Universidade de Lisboa

Faculdade de Farmácia

Development of a Formulation for sustained-release of Mebeverine Hydrochloride tablets by Hot-Melt Extrusion and 3D printing technology

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Trabalho de Campo orientado pelo Doutor Mateusz Kurek, Professor Associado da Jagiellonian University, e coorientado pelo Professor João F. Pinto, Professor Associado da Faculdade de Farmácia da Universidade de Lisboa

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

O objetivo do presente estudo foi desenvolver e fabricar comprimidos de libertação sustentada de cloridrato de mebeverina (MbH), utilizando o acoplamento de duas técnicas de processamento - a extrusão por fusão e a impressão tridimensional de modelação por deposição fundida.

Foram consideradas quatro formulações de MbH com 40% (w/w) de carga de fármaco. Numa das formulações foi utilizado o álcool polivinílico (PVA) como matriz polimérica e para as restantes três foram utilizados três graus diferentes de aceto-succinato de hidroxipropilmetilcelulose (HPMCAS), de tamanho de partícula médio: LMP, MMP e HMP. Foram realizados estudos de pré-formulação para avaliar as propriedades dos materiais para caracterizar os pós. Assim, foi estudada a termoestabilidade por análise termogravimétrica (TGA), a distribuição do tamanho das partículas por difração a laser, o seu escoamento e a molhabilidade (ângulos de contacto com água).

As matérias-primas foram misturadas e fundidas na extrusora para fabricar os filamentos. Os extrudidos foram analisados visualmente e avaliados quanto à sua elasticidade (módulo de elasticidade) e resistência à quebra a fim de avaliar se apresentavam as características necessárias para o processo de impressão. Para além disso, também foi investigado o teor de substância ativa (API) dispersa no filamento. Uma vez verificado que todos os filamentos apresentavam as propriedades desejadas, procedeu-se à impressão 3D dos comprimidos por FDM. Todos os filamentos foram imprimíveis.

Os comprimidos foram analisados por calorimetria diferencial de varrimento (DSC) para avaliar a qualidade da mistura do fármaco com a matriz polimérica, tendo-se observado que o fármaco se encontrava completamente dissolvido na matriz. Por último, foram analisados os perfis de libertação do fármaco dos comprimidos impressos, através de testes de dissolução realizados em meios que simulavam as condições gastrointestinais (primeiro 2h a pH 1,2, seguido de pH 6,8 durante 10h). Os resultados demonstraram que os comprimidos de HPMCAS impressos foram eficazes para a libertação entérica. Todos os filamentos impressos foram bem-sucedidos na libertação sustentada.

Palavras-chave: Dispersão sólida, extrusão a quente, modelação por deposição fundida, dispersão sólida, libertação gastroresistente, libertação sustentada.

Abstract

The aim of this study was to develop and manufacture sustained-release tablets of mebeverine hydrochloride (MbH), combining two processing techniques, melt extrusion and three-dimensional printing by fused deposition modeling.

Four MbH containing formulations were developed with 40% (w/w) drug loading. For one of the formulations, polyvinyl alcohol (PVA) was used as the polymeric carrier and for the remaining three, three different grades of hydroxypropylmethylcellulose acetate succinate (HPMCAS) of medium particle size were used: LMP, MMP and HMP.

Pre-formulation studies were conducted to evaluate the properties of the materials and characterizing the powders, namely thermostability (thermogravimetric analysis, TGA), particle size distribution (laser diffraction), powder flowability and wettability (contact angle).

The raw materials were mixed and melted in the extruder to produce the filaments. Once the extrudates had been obtained, they were visually analyzed and evaluated for their elasticity (modulus of elasticity) and strength at break in order to assess whether they had the necessary characteristics for the printing process. In addition, the content of active substance (API) dispersed in the filament was also investigated. After checking that all filaments had the desired properties, the tablets were 3D printed using FDM. All the filaments were printable.

The printed tablets were analyzed by differential scanning calorimetry (DSC) to assess the quality of the drug mixture with the polymer matrix. This analysis revealed that the drug was completely solubilized in the matrix. Lastly, the drug release profiles from the printed tablets were analyzed through dissolution tests conducted in media simulating gastrointestinal conditions (first 2h at pH 1.2, followed by pH 6.8 for 10h). The results showed that the printed HPMCAS tablets were effective for enteric release. All printed filaments achieved sustained release.

Keywords: Enteric Release, fused deposition modeling (FDM), hot melt extrusion (HME), solid dispersion, sustained release.

Abbreviations

API – Active Pharmaceutical Ingredient

ASD – Amorphous Solid Dispersion

Avg – Average

BCS – Biopharmaceutical Classification System

CAD – Computer-Aided Design

DDS – Drug Delivery Systems

DSC – Differential Scanning Calorimetry

FDA – Food and Drug Administration

FDM – Fused Deposition Modeling

GI – Gastrointestinal

GIT – Gastrointestinal Tract

HME – Hot-melt Extrusion

MSE – Multiple Screw Extruder

Ph. Eur. – European Pharmacopeia

TGA – Thermogravimetric Analysis

Tg – Glass Transition Temperature

Tm – Melting Temperature

SD – Solid Dispersion

SSE – Single Screw Extruder

StD – Standard Deviation

TSE – Tween Screw Extruder

3D – Three-Dimensional

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1. INTRODUCTION

1.1. Oral route of drug administration

The oral route of administration is considered the most convenient and beneficial form of drug administration due to its ease of administration, greater patient compliance, and flexibility of formulation (1,2). More than 60% of pharmaceutical dosage forms on the market are oral dosage forms (3). Despite the advantages of using these dosage forms, after administration, these drugs are exposed to a wide variety of physiological conditions along the gastrointestinal tract (GIT) (4). The main absorption site for APIs in the GIT occurs in the small intestine, due to its high vascularization and high absorption surface area (2,4). However, before they reach this area, APIs are exposed to the acidic and enzymatic conditions of the stomach and may suffer hydrolysis or degradation. In addition, it is necessary to take into account the possibility that the drugs may cause irritant effects on the gastric mucosa (4). Rapid gastric emptying is also a factor that can limit the bioavailability of conventional oral administration systems (1).

Conventional immediate-release oral dosage forms are unable to maintain therapeutic drug levels over a long period. This leads to a higher number of daily administrations required and, consequently, can result in poor adherence to therapy from the patient (3). For these reasons, several studies have been carried out to modify or control the release of drugs in the GIT (4).

1.1.1. Modified release oral dosage forms

The term "modified drug release" is the broad term used to describe any modification to the rate, time, and/or site of drug release. There are several types of modified release, namely delayed release, prolonged release, and targeted release (3,4).

In prolonged-release formulations, the drug's release is extended over a long period of time as it passes through the GI tract. This way, it is possible to reduce the daily dosage of the medication while also preventing the negative effects caused by fluctuations in the drug's plasma concentration (3). This release can be classified into two types: controlled release or sustained release, the distinction between the two being made by the rate of drug release. This way, controlled-release formulations maintain a constant release rate over time (zero-order kinetics) (3,4), while sustained-release formulations exhibit an inconsistent drug release rate, generally faster at the start of the release and then slower over a long period of time.

There are several inherent objectives of sustained-release systems, including reducing the frequency of administration, reducing the dose and providing uniform drug administration, reducing adverse effects, and improving patient comfort and compliance (1,3,4).

One of the most common approaches to modify drug release is the addition of inert materials, such as polymers. Furthermore, the chosen technique ant its parameters, drug solubility ant the addition of other components, like plasticizers, also play a significant role in modulating drug release (3).

1.2. Biopharmaceutical Classification System (BCS)

The Biopharmaceutical Classification System (BCS) was introduced in 1995 by Amidon et al. (5) and has since been used for the selection and development of oral drug formulations. This system categorizes drugs into four groups (Figure 1) based on two criteria: aqueous solubility and intestinal permeability (5,6). These drug properties are primarily responsible for the rate and extent to which the drug is absorbed from immediate-release solid pharmaceutical forms. In this way, a better understanding of the relationship between the release of the drug from the solid pharmaceutical form and the absorption process is possible (6,7).

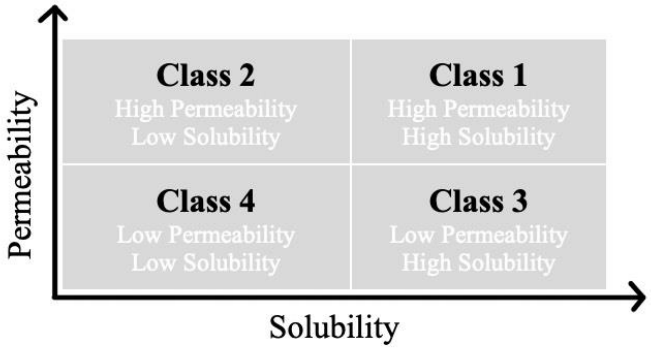


Figure 1. Biopharmaceutical Classification System (BCS)

(Adapted from (6))

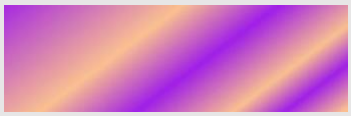
1.3. Solid Dispersion (SD)

A solid dispersion (SD) is commonly described as a solid matrix composed of a hydrophobic API and one or more hydrophilic carriers and can be either crystalline or amorphous form. The crystalline state of a drug is the lowest energy state and is therefore the

most stable. In contrast, the amorphous state represents a higher free energy state and is also more unstable, so it tends to recrystallize to become more thermodynamically stable. Due to the higher free energy, the amorphous state allows not only the dissolution rate to be increased but also the supersaturation, conferring greater bioavailability to the drug (5).

SD can be classified in different ways based on the carrier used and its molecular arrangement. Depending on the type of carrier used, SDs can be: first generation, also known as crystalline SDs, where a crystalline drug is dispersed in a crystalline carrier; second generation, which involves the use of amorphous carriers; third generation, where surfactants are added to the formulation to improve the dissolution profile; and fourth generation, which represents controlled release SDs, developed to overcome the problem of the short biological half-life of certain drugs (5,8). Moreover, based on the molecular state of the API distributed in the polymer matrix, they can be categorized as crystalline solid dispersions, amorphous solid dispersions and amorphous solid solutions (Table 1) (9).

Table 1. *States of Solid Dispersion (Adapted from (9))*

	Classification	API and Polymer Phases	A DSC will find
	Crystalline Solid Dispersion	Crystalline API dispersed in Amorphous Polymer	Tg+Tm
	Amorphous Solid Dispersion	Amorphous API dispersed in Amorphous Polymer	2 x Tg
	Amorphous Solid Solution	Amorphous API molecularly dissolved in Amorphous Polymer	1 x Tg

This technique is widely described as being advantageous for increasing the solubility and dissolution of poorly water-soluble drugs belonging to BSC classes II and IV (5,10). Its principal applications include the development of immediate-release dosage forms, drug supersaturation and precipitation inhibition, and the prevention of recrystallization during storage (10). Furthermore, with the right choice of carrier, this approach can be very beneficial in producing sustained or controlled release forms for drugs with a short half-life or that are soluble in water, making it possible to reduce the frequency of administration (10,11). Depending on the characteristics of the polymers selected, the drug can be released from these

systems by leaching, diffusion or erosion. Hydrophilic matrices tend to hydrate and swell in contact with water, forming a gel layer and releasing the drug by diffusion (9,12). On the other hand, in hydrophobic matrices, the surrounding medium penetrates the pharmaceutical form and the drug is dissolved and diffused through pores (9).

Different techniques can be used to prepare solid dispersions, such as spray drying, co-precipitation, supercritical fluid and hot melt extrusion (HME) (9,11).

1.4. Hot melt extrusion

The hot melt extrusion (HME) process first appeared in the 1930s, when it was widely used in the plastics, rubber, and food industries (13–18). In 1970, this method started to be used by the pharmaceutical industry in the formulation, development and manufacture of products (13,19). In this context, it has proved highly successful due to its vast range of applications for various drug delivery systems (DDS) (14,15,17,18), such as tablets, pellets, implants, granules, suppositories, ophthalmic inserts and transmucosal and transdermal systems (15,18). Some of these pharmaceutical formulations have been approved by the Food and Drug Administration (FDA), such as implants, tablets, and ocular inserts (3,17).

In general, this technique consists of melting, mixing and extruding the drug with polymers under high temperatures and pressure, resulting in a homogeneous mixture (3).

This technique has several applications, including taste masking, increasing the solubility of poorly water-soluble drugs, controlled, extended, sustained and targeted administration of drugs, and the preparation of nanoparticles (14,18). However, one of the main uses of HME is the preparation of amorphous solid dispersions (ASD) to improve the solubility and bioavailability of drugs (14,15,17).

1.4.1. HME Process and Equipment

This technology is a continuous pharmaceutical process where, during extrusion, a mixture of active substance, a thermoplastic polymer matrix and other processing agents such as plasticizers, antioxidants, thickening agents, release modifiers, bulking agents and thermal lubricants are heated and softened inside the extruder (19). The material is then forced through the die by one or two rotating screws inside the barrel (13,17). Extrusion is generally performed at temperatures above the glass transition temperature (Tg) of the polymer, although sometimes it is above the melting temperature (Tm) (1). The process is carried out at these high temperatures to obtain a molecular mixture of the active substances and the thermoplastic

binders, polymers or both. The extrusion process can be divided into several stages: heating the material, mixing and transportation, flow through the die and downstream processing of the material with auxiliary equipment for cooling, cutting or collecting the final product (15,17). All these stages must be carefully controlled to maintain the integrity of the final product (17).

Despite the HME processing technology has been in use in extensively in the plastics industry for many years, modifications to the extrusion equipment were necessary to enable its implementation in the pharmaceutical industry (15,18). The main changes involved the contact parts, which became inert and therefore non-reactive, non-additive and non-absorbent, to comply with regulatory requirements (15).

There are three major categories of extrusion equipment: barrel extruders, radial screen extruders and screw extruders, the latter is the most used in the pharmaceutical industry (13,15). Unlike the other extruders, the screw extruder allows the feed material to be continuously converted into the finished form. In general, the rotating screws force the material to move from the feed location to the die. The heat produced by the friction of the cylinder wall softens the feed material which, when it reaches the end of the screw, is in a viscous state and is forced through the die and molded into the desired shape (13).

There are three types of screw extruders on the market: (1). single screw extruders (SSE); (2). Twin-screw extruders (TSE); (3). Multiple screw extruders (MSE). Regardless of the type of extruder used during the manufacturing process, the rotational speed of the screw must be controlled to compensate for the torque and shear rate generated by the extrusion material (13).

The extrusion equipment available on the market is usually formed by a motor, responsible for driving the entire process; a cylinder, usually divided into sections fixed or screwed together; a rotating screw for conveying the material to be extruded; and a terminal die connected to the end of the cylinder, for passing the molten material providing the desired dimensions to the finished product (Figure 2) (13,17).

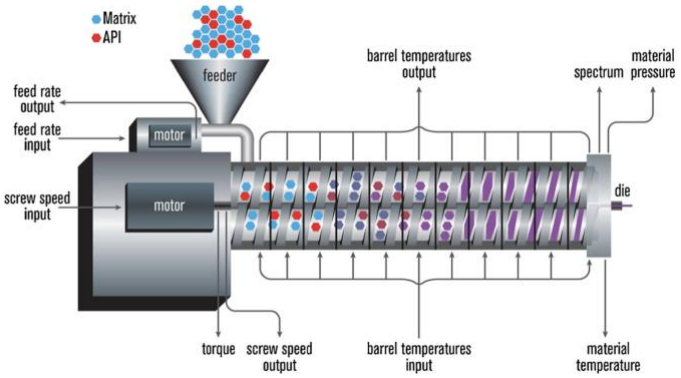


Figure 2. Schematic of extrusion equipment (13).

Connected to the extrusion equipment is an electronic control unit, which allows the process parameters inherent to extrusion to be controlled, such as the screw speed (rpm), the feed rate, the temperatures obtained in the different sections of the cylinder and die and the vacuum level for devolatilization (13,17). Additionally, the control panel allows you to read the pressure, melting temperature, motor amperage, material viscosity and specific energy consumption (13). Other additional systems can be attached, such as a heating and cooling device for the barrel, a degassing unit, a caterpillar with a conveyor belt to allow the material to cool and stretch after exiting the die and also an in-line laser to measure the diameter of the extruded material (13,17).

1.4.1.1. Single screw extruder (SSE) - Single-screw extruders are the simplest, with few changes since their development in 1897. As a result of their simplicity, they are also the most widely used. The equipment is similar to the other extruders, with the difference that it only has one continuously rotating screw (13).

1.4.1.2. Twin-screw extruder (TSE) - The first twin-screw extruder was developed after the single-screw extruder, in the late 30s. The extruders are composed of two screws installed in parallel, allowing different configurations and processing applications.

The screws can rotate in the same direction (co-rotating) or opposite directions (counter-rotating) (Figure 3) (14).

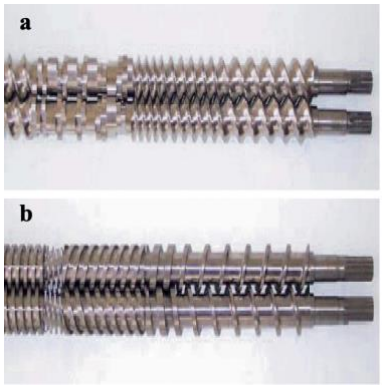


Figure 3. Screw rotation direction: (a) counter-rotating and (b) co-rotating screws (14).

They can also be non-intermeshing or intermeshing, the latter being the most popular extruder due to the greater interaction of the mixture with the screws and for allowing self-cleaning of the barrel. However, non-intermeshing twin screws are especially beneficial for processing highly viscous materials since the screws are positionally separated, avoiding the generation of high torque (14,17).

Compared to single-screw extruders, twin-screw extruders have several advantages when it comes to producing pharmaceutical formulations, such as reduced residence time, self-cleaning characteristics which ensure that the entire contents of the equipment are emptied and therefore reducing product waste, continuous material feed and easy changes to operating parameters, which allows a larger variety of formulations to be processed (13). It also guarantees better-mixing quality, both dispersive and distributive (18).

1.4.1.3. Multiple screw extruder (MSE) **-** Multi-screw extruders are composed of more than two screws, so depending on the number of screws, different assemblies are possible. MSEs allow a positive displacement flow of the material to be extruded, resulting in lower shear forces compared to SSE. As a result, less heat is produced, allowing thermolabile materials to be used (13).

1.4.2. Polymers characteristics for HME

The selection of materials used in the extrusion formulation should be determined based on several factors, including the nature and mechanical properties of the materials. These factors affect the processability of the extrusion, the stability of the final product and the type of drug release (3,13). As polymers are subjected to high pressures during extrusion, they need to be resistant and elastic. In addition, they must be thermally stable, miscible with the API and have an adequate melt viscosity (13). Various methods can be used to evaluate the properties

of the formulation, namely: differential scanning calorimetry (DSC), used to determine the melting temperature (Tm) and glass transition temperature of the materials; and thermogravimetric analysis (TGA), used to measure the temperature at which the materials degrade (3). Once these factors, it is possible to establish the optimum temperature at which extrusion should be performed, avoiding thermal degradation of the materials (3,13).

1.4.3. Advantages and Disadvantages of HME

HME has emerged as an appealing alternative compared to other conventional techniques due to its numerous advantages. It is a continuous and highly efficient process, with a relatively simple scale-up capability (3,15). Thought the procedure, no solvents are required. Organic solvents have the drawback of being toxic and contributing to environmental pollution. It also eliminates the need for water usage, resulting in a reduction of essential steps, such as drying. The intense mixing and agitation caused by the rotating screws facilitate the disintegration of particles suspended in the polymer, leading to a more uniform dispersion (15).

Despite the numerous advantages offered by HME, there are some limitations associated with this technique. HME processing requires the application of high processing temperatures that can lead to degradation of heat-sensitive materials. Consequently, the selection of the materials is limited to those that exhibit stability at elevated temperature (20).

1.5. Three-Dimensional (3D) Printing

3D printing, also referred to as additive manufacturing (AD), was introduced in the pharmaceutical industry in the 90s. This technology has proven to be highly promising for personalized medicine as it enables the automated fabrication of solid medications with various shapes and dosages (21–24). The 3D object is printed by depositing molten material layer by layer, following a predefined 3D model (25). The 3D model can be created using computer-aided design (CAD) software (26), which optimizes the desired geometry for the final product (22,23). This model is then converted into an STL (Standardized Triangular Language) file to be recognized by the printer. Lastly, the various printing layers are created and the object is manufactured by depositing the layers (24,27).

3D printing is a useful tool for the pharmaceutical industry since it has proven to be a flexible technique, capable of producing dosage forms with individually adapted compositions and release rates. The release profile of printed drugs can be altered by changes to the product's internal structure, geometry, selected polymers and drug loading. As well as being a low-cost

technique, it has high precision (28). However, some of the limitations include the slow printing speed, which makes this process ineffective for large-scale production (21).

Different 3D printing techniques solidify the layers using different methods. The techniques most used by the pharmaceutical industry are stereolithography (SLA), a laser-based system; inject powder bed, based on binder; and fused deposition modeling (FDM), based on thermal extrusion (3). However, FDM is the technique that has attracted the most interest due to its advantages, such as its low cost and ease of operation (21,27).

1.5.1. Fused Deposition Modeling (FDM)

FDM is the most commonly used 3D printing method for producing personalized dosage forms (24). In order to apply FDM 3D printing, it is necessary to prepare drug-loaded filaments for use in the printing process. Generally, the filaments used in the FDM technique are produced using HME technology (23). The filament is placed in the heated nozzle where it is melted and subsequently deposited layer by layer, solidifying in the form of a three-dimensional object (Figure 4) (18,21,22,26,29).

Several solid dosage forms can be formulated by FDM, including implants, tablets, capsules, vaginal rings and oral films, and devices such as mouth guards and catheters (18).

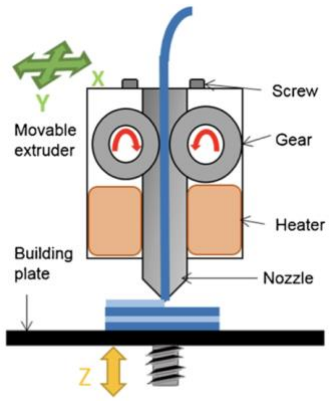


Figure 4. Scheme of the mechanism of Fused Deposition Modeling (FDM) 3D printing. (Adapted from (29))

Several inherent parameters of the FDM technology have to be controlled to ensure the quality of the final product, such as infill density, layer height, extrusion speed, and nozzle and bed temperatures. Additionally, filament properties play a crucial role in the successful execution of the printing, such as mechanical strength, flexibility, and thermal properties (thermoplasticity) (26,29). The process conditions in FDM differ from HME, particularly in

the contact time of the materials with the nozzle and the reduced extrusion shear stress. Consequently, printing process temperatures are normally higher than those used in the HME technology (26,24).

1.6. FDM-HME coupling

Using HME to produce filaments for FDM offers several advantages such as improved drug loading on the polymeric filament (3,23) and allows FDM to become a solvent-free technique. One of the biggest limitations to the application of the FDM is the necessity for the materials to have the required thermal and mechanical properties to support the high temperatures and tensile and compressive forces during printing. By using HME, it is possible to improve the characteristics of filaments with poor printability by, for example, efficiently mixing other excipients into the formulation, such as plasticizers. This way, HME makes it possible to increase the range of polymers that can be used for FDM (3,21).

Another advantage of this coupling is the possibility of a continuous process, with fewer steps and no intermediate steps (Figure 5). HME filaments, when used in FDM, do not require post-processing and the final product is obtained by FDM (3,17).

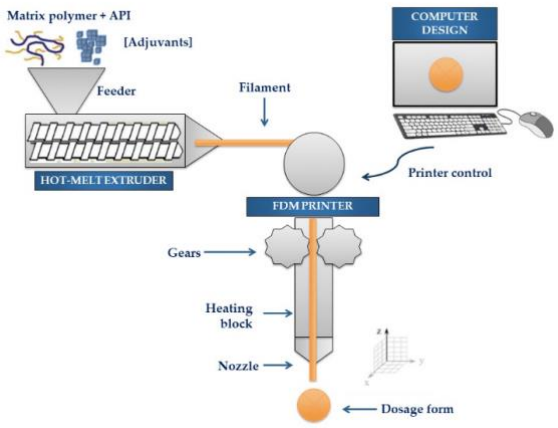


Figure 5. Schematic representation of the coupling of hot melt extrusion (HME) with fused deposition modeling (FDM) for pharmaceutical applications (26).

1.7. Formulation

1.7.1. Mebeverine hydrochloride

Mebeverine hydrochloride (MbH) is a drug employed as a musculotropic antispasmodic, primarily prescribed for managing irritable bowel syndrome and various other medical conditions (Figure 6). This drug is classified as class I by the BSC system, meaning that it has high solubility and permeability. Its plasma half-life is short, around 2.5 hours, so the rate of administration needs to be frequent. Binding to plasma proteins is 75% and, after oral administration, it is rapidly absorbed in the upper part of the gastrointestinal tract, with peak plasma concentration 1-3 hours after administration. Since it is a drug with the pharmacokinetic and physicochemical characteristics necessary for sustained release, it was selected as the model drug for this study (1,30).

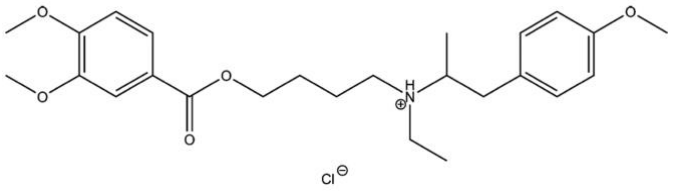


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Figure 6. Chemical structure of MbH.
(Adapted from (30))

1.7.2. Polymers

1.7.2.1. Hydroxypropylmethylcellulose acetate succinate (HPMCAS)

Hydroxypropylmethylcellulose acetate succinate (HPMCAS) is an enteric polymer composed by a mixture of acetyl and succinyl esters of cellulose (Figure 7) (31). This polymer is commercially available in three different grades with different particle sizes (fine, medium, and granular) and levels of chemical substitution, depending on the ratio of acetyl and succinyl groups (L, M, and H) (Table 2). Therefore, grade L has the highest proportion of succinyl groups, while H grade has a higher proportion of acetyl groups (12,31,32).

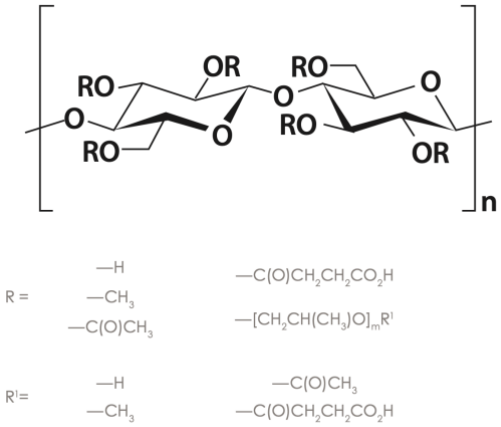

Figure 7. Structure of an HPMCAS molecule with the representation of the polymer chain composed of 2-hydroxypropoxy (-OCH2CH(CH3)OH), methoxy (-OCH3), acetyl (-COCH3) and succinyl (-COCH2CH2COOH) groups.

(Adapted from (31))

HPMCAS demonstrates pH-dependent solubility, with the pH solubility threshold varying according to the polymer grade: pH≥5.5 (L grade), pH≥6.0 (M grade), and pH≥6.5 (H grade) (Table 3). This polymer is suitable for filament production through HME technology due to its good physical stability, low hygroscopicity, relatively low Tg, and high degradation temperature (12). Furthermore, it exhibits thermoplastic properties, making it a promising candidate for formulating delayed and sustained-release dosage forms produced by FDM (12,32).

Table 2. *HPMCAS grades. (Adapted from* (31))

Grade	Acetyl Content	Succinyl Content	Methoxyl Content	Hydroxypropoxy Content
L	5-9%	14-18%	20-24%	5-9%
M	7-11%	10-14%	21-25%	5-9%
H	10-14%	4-8%	22-26%	6-10%

Table 3. *HPMCAS pH solubility and particle types. (Adapted from* (12,31)*)*

pH Solubility	Particle Type		
	Fine	**Medium**	**Granular**
≥5.5	AS-LF	AS-LMP	AS-LG
≥6.0	AS-MF	AS-MMP	AS-MG
≥6.5	AS-HF	AS-HMP	AS-HG

1.7.2.2. Polyvinyl alcohol (PVA)

Polyvinyl alcohol (PVA) is a polymer composed of vinyl acetate and vinyl alcohol with advantageous properties for pharmaceutical applications, including hydrophilicity, non-toxicity, non-carcinogenicity, and biodegradability (Figure 8) (30,32).

There are different grades available on the market which vary according to the degree of hydrolysis and molecular weight (MP), giving PVA different characteristics such as melting point, viscosity, and pH, among others. Parteck® MXP 4-88 is a grade of PVA designed with a specific particle size for suitability in HME applications (32). This thermoplastic polymer exhibits excellent thermal stability and compatibility with a wide range of APIs, enabling the development of stable formulations with high drug loads. For this reason, it is widely employed in the production of drug-loaded filaments by HME for use in fabricating immediate or sustained-release dosage forms through FDM (30,32).

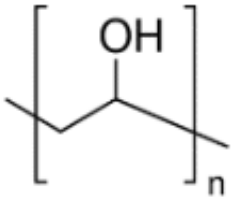

Figure 8. Schematic representation of the structure of polyvinyl alcohol (PVA) (26).

2. MATERIALS AND METHODS

2.1. Materials

Mebeverine hydrochloride ((RS)-4-(Ethyl[1-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate) was used as the model active ingredient. Poly (vinyl alcohol) (PVA, Parteck® MXP, Merck®- KGaA, Darmstadt, Germany) and hydroxypropylmethylcellulose acetate succinate (HPMCAS, Aqoat®, Shin-Etsu) in three medium particle size grades: AS-LMP, AS-MMP and AS-HMP were used as matrix forming polymer for the preparation of the filaments and 3D printed tablets. Hydrochloric acid solution and tri-sodium phosphate dodecahydrate (both from Merck® KGaA Darmstadt, Germany) were used to the dissolution media. The water used in all experiments was produced by the Elix 15UV Essential reverse osmosis system (Merck® KGaA, Darmstadt, Germany).

2.2. Methods

2.2.1. Characterization of the raw materials

2.2.1.1. Particle sizing (Laser diffraction) **-** The particle size distribution of the polymers (PVA and HPMCAS) was determined using a Mastersizer Malvern 3000 (Malvern, UK) equipped with an Aero S unit. The Fraunhofer approximation was considered as a diffraction model as the median particle size was expected to be above 50 μm. The D50 values, calculated by averages of 10 measurements taken from each sample, and the distribution spans were reported.

2.2.1.2. Flowability (Angle of repose) **-** To determine the angle of repose, a sample of powder was poured into a sieve container, mounted 70 mm above a round horizontal surface, 60 mm in diameter, so that the cone was formed. The measurement was made using the measuring rod attached to the angle and metric scale. In this way, the angle of repose corresponds to the maximum angle formed between the slope of the cone and the horizontal surface. The measurements were done in triplicate and an average value was calculated.

2.2.1.3. Contact angle measurements **-** The sessile drop technique was used to evaluate the wettability of the substances. The contact angle was measured using a DSA25 drop shape analyzer (Krüss, Hamburg, Germany). The drop of distilled water was generated by an automated syringe with a volume of 2 μL and deposited manually on the surface of the tablets prepared using the examined substances. The tablet preparation was performed with an Atlas^{TM} manual 15ton hydraulic press (Specac, Kent, UK). The contact angle was measured 6 times for each sample. For the measurement, the image immediately after the deposition of the drop on

the substrate was considered to minimize the effect of the water penetration into the compressed powder.

2.2.2. Preparation and characterization of filaments

2.2.2.1. Hot-melt extrusion **-** The extrusion processes for filament preparation were performed using a 12 mm in diameter, 40D long, co-rotating twin screw extruder (RES-2P/12A Explorer, Zamak Mercator, Skawina, Poland), equipped with a gravimetric feeder (MCPOWDER® Movacolor®, Sneek, The Netherlands), an air-cooled conveyor belt (Zamak Mercator®, Skawina, Poland), and a two-dimensional laser diameter gauge (LDM25XY, Mercury-Tech Co, Ltd., Zhengzhou, China).

Mixtures of Mebeverine HCL with polymer were prepared in a fraction of 40% (w/w) of drug and extruded through a 1.75mm die. A 100g batch of each formulation was extruded. The screw speed was set at 100 rpm. The temperature profiles were optimized according to the thermal properties of the different mixtures. The process was evaluated by monitoring various parameters such as torque, temperature of the individual heating zones, die pressure and motor loads (Table 4).

Table 4. *Extrusion conditions for the production of hot-melt extruded filaments*

Formulation	Torque (Nm)	Avg. Temperature (ºC)							
		Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Coupler	Die
MbH/PVA	2.95	100.36	158.21	159.57	159.33	159.18	159.03	160.37	159.86
MbH/AQOAT-HMP	4.18	100.00	133.82	134.61	134.42	134.32	134.19	135.01	135.01
MbH/AQOAT-MMP	4.30	100.00	133.81	134.60	134.44	134.34	134.19	135.02	135.00
MbH/AQOAT-LMP	3.82	99.99	133.88	134.59	134.43	134.34	134.14	135.04	134.92

2.2.2.2. Evaluation of filament's physical properties (diameter and mechanical properties) **-** The filament's diameter was measured in-line using a two-dimensional laser gauge (LDM25XY, Mercury-Tech Co., ltd., Zhengzhou, China) to optimize the extrusion process parameters.

To evaluate the mechanical properties, an elongation test was performed using an EZ-SX tensile tester (Shimadzu®, Kyoto, Japan) with specially designed grips. Six pieces of filament from each formulation were randomly selected for measurement. The total length of

each piece was 130 mm, with the measurement length being 100 mm. After selection and diameter measurement, the pieces were placed in the grips of the tensile tester and stretched to failure. The hardness and elasticity of the filaments were determined.

2.2.2.3. Determination of drug content **-** Three randomly selected pieces of each extrudate were accurately weighed to determine API content. The samples were placed in conical flasks filled with 50 mL phosphate buffer, stirred at 37º for 24 h in a Memmert® water bath (WNB 22, Schwabach, Germany), and filtered through CHROMAFIL® Xtra CA45/25 syringe filters. The concentration of Mebeverine HCL was determined spectrophotometrically at 264 nm using a Jasco V-530 spectrophotometer (Tokyo, Japan). The specificity of the analytical method was checked.

2.2.3. Preparation and characterization of tablets

2.2.3.1. Tablets design and surface analysis **-** The tablets were designed with basic shape using Blender 2.90 software (Blender Foundation, Amsterdam, The Netherlands). Tablets containing PVA were created based on the design of oblong tablets 20 mm long and 10 mm wide. The design of the AQOAT tablets was oblong tablets of 28 mm in length and 10 mm in width. Then, the designs were exported to the Voxelizer slicing software (version 1.4.18, Zmorph S.A., Wroclaw, Poland) to create accurate tablet models and calculate the amount of filament needed to print the tablets. The settings applied for the slicing process were optimized to obtain 200 mg API in each formulation, according to the drug loading in the filament and filament diameter. The filament diameter varied between 1.65 mm and 1.80 mm according to the measured diameter of each filament, and the layer height was 0.15 mm.

2.2.3.2. Preparation of 3D printed tablets **-** The tablets were manufactured using a ZMorph® 2.0 S FDM 3D printer (Wroclaw, Poland) equipped with a commercially available 1.75 mm printhead with a 0.2 mm nozzle. The printing parameters, such as nozzle and printing table temperature, and printing speed were adjusted to the different formulations. Differences between actual and theoretical filament diameters were compensated by changing the settings in the cutting software. The molten filaments were deposited through the print head onto the printing table, covered with COROPad™ adhesive pad (HMF Chemicals, Grodzisk Mazowiecki, Poland). Depending on the composition of the silage, the printing temperature varied between 150 and 170°C. The tablets were weighed after printing and stored at room temperature.

2.2.3.3. Dissolution test **-** Dissolution studies were performed for tablets based on all formulations to determine the release of MbH using an SR8-Plus Dissolution Test Station

apparatus (Hanson Research, Chatsworth, CA, USA). The tests were performed on 3 tablets from each series. The temperature was maintained at 37 ± 0.5°C and the paddle speed was set to 50 rpm. To simulate the absorption of the drug in the GI tract in a simplified way, the following biorelevant dissolution media and residence times were used, with sequential pH changes: initial release of MbH was performed in a 0.1N HCl solution at pH 1.2 (simulated gastric fluid) for 2 hours, followed by a phosphate buffer at pH 6.8 (simulated intestinal fluid) for 10 hours. The dissolution media were prepared according to the European Pharmacopeia (Ph. Eur.). Fifteen samples were taken at predetermined time points and then analyzed spectrophotometrically with a Jasco V-530 UV-VIS spectrophotometer (Tokyo, Japan) equipped with a 2 mm optical path flow-through cuvette. The samples were analyzed at λ = 264 nm, with six repetitions (n=6), and the results represent averages with their corresponding standard deviations (StD).

2.2.4. Thermal analysis

2.2.4.1. Thermogravimetric analysis (TGA) **-** The thermal stability of each component of the formulations, active substance and polymers, was evaluated using a Mettler TG50 thermogravimetric analyzer (Mettler-Toledo, Greifensee, Switzerland) connected to a Mettler MT5 balance (Mettler-Toledo, Greifensee, Switzerland). The samples were placed in a standard 100 µL aluminum TGA container and placed in an oven under a nitrogen purge of 60 ml/min and heated at 10 K/min over a temperature range of 303 K to around 723 K. The degradation of the samples was determined by the percentage weight loss over the temperature range studied.

2.2.4.2. Differential scanning calorimetry (DSC) **-** The thermodynamic properties of the raw materials and filaments were analyzed using the DSC 1 STAR system (Mettler-Toledo®, Greifensee, Switzerland). The apparatus was equipped with an HSS8 ceramic sensor (heat flow sensor) with 120 thermocouples and liquid nitrogen cooling attachment. Calibration of the instrument's temperature and enthalpy was performed using zinc and indium standards. Samples were measured in 40 µL aluminum crucibles with pins in a nitrogen atmosphere. All measurements were performed under constant flow of 10 mL/min nitrogen and heating rate 10 K/min and all samples were investigated at temperatures between 280 K and 420 K. A sample of amorphous MbH was also prepared by heating the substance 10ºC above its melting point and then allowing it to cool to the test temperature. Pure crystalline MbH and amorphous MbH were used as controls.

3. RESULTS AND DISCUSSION

3.1. Powders characterization

Prior to the extrusion process, tests (particle size distribution, wettability and angle of repose) were carried out on the individual powders (API and polymers) of the blends (Table 5).

The average particle size of each powder is represented by D50. HPMCAS-LMP was the powder with the largest average particle size, at around 337 μm. The average particle sizes of the different grades of HPMCAS were close to 300 μm, which is in accordance with the values presented in the literature (33). In contrast, PVA had the smallest average particle size, at 58.6 μm. The polymers showed lower span values (no more than 1.97) in comparison with MbH (2.68). According to the Mastersizer 3000 User Manual, the lower the span value, the narrower the particle size distribution and therefore the more uniform the powders (34).

Contact angle measurements were performed for the powders immediately after the water droplet contacted the surface of the compressed powder. These measurements allow the hydrophilicity or hydrophobicity of the powders to be verified.

Compressed PVA had the highest contact angle (72.81 ± 8.35 °), while MbH was the compressed powder with the lowest contact angle (42.93 ± 6.61 °). All the contact angles were less than 90°, so all the powders proved to be hydrophilic under the test conditions (35).

However, it should be taken into account that the compression of powders can cause various complications, for example, the creation of pores with different structures and roughness on the surface, which can affect the absorption and spreading of the droplets (36). Therefore, to ensure that these effects do not have a significant influence on the wettability test, more research is needed (37).

Angles of repose were also measured for the various powders, with the exception of MbH since this is an extremely cohesive powder and is therefore practically non-fluid (38). This parameter is related to interparticle friction or resistance to movement between the particles, so it is commonly used to evaluate the force between the particles. It is therefore the simplest method for expressing the flowability of powders (39). All the polymers had high contact angles, with PVA's (42º) being the highest compared to the other polymers (33.67º-39º). However, all the polymers showed poor flowability (1,40).

Table 5. *Properties of the formulation powders.*

Substance	Particle Size Distribution				Contact angle ± StD (º)	Angle of repose
	D_{10} (µm)[1]	D_{50} (µm)[1]	D_{90} (µm)[1]	Span[2]		
MbH	3.78	10.8	32.7	2.678	42.93 ± 6.61	-
PVA	17.1	56.8	129	1.968	72.81 ± 8.35	42.00
AQOAT-HMP	79.2	273	556	1.747	68.56 ± 3.46	36.33
AQOAT-MMP	131	297	579	1.512	72.15 ± 6.08	33.67
AQOAT-LMP	152	337	651	1.485	71.80 ± 4.18	39.67

[1] D_{10}, D_{50} and D_{90} refer to the diameter at which 10%, 50% and 90% of the particles, respectively, are smaller than this diameter.

[2] Span value = $(D_{90} - D_{10})/D_{50}$

3.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was used to study the thermal stability of the different materials used to produce the tablets (Figure 9). This analysis is a prerequisite for determining the degradation temperature of the API and the polymers which, in turn, makes it possible to define the processing temperatures for extruding and printing the tablets (41). Therefore, both the extrusion process and the 3D printing of the tablets of each formulation were carried out below the degradation temperatures of the polymers to avoid their decomposition. MbH loses mass through thermal degradation at around 500 K and decomposes at around 600 K. The polymers decompose at higher temperatures than the active substance. AQOAT decomposed at temperatures of around 550 K, values close to those described in other publications (22,31). PVA decomposed in two phases, which is consistent with the literature description of the decomposition of this polymer. The first decomposition phase occurred at temperatures of around 570 k and was due to the degradation of the main chain of the PVA membrane (42). The second decomposition phase, at around 663 K, can be attributed to the carbonation of the polymer matrix (42). The decomposition of PVA was also faster than the other polymers. Based on these results, the extrusion process temperature was established at around 450 K, as this is the temperature where the substances showed thermal stability.

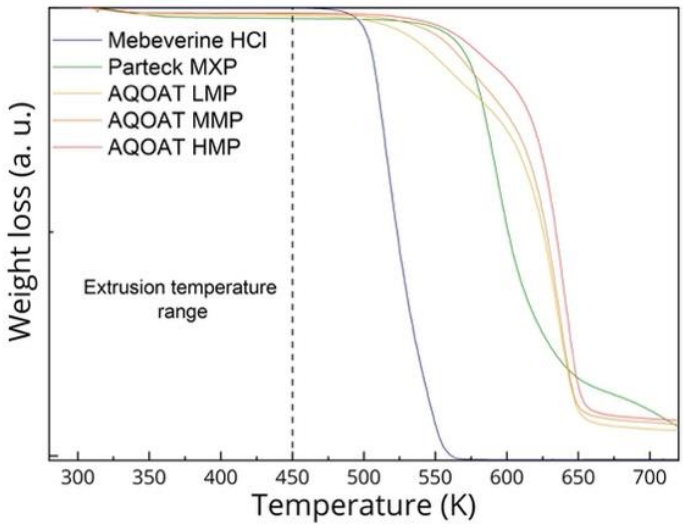

Figure 9. Thermographic analysis (TGA) graph of mebeverine HCl and polymers Parteck MXP, AQOAT-LMP, AQOAT-MMP and AQOAT-HMP.

3.3. Differential Scanning Calorimetry (DSC)

To evaluate the effect of the polymers used on the physical stability of MbH in filament forms, the extruded materials from different formulations were measured by non-isothermal Differential Scanning Calorimetry (DSC) (Figure 10). Analysis of the thermogram of pure crystalline MbH revealed an endothermic peak corresponding to the melting point of the active substance at around 410 K. The thermograms of the mixtures showed no endothermic peaks corresponding to the melting of MbH, which confirms its amorphous state in the polymer matrix (9,43). MbH (2 runs) also exhibited no endothermic peaks, confirming its amorphous state (44). For the thermograms of all the mixtures and amorphous MbH, two endothermic events were observed: the first event corresponded to the glass transition temperature (Tg) of MbH, and the second to the evaporation of water. The presence of the last can be concerning, as it can affect the stability of the filaments since water can degrade the active substance or affect the physical properties of the polymer (21). Its presence can be related to the time and storage conditions of the filaments or the formulation process, including the properties of the API and the properties of the other components of the matrix. For all formulations, only one Tg was verified, indicating a single-phase system for each formulation (single-phase amorphous solid dispersion) (9). The midpoint of the Tg increases between the different mixtures as follows: PVA < AQOAT-LMP < AQOAT-MMP < AQOAT-HMP. The Tg of the filament with PVA was lower compared to the Tg value of MbH, which can indicate that the PVA exerted a plasticizing effect (45). The highest Tg values were obtained for the various

grades of AQOAT, which were between 310 K and 330 K. These values were lower than the ones reported in the literature so it was not possible to confirm the purity of the material during the measurement (44).

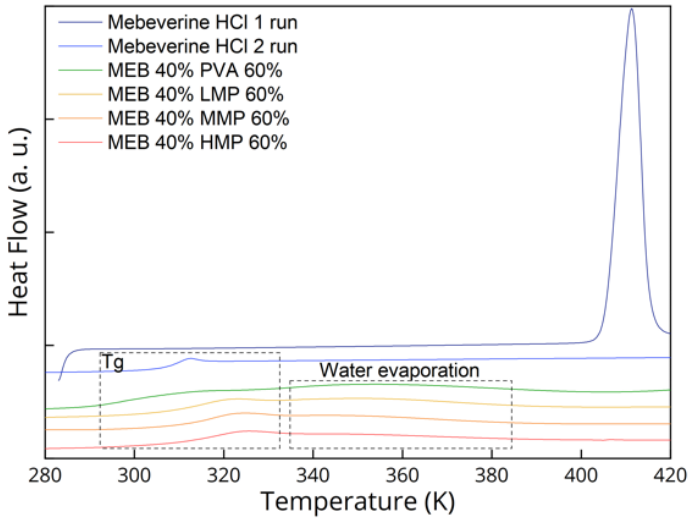

Figure 10. Thermograms (DSC) of crystalline (1 run) and amorphous (2 run) mebeverine HCl, and the MEB 40% PVA 60%, MEB 40% LMP 60%, MEB 40% MMP 60% and MEB 40% HMP 60% filaments.

3.4. Processability of hot-melt extrusion and characteristics of the filaments

The aim of the extrusion process was to prepare drug-loaded filaments with the attributes requires for FDM 3D printing. After completing the powder characterization and determining the optimal processing temperatures, the formulations were extruded. PVA (60% w/w) was chosen as the hydrophilic matrix-forming polymer for the preparation of one of the drug-loaded filament formulations. For the remaining three filament formulations, three grades of HPMCAS (LMP, MMP, and HMP) (60% w/w) were selected as enteric polymers. In all filament formulations, MbH (40% w/w) was chosen as the model drug.

The process continuously and smoothly, and the process parameters were carefully controlled to ensure the reproducibility and quality of the filaments. One of the critical parameters to consider throughout the extrusion process is the torque, as it represents one of the main limitations of this process. It remained low as a result of the optimization of the barrel temperature. The torque value was lower for the filaments with PVA, increasing in the filaments containing AQOAT. Optimization of the temperature profiles also made it possible to produce filaments with good durability and smooth characteristics. All filaments obtained

were opaque and creamy yellow in color. Table 2 summarizes the properties of the filaments obtained. The filaments produced showed good quality, i.e., the surfaces were smooth, and the content and uniformity of mebeverine in the filaments was satisfactory, close to the established value.

The filaments were evaluated for their mechanical properties, i.e., the tensile strength of the filaments and their elasticity were evaluated to ensure that the filaments had the critical quality attributes required for the 3D printing process (Table 6). The filaments containing PVA demonstrated higher mechanical strength (30.16 MPa) compared to the various grades of AQOAT. The lowest mechanical strength was LMP (11.58 MPa), and the others showed intermediate mechanical strengths. The elasticity of the filaments was also measured, expressed as the modulus of elasticity. The filaments containing AQOAT-LMP and PVA showed a lower value of elastic modulus (366.91 and 1534.48 MPa, respectively) compared to the AQOAT-HMP and MMP filaments (2212.43 and 2350.92 MPa, respectively. This therefore indicates that the filaments containing PVA and AQOAT-LMP showed higher elasticity.

All filaments showed the characteristics and quality required to be printed by the ZMorph® 2.0 S FDM 3D printer.

Table 6. *Hot-melt extruded filaments characteristics.*

Formulation	API content [1] ± StD (%)	Tensile strength [2] ± StD (MPa)	Elastic modulus [2] ± StD (MPa)
MebH-PVA	32.98 ± 2.45	30.16 ± 2.80	1534.48 ± 154.20
MebH-HMP	35.16 ± 2.85	19.72 ± 4.13	2212.43 ± 161.60
MebH-MMP	38.43 ± 0.31	22.76 ± 9.30	2350.92 ± 65.48
MebH-LMP	36.16 ± 3.44	11.58 ± 2.48	366.91 ± 107.27

[1] n=6; [2] n=2

3.5. 3D printing process

Different mechanical properties were observed between the different filament formulations; however, all filaments were printable. The required API dosage to be achieved in the tablets was 200 mg. Tablets with slightly different API masses were obtained, however these differences were always less than 10 mg, which within ± 10% threshold of the required value (46). Table 7 summarizes the attributes of the printed tablets. Three tablets from each filament series were printed.

The HPMCAS filaments showed relatively low mechanical strength and flexibility, which caused them to break during the printing process by the feeding mechanisms. This

problem was overcome by preheating the filaments, which made them softer and more flexible, and by releasing the screws so that they would not be so tight. However, due to the loosening of the screws, there was less uniformity in the deposition of the extruded material during the printing process which led to greater differences between the masses of the tablets and, as a result, there were higher StD values with the mass differences between the tablets being higher. The PVA filaments showed very good printability and the printing went smoothly.

Table 7. *Attributes of 3D printed tablets.*

Formulation	Printing temp. [1] (ºC)	Tablets' mass [2] ± StD (mg)	MebH dose [2] ± StD (mg)
Meb-PVA	170/60	625 ± 12.53	206.25 ± 4.13
MebH-HMP	170/60	534.33 ± 20.50	205.34 ± 7.88
MebH-MMP	170/60	581.33 ± 19.86	204.40 ± 6.98
MebH-LMP	170/60	570 ± 15.62	206.11 ± 5.65

[1] nozzle temp./printer table temp.; [2] n=3

3.6. Dissolution studies

The dissolution rate of the API depends not only on the disintegration time, but also on the solubility of the drug and the properties of the excipients (46). The dissolution profiles of all the mebeverine tablets with different polymers are shown in Figure 11.

The data from this test showed that for mebeverine tablets containing HPMCAS as a polymer, there was a low release (<10%, at pH 1.2, 2h of testing), increasing only in phosphate buffer (pH 6.8). This dissolution rate fulfills the USP criteria for delayed-release formulations (less than 10% of the drug released in the first 2h at pH 1.2). The low dissolution rate at pH 1.2 is consistent with the characteristics of these polymers, which are insoluble in acidic media and soluble at pHs above 5.5, 6.0, and 6.5, depending on the L, M, and H grades, respectively (31). Different dissolution profiles were observed between the different grades of HPMCAS, in the following order of release length: AQOAT LMP > AQOAT MMP > AQOAT HMP. Therefore, it can be observed that the grade of this polymer plays an important role in the dissolution kinetics. After 12 hours of testing, almost 100% of the MbH was released from the AQOAT LMP tablets. AQOAT MMP and AQOAT HMP tablets, however, took 12 hours to release around 50 and 40% of MbH, respectively.

In contrast, the formulation containing the hydrophilic polymer, PVA, exhibited a high dissolution rate in acidic media (>90% in the first 2 hours of testing). In addition,

supersaturation was maintained during the following 10 hours of testing. This polymer has pH-independent solubility and several studies have reported that PVA forms a hydrogel system through which dissolution occurs by erosion mechanisms (23,47). The dissolution test revealed that the polymers were suitable for the development of a sustained-release dosage form.

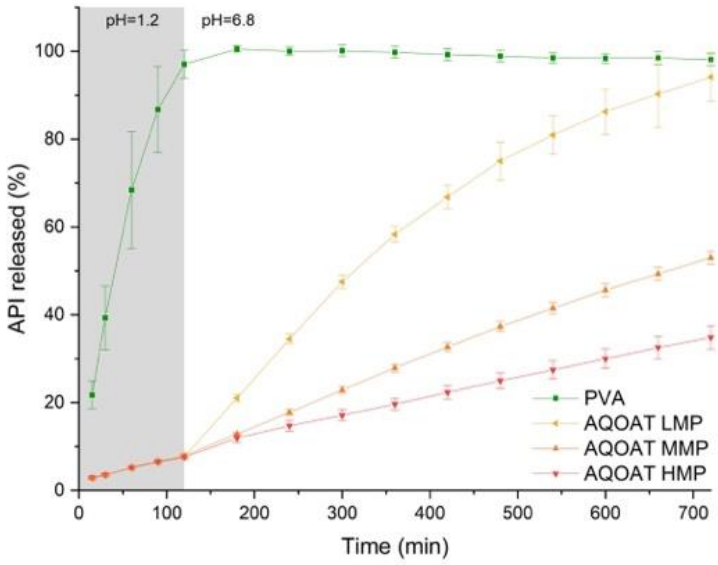

Figure 11. Drug dissolution profiles of mebeverine HCl released from 3D printed tablets, at pH 1.2 (2h) and pH 6.8 (10h). (n=3).

4. CONCLUSION

This study has proven that combining HME with FDM 3D printing is an efficient and economical alternative for producing sustained-release drug delivery systems.

The ease with which formulations can be adapted using different polymers to obtain the desired profile of the final product using HME makes this technique very advantageous compared to conventional techniques. For this reason, this technique is very useful for the production of drugs and other personalized pharmaceutical forms.

The process of extrusion was smooth and filaments loaded with MbH were produced in an amorphous state within the polymer matrix. The filaments produced by extrusion had acceptable physical and mechanical characteristics for the printing process.

The tablets were successfully manufactured using the filaments and FDM 3D printing technology. The PVA formulations exhibited a higher release rate than the HPMCAS formulations, and in acidic media, with a sustained release profile over the following 10 hours. The HPMCAS formulations also showed a delayed release profile, releasing a very small amount of MbH in acidic media and increasing the release rate only at pH 6.8. This way, this polymer demonstrated the necessary characteristics for gastroretentive formulations, allowing the tablet to pass through the stomach without releasing a considerable dose of the drug.

In conclusion, this work demonstrates that the manufacture of sustained releases of water-soluble drugs is possible using the HME and 3D FDM printing methods. Furthermore, by choosing the polymers used in the formulation, it is possible to modify and control the release profile, producing tablets with gastroretentive release.

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