composition were printed using parameters identified below, in order to exemplify non-limiting examples of conditions that can be used within the system 5.

Tables 1 and 2 exemplifies non-limiting modifications of individual set points used with regards the extruder speed, extruder output temperature, and dispensing module temperature to generate the 3D printed dose forms across a range of conditions and compositions.

Table 1: Composition variance

% Acetaminophen: Total Acetaminophen + Plasdene Mass	Extruder Exit and Deposition module Temp (°C)	Extruder Speed (rpm)
10	170	100
20	155	100
30	140	100
40	140	100
50	140	100
60	140	100
70	140	100

Table 2: Within a composition of 10% Acetaminophen – Plasdone composition the following, non-limiting conditions were used:

Process print sequence	Extruder Exit and Deposition module Temp (°C)	Extruder Speed (rpm)
1	180	100
2	170	100
3	160	100
4	155	100
5	150	100
6	145	100
7	140	100
8	140	50
9	135	100
10	135	75
11	135	50

5

Example 2. Printing of a Plasdone S630- Acetaminophen formulations into a receiving container such as a sachet/blister pack

As in the previous example, this formulation of components is used to illustrate a formulation system that is typically *not* suitable for printing using existing fused filament fabrication (FFF 3DP) methods, but can be printed using the present system and method. This example illustrates the deposition directly into a blister pack/sachet container that is then used as a component of primary packaging for the product.

(2A) PREPARATION OF SYSTEM:

The preparation relating to the extruder 101 was similar to the preparation described in example 1, but with a feed rate set to 0.11kg/hr.

A blister pack of pre-determined, suitable geometry was placed and retained on the print platform 310.

The screw 118 speed set point was set to 100 rpm (using controller of drive motor (118)).

The print platform bed 385 and hence receiving container/blister pack was set to 30°C and monitored/controlled by temperature sensor 386.

Using CAD software, an oral solid dose form was drawn (in this case an 8 mm diameter by 3 mm tall cylindrical tablet shape) and a G-code file was generated to control the X-Y-Z motion of the printer platform 310 and the deposition rate/motion of the piston 270 of the regulating module 260 during the printing of the composition 111. It will be appreciated that singular or multiple dose forms can be drawn in CAD software and laid out spatially to generate a suitable 3D print G-code for multiple object printing, as is known in the field.

In this case, the multiple printing head configuration illustrated in **Figures 7-9** was used to generate simultaneous printing of multiple dose forms.

The piston 570 in each module 560 was set to its retracted position and the heating element 564 was set to 180°C to maintain the temperature of the composition 111 in the regulating module 560. The directional flow valve 560 was set to its first of “feed” configuration to allow the composition 111 to flow from the extruder outlet 129 to the chamber 562 of the regulating modules 560.

(2B) CHARGING OF THE DEPOSITION MODULE

Step 2B was as described in step B above, except that the powder feed mixture 110 was charged to the system hopper 112 at 0.11kg/hr. Once the pressure in each of the dispensing apparatus 500 reached 20 bar, the feeding of the materials 110 into the extruder 101 and the rotation of the extruder screws 118 was paused.

(2C) PRINTING OF THE DOSE FORM(S)

The operation of the print phase was commenced by activation of the G-code which compensates for the geometry of the receiving blister/container package and controls the X-Y-Z motion of the print platform 310 via motors 381,382,383 and materials deposition via motors 572 of each regulating module 570 to dispense the composition 111 from each chamber 562. Simultaneously, the directional flow valve 260 were set to their second or “dispense” configuration to create the flow path for the composition 111 from chambers 562 to nozzles 552. The composition 111 was then printed by deposition of additive layers governed by the G-code. As the deposition commences the deposited composition 111 solidified as it cooled to form the oral solid dose forms. Printed dose form weights were confirmed by weight sensor 387. The oral solid dose forms were then recovered from the print platform 310.

Utilising the above steps multiple dose forms were printed by repetition of the operation of the print phase and by use of suitable G-code generated from a CAD drawing of a multiple of dose forms in conjunction with the geometry of the packaging thus generating a multiple object print to fill the packaging as described above.

5

(2D) EXTENSION OF DEPOSITION AND PRINTING FOR PRODUCTION AND REFILLING THE DEPOSITION DEVICE

This step was performed as in paragraph 1D above, for each dispensing module 500.

10

Example 3. Printing of an Affinisol- Acetaminophen formulation

This formulation of components in this example are used to illustrate a formulation system that is *not* suitable for printing using existing fused filament fabrication (FFF 3DP) methods, but can be printed using the present system and method.

Affinisol™(hydroxyl-propyl-methyl-cellulose) - Acetaminophen formulations post extrusion only have the correct mechanical properties for conventional 3D-FFF printing at compositions of below about 20wt% and above about 40wt% of drug, whilst intermediate compositions having a drug concentration between about 20 and 40 wt% have insufficient mechanical strength and flexural modulus to enable FFF methods.

The sequence of step 3A-3D in this example was generally similarly to steps 1A-1D described in relation to example 1, except that:

- In step 3A, the extruder feed rate was set to 0.11 kg/hr;
- In step 3B, feeding the composition 111 from the extruder 101 was continued until the pressure in the dispensing apparatus 200 reached 30 bar.

It will be appreciated that the adjustment in the feed rate and/or maximum “filling” pressure of the piston chamber 262 depends on the particular composition being used, including for example its rheological properties.

This process was conducted for a range of non-limiting Affinisol-Acetaminophen mixture compositions with the following parameters shown in Table 3:

Table 3: Composition variance

% Acetaminophen: Total Acetaminophen + Affinisol Mass	Extruder Exit and Deposition module Temp (°C)	Extruder Speed (rpm)	X-Y-Z bed temperature
10	180	100	100
10	170	100	100
10	160	100	100
10	150	100	100
10	150	50	100
20	150	50	100
20	145	50	100
30	140	100	90
30	145	100	90
40	145	50	100
40	145	50	80
50	145	100	80

Example 4. Printing of a Soluplus – Mefanamic Acid formulation

5

This formulation of components in this example are used to illustrate a formulation system that can *not* be printed using existing fused filament fabrication (FFF 3DP) methods. Soluplus™ (Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer from BASF) is conventionally mixed with a plasticiser (see e.g. Hanpin Lim, Stephen W Hoag., Plasticizer Effects on Physical–Mechanical Properties of Solvent Cast Soluplus® Films, May 2013, AAPS PharmSciTech) in order to produce mechanical properties to support its downstream processing and handling. This renders Soluplus difficult to fabricate and 3DP by conventional FFF means. Beneficial aspects of Soluplus and Mefanamic Acid systems are described in e.g. “Improving Consistency for a Mefenamic Acid Immediate Release Formulation”, Elke Prasad John Robertson & Gavin W. Halbert, Journal of Pharmaceutical Sciences, Volume 109, Issue 11, November 2020, Pages 3462-3470.

The sequence of step 4A-4D in this example was generally similarly to steps 1A-1D described in relation to example 1, except that:

20

- In step 4A:
 - o the staged heating elements 122 of the melt extruding apparatus 100 were set to 20°C at the funnel inlet 114 and suitable temperature profile to raise the temperature of the materials 111 conveyed along the length of the extruder 101 from the feed funnel 114 to 125°C at a discharge end 129 thereof;
 - o the screw 118 speed set point was set to 50 rpm (using controller of drive motor (118));
 - o The print platform 610 of the printing apparatus 300 was set to 100°C and monitored/controlled by temperature sensor 386;
 - o The heating element 264 was set to 125°C to maintain the temperature of the composition 111 in the regulating module 260.
- In step 4B:
 - o the extruder module screws 118 were rotated at 50 rpm;
 - o feeding the composition 111 from the extruder 101 was continued until the pressure in the dispensing apparatus 200 reached 30 bar;
- In step 4D, refilling the composition 111 was continued until the pressure in the dispensing apparatus 200 reached 30 bar.

20 **Example 5: Printing of a PVA – Acetaminophen formulation**

This formulation of components in this example are used to illustrate a formulation system that can *not* be printed using existing fused filament fabrication (FFF 3DP) methods.

25 Polyvinyl Alcohol (PVA) is conventionally mixed with a plasticiser such as sorbitol to enable its post extrusion handling. (see for e.g. "Effect of Sorbitol Plasticizer on the Structure and Properties of Melt Processed Polyvinyl Alcohol Films" Huafeng Tian, Di Liu, Yuanyuan Yao, Songbai Ma, Xing Zhang, Aimin Xiang. J Food Sci. 2017 Dec; 82(12):2926-2932.). This renders PVA-based formulations difficult to fabricate and 3DP by conventional FFF means.

The sequence of step 5A-5D in this example was generally similarly to steps 1A-1D described in relation to example 1, except that:

- In step 5A:

- 5
- a powder mixture of acetaminophen and PVA (50:50 wt% composition) was prepared (offline) in a suitable powder mixer;
 - the staged heating elements 122 of the melt extruding apparatus 100 were set to 20°C at the funnel inlet 114 and suitable temperature profile to raise the temperature of the materials 111 conveyed along the length of the extruder 101 from the feed funnel 114 to 135°C at a discharge end 129 thereof;
 - the screw 118 speed set point was set to 50 rpm (using controller of drive motor (118));
 - 10 ○ The print platform 610 of the printing apparatus 300 was set to 80°C and monitored/controlled by temperature sensor 386;
 - The heating element 264 was set to 135°C to maintain the temperature of the composition 111 in the regulating module 260;
 - In step 5B:
 - 15 ○ the extruder module screws 118 were rotated at 50 rpm;
 - feeding the composition 111 from the extruder 101 was continued until the pressure in the dispensing apparatus 200 reached 30 bar;
 - In step 5D, refilling the composition 111 was continued until the pressure in the dispensing apparatus 200 reached 30 bar.

20

It will be appreciated that the above examples are for illustration purposes only, and are not intended to limit the scope of the invention.

CLAIMS:

1. A dispensing apparatus configured for dispensing a pharmaceutical composition, the dispensing apparatus comprising:
 - 5 at least one inlet configured for receiving a pharmaceutical composition;
 - at least one outlet configured for dispensing the composition;
 - at least one directional flow valve located between the at least one inlet and the at least one outlet; and
 - at least one regulating module in fluid communication with a respective
 - 10 directional flow valve, wherein the at least one regulating module is configured to control and/or regulate flow of the composition to at least one outlet.
2. A dispensing apparatus according to claim 1, wherein the regulating module is a volumetric regulating module.
 - 15
3. A dispensing apparatus configured for dispensing a pharmaceutical composition, the apparatus comprising:
 - at least one inlet configured for receiving a pharmaceutical composition;
 - at least one outlet configured for dispensing the composition;
 - 20 at least one volumetric regulating module configured to control and/or regulate flow of the composition to at least one outlet in a volumetric manner.
4. A dispensing apparatus according to claim 3, wherein the apparatus further comprises at least one directional flow valve located between the at least one inlet and the at least one outlet, and wherein the at least one volumetric regulating module is in fluid communication with a respective directional flow valve.
 - 25
5. A dispensing apparatus according to any preceding claim, wherein the at least one inlet is arranged to be in fluid communication with a delivery apparatus configured to deliver the composition in a molten state.
 - 30
6. A dispensing apparatus according to claim 5, wherein the delivery apparatus comprises an extrusion apparatus.

7. A dispensing apparatus according to any preceding claim, wherein the at least one outlet is arranged to be in fluid communication with a printing apparatus or part thereof.
- 5 8. A dispensing apparatus according to any preceding claim, wherein the at least one directional flow valve is configured to control a flow path of the composition between the/an inlet and the/an outlet.
9. A dispensing apparatus according to any preceding claim, wherein the/each
10 directional flow valve has a plurality of configurations.
10. A dispensing apparatus according to claim 9, wherein the/each directional flow valve has a first or “feed” configuration configured to allow flow of the composition from the inlet or from a respective inlet to the regulating module or to a respective regulating
15 module; and a second or “dispense” configuration configured to allow flow of the composition from the regulating module or from a respective regulating module to the outlet or to a respective outlet.
11. A dispensing apparatus according to claim 9 or claim 10, wherein the/each
20 directional flow valve has a third or “recirculation” configuration configured to allow flow of the composition from the/an inlet to a recirculation outlet, the recirculation outlet being configured to be in fluid communication with or to be associated with a feeding inlet of the delivery apparatus.
12. A dispensing apparatus according to any of claims 9 to 11, wherein the/each
25 directional flow valve has a fourth or “discharge” configuration configured to allow flow of the composition from the inlet to a discharge port.
13. A dispensing apparatus according to any of claims 9 to 12, wherein the/each
30 directional flow valve has a fifth or “closed” configuration configured to prevent flow of the composition within the dispensing apparatus.
14. A dispensing apparatus according to any preceding claim, wherein the/each
35 regulating module comprises a chamber configured to receive the composition.

15. A dispensing apparatus according to claim 14, wherein the chamber has a chamber inlet in fluid communication with a respective directional flow valve.
16. A dispensing apparatus according to claim 14 or claim 15, wherein the/each regulating module comprises a regulation actuator configured to actuate filling of the chamber with the composition and/or dispensing of the composition from the chamber.
17. A dispensing apparatus according to any one of claims 14 to 16, wherein the/each regulating module comprises one or more pressure sensors and/or temperature sensors.
18. A dispensing apparatus according to any one of claims 14 to 17, wherein the/each regulating module comprises at least one positioning sensor configured to detect the configuration of the regulation module and/or the position of the regulation actuator.
19. A dispensing apparatus according to any one of claims 14 to 18, wherein the dispensing apparatus comprises and/or is associated with analytical means to monitor and/or analyse one or more parameters of the composition.
20. A system for manufacturing a solid pharmaceutical dose form, the system comprising:
at least one delivery apparatus configured to deliver a pharmaceutical composition;
at least one printing apparatus and/or part thereof; and
at least one dispensing apparatus according to any of claims 1 to 19 provided between the at least one delivery apparatus and the at least one printing apparatus or part thereof.
21. A system according to claim 20, wherein the delivery apparatus comprises an extrusion apparatus configured to deliver the composition in a molten state.
22. A method of dispensing a pharmaceutical composition, the method comprising:
receiving a pharmaceutical composition from at least one inlet to at least one regulating module via at least one directional flow valve; and

dispensing the composition from the at least one regulating module to at least one outlet via the at least one directional flow valve.

23. A method according to claim 22, comprising controlling and/or regulating a flow of the composition to at least one outlet via the at least one regulating module.

24. A method of dispensing a pharmaceutical composition, the method comprising:
receiving a composition from at least one inlet to at least one volumetric regulating module; and
dispensing the composition from the at least one volumetric regulating module to at least one outlet in a volumetric manner.

25. A method according to claim 24, comprising receiving the composition from the at least one inlet to the at least one volumetric regulating module via at least one directional flow valve, and dispensing the composition from the at least one volumetric regulating module to the at least one outlet via the at least one directional flow valve.

26. A method according to claim 24 or claim 25, comprising controlling and/or regulating a flow of the composition to at least one outlet via the volumetric regulating module.

27. A method of manufacturing a solid pharmaceutical dose form, the method comprising dispensing a pharmaceutical composition to a printing apparatus and/or onto a printing platform using a dispensing apparatus according to any of claims 1 to 19, a system according to any of claims 20 to 21, or according to a method of any of claims 22 to 26.

28. A solid pharmaceutical dose form manufactured using a method according to claim 27.