Universidade de Lisboa

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3D printing of personalized medicines for paediatric use

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Resumo

Sendo bastante heterogénea, a população pediátrica divide-se em diferentes faixas etárias, tendo em conta os distintos estados fisico, cognitivo e psicossocial durante o seu desenvolvimento. Aqui, evidenciam-se as diferenças farmacodinâmicas e farmacocinéticas que têm impacto na terapêutica medicamentosa no que diz respeito às substâncias activas mas também aos excipientes.

Consequentemente, a terapêutica medicamentosa em pediatria pode ser um verdadeiro desafio. Primeiramente, é frequente a inadequabilidade ou até mesmo, a inexistência das doses e das formas farmacêuticas disponíveis no mercado. Adicionalmente, as doses e as formas farmacêuticas disponíveis podem não ser adequadas e usadas de forma transversal em pediatria. Por outro lado, os elevados custos bem como, as questões éticas associadas aos ensaios clínicos e, ainda, o facto de estes terem de ser realizados nas distintas faixas etárias, leva a que continue a haver obstáculos para colmatar essas mesmas lacunas existentes na farmacoterapêutica pediátrica. Tal, leva à necessidade recorrente do uso *off-label*, isto é, a utilização de um medicamento para outros fins que não os descritos na sua Autorização de Introdução no Mercado. Contudo, as crianças não são adultos em miniatura e, portanto, o uso *off-label* pode acarretar graves consequências.

Por sua vez, é nos Serviços Farmacêuticos Hospitalares onde o uso *off-label* é frequentemente utilizado para contornar o desafio da farmacoterapêutica pediátrica e onde é cada vez mais urgente preencher as lacunas existentes nesse campo de acção, sendo fulcral adoptar sistemas que permitam a personalização da terapêutica, particularmente importante em populações especiais como é o caso da pediatria devido às suas necessidades específicas.

Com este objectivo, têm surgido tecnologias promissoras como a impressão tridimensional (3D) que inclui diversas técnicas apoiadas por software onde é inserida a informação necessária à impressão da forma sólida personalizada. Ao contrário do que é expectável, como estes sistemas permitem imprimir formas farmacêuticas sólidas com dimensões muito reduzidas e formas variadas, é possível anular a disfagia inerente às crianças. Ainda assim, tem-se estudado a hipótese de imprimir formas orodispersíveis. Para que a implementação de um sistema de impressão 3D em Serviços Farmacêuticos Hospitalares possa ser feita com sucesso, é fundamental averiguar e adaptar a melhor técnica que permita a impressão de

medicamentos personalizados e adequados às preferências e particularidades de cada criança, sem custos dispendiosos para o Estado e com a propensão para aumentar a adesão à terapêutica.

Também os excipientes têm um papel essencial para que a impressão do produto final seja realizada com êxito. Neste sentido, os excipientes devem reunir as características físico-químicas e toxicológicas que se adequem não só às condições de impressão mas também às faixas etárias a que os medicamentos se destinam. Não obstante, na impressão 3D é possível melhorar factores que, geralmente, promovem a falência da terapêutica em idades jovens e, nesse âmbito, os excipientes poderão funcionar como adjuvantes no melhoramento das características organolépticas, especialmente a palatabilidade.

Contudo, apesar do seu grande potencial, ainda existem grandes obstáculos na sua aplicação uma vez que, a impressão 3D de formas sólidas para uso oral dá agora os seus primeiros passos e, como tal, ainda várias questões procuram ser respondidas nomeadamente questões do ponto de vista regulamentar e legislativo, existindo uma enorme lacuna no que diz respeito ao controlo de qualidade dado que, ainda não existem documentos nesse sentido.

Palavras-chave: Medicamentos personalizados; impressão 3D; pediatria; excipientes; segurança; controlo da qualidade

Abstract

Paediatric population is quite heterogeneous, being subdivided into different age groups, attending to the the different physical, cognitive and psychosocial states during its development.

In that way, paediatric pharmacotherapy can be a real challenge. First, there is often the inadequacy or even the default of doses and pharmaceutical forms available on the market. In addition, doses and available pharmaceutical forms may not always be suitable and used in the different paediatric age subgroups in a transversal way. On the other hand, the high costs as well as the ethical issues associated with clinical trials, and the fact that they have to be carried out in different age subgroups, mean that there are still difficulties in filling the gaps existent in paediatric pharmacotherapy. This leads to the recurrent off-label use, that is the use of a medicine outside its purposes described in its Market Introduction Autorization. However, children are not miniature adults and therefore off-label use can have serious consequences from reactions associated with toxicity and may even, in more serious cases, result in death.

At the Hospital Pharmacy Services, it is increasingly urgent to fill in the gaps in pediatric pharmacotherapy, and it is crucial to adopt systems that allow personalization of therapy, particularly important in special populations such as pediatry due to their specific needs. Thereby, promising technologies such as 3D printing have emerged. 3D printing includes several techniques, supported by software, being fundamental to the success of its implementation in Hospital Pharmaceutical Services, to evaluate and adapt the best technique that allows the printing of personalized medicines and adapted to the preferences and particularities of each child with the propensity to increase therapy compliance.

Also the excipients have an important role so that the printing of the final product is accomplished successfully. Thus, the excipients must have certain physico-chemical characteristics not only to be adequate to the printing process conditions but also to be safe to the age subgroups to which the medicines are intended due to the toxic potential of some excipients in some age subgroups. However, in 3D printing the excipients may also function as adjuvants in the masking or enhancement of organoleptic characteristics, especially palatability. The last one is one of the main causes of therapeutic failure in paediatric, and it is

important to analyze excipients and techniques that can be associated with 3D printing in order to improve it.

However, despite its great potential, there are still major difficulties since 3D drug printing is now taking its first steps. The difficulties are mainly related to regulatory and legislative issues, and there is a huge gap with regard to quality control of pharmaceutical forms produced by 3D printing since there are no documents to this effect.

Keywords: Personalized medicines; 3D printing; paediatry; excipients; safety; quality control

Abbreviations

3D	Three dimensional
ABS	Acrylo-nitrile butadiene styrene
ADI	Average Daily Intake
AM	Additive manufacture
API	Active Pharmaceutical Ingredient
BPCA	Best Pharmaceuticals for Children Act
CAD	Computer-aided design
CARS	Coherent Anti-Stokes Raman Scattering
CD	Cyclodextrins
CIJ	Continuous inkjet printing
DBP	Dibutyl phthalate
DEP	Diethyl phthalate
DOD	Drop-on-demand printing
DSC	Differential scanning calorimetry
EDTA	Ethylenediamine tetraacetic acid
EMA	European Medicines Agency
EVA	Ethylene vinyl acetate
FDA	U.S. Food and Drug Administration
FDAMA	FDA Modernization Act
FDM	Fused deposition modelling
HME	Hot Melt Extrusion
HPLC	High performance liquid chromatography
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methyl cellulose

IER	Ion Exchange Resins
IR	Infrared
MVA	Multivariate data analysis
NIR	Near-infrared spectroscopy
ODT	Orally disintegrating tablet
PAM	Pressure-assisted microsyringes
PAT	Process analytical technology
PCL	Polycaprolactone
PDMS	Polydimethylsiloxane
PEG	Polyethylene glycol
PEO	Polyethylene Oxide
PLA	Polylactic acid
PMMA	Poly methyl methacrylate
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
RP	Rapid Prototyping
RTD	Residence Time Distribution
SEM	Scanning electron microscope
SLS	Selective laser sintering
SLA	Stereolithography
SSNMR	Solid state nuclear magnetic resonance
Tg	Glass transition temperature
Tm	Melting temperature
TPGS	D-α-tocopheryl PEG 1000 succinate
TRPM5	Transient Receptor Potential Member 5

TRS	Transmission Raman Spectroscopy
VA	Vinyl Acetate
XRPD	X-ray powder diffraction
WAI	Wide Angle Illumination

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1 Introduction

In the 1960s children were considered as “therapeutic or pharmaceutical orphans” (1). Nowadays, this widely heterogeneus and vulnerable population which corresponds to approximately 25% of the EU’s total population (2) continues to face some barriers from the pharmacotherapeutic point of view. These barriers include the widespread lack of medicines suitable for paediatric use and the hindrances associated to the dificulties inherent to the realization of clinical trials in children. Consequently, off-label use is recurrent with all the consequences that this may entail with regard to safety and efficacy.

However, several technologies have emerged in order to simplify and turn the process of adapt medicines and their administration to paediatric population a process safer, more effective and more convenient for both children and caregivers. These technologies enclose 3D printing which in turn includes several different systems since Printing-Based Inkjet Systems and Stereolithography (SLA) or even Nozzle-Based Deposition Systems such as Fusion Deposition Modelling (FDM) and Pressure-assisted microsyringes (PAM) (3). Is important to refer other techniques that may be act as adjuvants to some systems as for example Hot Melt Extrusion (HME) that produces polymeric filaments that will be the point of start to FDM. Frequently, PVA is the polymer choosed since it is safe and has suitable properties (3,4).

Thus, the aim of the present work is to consider all of these systems and to evaluate firstly, which one may be more effective to answer to the main problems that paediatric pharmacotherapeutic involves such as: dose accuracy and flexibility, organoleptic characteristics, taking into account individual preferences of each children. Then, is pretended also to assess which system may be more suitable to implement in portuguese hospitals pharmaceutical services. Nevertheless, to that may be possible there are still several gaps to be filled with regard to regulatory and legislative issues. Also, to ensure the best quality, safety and efficacy of 3D printed medicines is crucial to establish quality control processes, systems and processes parameters and the excipients that may be used without compromising their stability and role. These issues will be also target of study of this work.

2 Personalized medicines: a necessity in paediatric population

According to EMA and to FDA, paediatric population is defined as the individuals who has less than 18 years old and can be subdivided into five groups based on physical, cognitive, and psychosocial factors (Table 2.1) (5).

Table 2.1 Paediatric population subgroups (5).

Preterm newborn infants	Born before gestation term
Term newborn infants	0 to 27 days
Infants and toddlers	28 days to 23 months
Children	2 to 11 years
Adolescents	12 to 16-18 years (dependent on region)

European Commission's proposals refer that between 50% to 90% of the medicines approved are administered to children even though they were not been tested or authorised for paediatric use (2). The gap existent in medicines specially developed for pediatric use leads to that medicines are used outside of the specifications described in their licence with regard of formulation, indications, contraindications or age, constituting off-label and off-licence use with an incipient or even without any backup about bioavailability, stability and safety studies in paediatric population. Also, dose errors may occur: whether overdosage or underdosage which may direct to toxicity and treatment failure, respectively (6,7). Some alternatives to achieve the pretended dose may include dispensing of multiple low dose tablets to obtain a higher dose or splitting larger sized tablets. However, the last one may cause dose variations due to uneven weight distribution after splitting and may has an impact on release kinetics, particularly for controlled or extended release formulations or in case of tablets with a coating system APIs may be release prematurely (8). Ideally, dose adjustment must be done attending to clinical trials results previously. However, for the medicine be approved to paediatric use is necessary to realize clinical trials and the medicine must obbey to some criteria from the point of view of aroma, taste, texture, shape and colour. Furthermore, clinical trials realization are difficulted by ethic concerns, the low prevalency and incidency of specific pathologies in

children (orphan diseases) and development and age heterogeneity requiring different study groups. There is no financial return to pharmaceutical industries that justify such investment (9–11). In that way, emerging the FDA Modernization Act (FDAMA) of 1997 and the Best Pharmaceuticals for Children Act in 2002 (BPCA) with the aim to incentive pharmaceutical industries to realize clinical studies in paediatric population by given them exclusivity incentives and a 6 months patent extension for performing additional clinical studies in paediatric population. In 2007, was implemented also in Europe with the Prescription Drug User Fee Act and Food and Drug Administration Amendments, paediatric regulation governing the development and authorization of medicines for pediatric use in which medicines development should also include additional clinical bridge studies to assess pharmacokinetics and pharmacodynamics differences between adults and children (1,12).

2.1 Paediatric target-group for 3D printing personalised medicines

Solid dosage forms when compared with liquid ones have several advantages: stability, convenience, greater acceptability of APIs whose taste is not possible to mask in liquid forms and offer the possibility to incorpore a film or sugar coats or even both at same time to improve palatability. Also, it is possible to develop modified-release formulations which in liquid formulations is technically challenging as similar to APIs with poor solubility. In addition, liquid forms often require the administration of large volumes which may compromise therapy compliance and nonsterile oral powder after reconstitution besides its close expiration date may cause stability or safety risks, depending on quality water used. However, the use of liquid dosage forms remain the first choice for young children since they allow easily the dose personalisation only by adjusting the volumes administered and allow to overcoming swallowing difficulties which can exist with solid dosage forms (6,8,13). Thus, a single formulation can not be established as ideal across paediatric population but some important considerations must be taken into account: convenience, stability, appelative, minimal frequency of administration (easy and reliable), minimal impact and stresse during treatment, minimum or non-toxic excipients and their costs and commercial viability must be favourable (13).

EMA created a matrix (see A1) which matches different age groups, routes of administration and dosage forms according to the answers to questionnaires shown to about 40 persons from several European countries, including paediatricians, pharmaceutical scientists and parents.

The matrix shall be interpreted as follows: for early ages, the code observed in the matrix has to be interpreted with respect by the applicability of the route and the dosage form from 1 to 5 attending to the ascending order of applicability from 1- not applicable to 5- best and preferred applicability. Still, for older children, due to the development of the capacity to swallow solid dosage forms, almost all dosage forms might be applicable, but with increasing age the children can take decision and have preferences and therefore the code has to be interpreted taking into account acceptability from 1 to 5 by ascending order from 1- not accepted to 5- dosage form of choice. That is, from left to the right columns of the matrix occur transition from the applicability to the preference. This matrix pretends to act as a general guide of acceptability of the various dosage forms depending of the age. Due to that generality, obviously is necessary more research about that question (13).

The capacity to use different dosage forms is extremely variable and not only depends on age but of all adjacent factors such as physical development and coordination, psychological development and even their training and the support that they receive from healthcare professionals and caregivers (13). Observing the matrix and based on evidences it may possible to suggest that children starting from school age, around 6 to 11 years old can be able to swallow and accomplish drug therapy with solid forms such as capsules and tablets depending on their size. This is merely indicative since children around 3 to 5 years old with long-term illness requiring continuing medication may be supported and trained to take solid dosage (12–14). It was already demonstrated by Thomson et al., that pre-school children (since 2 to 5 years old) are able to swallow mini-tablets with a diameter less than 3 mm diameter with some water. These mini pharmaceutical forms can be consumed with or without water and can also be mixed with some food (12). Nevertheless, may be advantageous to administrate whenever possible orally disintegrating tablets (ODTs) because they disperse or melt within seconds just in contact with saliva, allowing to overcome swallowing problems being easily and comfortably administered (12).

3 3D printing: a promising tool for paediatric personalized medicines

3D printing technologies, also recognized as additive manufacturing (AM) are an important rapid prototyping (RP) tool that has been playing a prominent role in terms of innovation and completely revolutionize many industries (3,11,15,16). Currently, biomedical and pharmaceutical sectors are embracing 3D printing as a promissing technology (15). Highlighting pharmaceutical field, these technologies have gain a huge attention by the pharmaceutical field due to their capacity of possibly attend to some shortcomings that still challenge it such as: the conventional manufacturing processes with the employment of several steps (mixing, granulation, drying and others) in large-scale manufacturing make difficult to have the flexibility needed to achieve personalized dosage forms with doses suitable to each patient (8). 3D printing may act as a crucial tool to partner personalized medicines and therapeutic compliance by embracing patient-tailored formulation (17,18). Personalized medicines allow to increase therapeutic success because medicines are adjusted to pharmacogenomics, anatomical and physiological particularities (19,20). In addition, its versatility and flexibility allow to modify the shape and size of the dosage form according to what is requested by individuals or clinicians that facilitates for example, administration in individuals that has difficulties in swallowing. 3D printing also enables to manipulate easily the dose with more accuracy, which is particularly important in some vulnerable groups such as paediatry and geriatry, where is needed often to have a wide range of doses and the incidence of adverse effects and toxicity is quite significant (3,8,16,21). This allow to improve not only therapeutic compliance but also making therapeutic easeful and convenient to child and caregivers (11,16,22). The first 3D printed medicine for oral administration for treatment of convulsions on epilepsy named Spritam ® developed by Aprecia Pharmaceuticals was aproved by FDA in 2015. Spritam ® is manufactured by a ZipDose ® 3D printing system that allows fast disintegrating formulations increasing therapeutic compliance because is enable to incorpor high doses of levetiracetam, up to 1000 mg, and also, to ensure intake in individuals who has swallowing problems (15,23).

With the uprising of 3D printing in health field, it has also emerged the concept of "polypill" specially thought for chronic polymedicated individuals with metabolic diseases where the risks of drugs interactions, adverse effects but most important, therapeutic failure are higher.

The "polypill" allows to combine two or more different APIs in the same dosage form with different release profiles (by adjusting polymer content, geometry, compartimentation or infill template) which is useful to increase therapeutic compliance especially in children since only is necessary to administrate one dosage form and less times a day. Nevertheless, FDA requires that at least, the new formulation has to be submitted to clinical studies to show safety and efficacy. So, there are still many regulatory barriers in which concerns to the norms that guarantee quality control of the manufacturing process and also their safety which will clearly be reflected in the costs (3,11,24–26).

3.1 3D printing techniques

3.1.1 Printing-Based Inkjet Systems: continuous inkjet printing (CIJ) and drop-on-demand (DOD)

Printing-based inkjet systems include continuous inkjet printing (CIJ) and drop-on-demand (DOD) printing, which are often decribed as a 2D approach. These techniques are supported by Lord Rayleigh's Theory of instability of 1878. According to this theory, a flow or a jet of liquid can be split into drops due to a factor subjacent of these systems. They differ from 3D printing systems just because it assents in impression of drops of drug solutions onto flat substrates while 3D printing systems allow to fabricate dosage forms directly from beginning (11,21). However, the use of toxic solvents and the possible presence of impurities mean that the final printed products must be submitted to a heat post-treatment to eliminate them. Moreover, the great gap of this method is that the printed structures are very fragile and irregular due to the high porosity (3).

3.1.2 Laser-Based Writing System: Stereolithography (SLA)

Being the most used method in the area of tissue engineering, this approach is established based on photopolimerization principle. It consists of the incidence of a laser compose of ultraviolet beam or other high-energy light source in a photopolymerizable liquid resin which has to solidify quickly and to be approved and establish as safe by FDA for human use (3,27,28). Unfortunately, studies showed that residual resin presents risk of toxicity as genotoxicity or carcinogenesis. Since resins are photosensitive, their long-term stability is quite questionable (8,28).

3.1.3 Nozzle-Based Deposition Systems

3.1.3.1 Fused Deposition Modelling (FDM)

FDM is based on the thermoplastic behaviour of the polymers since their melting point are low, making them able to melt, maintaining a suitable viscosity: high enough to allow their preparation but low enough to allow their extrusion (29). During the process, the mixture is arranged to cross through a heated extruder nozzle. Since the nozzle is above the melting temperature of the components employed, the mixture melts and deposits on a build plate attending to the x-y dimensions. The build plate gets down and the next layer is deposited and the final product which was previously designed with computer-aided design (CAD) software is formed layer by layer (3,23,30). In that way, for the process be successful, the materials applied must have adequate characteristics as regards their rheological behavior. These characteristics are obviously associated which some parameters inherents to the process as the nozzle diameter, the pressure drop and the feed rate (3). The force necessary to push the melt through the nozzle is determined by pressure drop in the nozzle. This depends on print head's geometry and of the viscosity of the melt (31). The thermal properties of the materials are also extremely relevant acting as a key-factor for the FDM application such as thermal conductivity, density and the glass transition temperature (Tg) (3). Nevertheless, the characteristics of the build plate play an important role: adherence of the extruded components to the build plate must be sufficient to hold materials in place during its print but not to high to difficult separation of the final print product from the build plate (31). To obbey to Good Manufacturing Practices, all the printer sections, mostly that which are in direct contact with the previous extruded filament such as the extruder head, the nozzle and the build platform, should be made of an inert material that can be easily cleaned, being stainless steel the most recommended (32).

FDM 3D printing system is so versatile that allows to obtain drug delivery systems with multiple APIs and in that way, FDM may act as a shortcut to the concept "polypill" so prominent with regard to 3D printing in the revolution of the pharmaceutical sphere (8,31). That is possible due to the capacity to have more than one nozzle controlled by its individual software settings working independently, making possible to print two or more polymers with different drugs, simultaneously. To have different release profile it is enough intercalate drug-loaded filaments with free filament or to use distinct filaments constituted by polymers with different characteristics (31).

As disadvantages, FDM has the limited number of biodegradable thermoplastic polymers that can be employed and carries the risk of degradation of molecules due to high temperature (29). Withal, Kollamaram G. et al., studied the potential to decrease the FDM printing temperature to a temperature range 70-90 °C to employ print low-melting and thermolabile APIs (33). Alhijjaj, M. et al., investigated the feasibility of polymers blends such as PEG, PEO and Tween® 80 as a plasticizer, with either Eudragit EPO, to overcome the lack of thermoplastic polymers suitable for FDM and the impact of polymers blends to accomplish 3D printing medicines with different release profiles (34).

3.1.3.2 Pressure-assisted microsyringes (PAM)

PAM system uses as a extruder a syringe which is induced by a pressurized air piston to deposit a viscous and semi-liquid material layer by layer, originating the printing manufacture (29). PAM system is mostly applied to scaffolds and for complex drug delivery systems because the solvents used can be toxic and can cause a loss of stability of some APIs (3).

3.2 Design

One of the first steps before 3D printing requires the previous design of the final product. That is done thanks to a software named computer-aided design (CAD) that allows to create, modificate, optimisate and to analyse the 3D designs just attending to an electronic file as output (23,31). This software allows to input and to adjust the desired processing parameters like the extrusion and platform temperature, speed of printing, infill percentage and others critical parameters (35). A great advantage of 3D printing systems supported by CAD software is the limitless possibility of printing a diverse range of geometries which is not possible with traditional manufacturing methods. For example, 3D printing allows the print of hollow or partly filled tablet designs which are impossible to produce by using conventional compression techniques (8,29). Also, the drug-release kinetics can be controlled by the design of the drug delivery system depending of the right selection of polymers and their combinations (20). When the target-group is children the visual look as the colours and the shapes are crucial to the therapetic compliance. However, apart from the flexibility of becoming the medicines visually more appealing for the children, it is possible to print solid pharmaceutical forms more easily swallowed. Furthermore, by using 3D printing systems is feasible to print solid forms with a geometry easier to swallow and with reduced dimensions.

In the last case, only use the scaling factor in the printer driver software to create solid dosage forms of varying size (21). With regard to geometry, tablets with geometry in shape of capsule are more easier to swallow and even to print when compared to plane round tablets due to the smaller surface in contact with the build plate, which reduces adherence to it (23). FDM tends to produce highly resistant tablets and is also adequate to produce dosage forms with rounded edges and corners and with an elevated degree of repeatability of weight and physical dimension (8,21,29).

Different shapes and geometries of dosage form can be also used to achieve different release profiles. The introducing modifications in matrix shape may result in constant, pulsed, increasing or decreasing drug release profiles (8).

Also, there is still a need to study and investigate widely the possibility to print orally disintegrating dosage forms such as mini-tablets and films, which are more suitable for young child with dysphagia inherent to the young age (25). Initial studies showed that this can be done by printing thin polymer substrates by using a 3D printer, which allows a flexible dosing approach by adjusting area, thickness, and infill percentage (11).

Still to be studied is an intelligent 3D design software, which can be fed with the child's information as: body weight, maximum tablet size that can be swallowed and dose needed. This will allow to create a dosage form suitable, with the right dimensions and dose, in an individual mode. Thought up that this software could also be able to calculate the release kinetics only based on the surface area and shape of the dosage form to be printed, however since the shape and surface area of the printed dosage form are known to affect the release profile, this area needs to be quite deepen and studied (11).

4 3D printing techniques able to be use in a hospital pharmacy context: conjuction HME-FDM

About dosing recommendations in paediatric population, since the data from clinical trials in children are scarce, it becomes important to have a method with a rapid prototyping and versatility to incorpore concentration gradients within the polymer matrix and that allows to obtain a good dose accuracy (31). 3D printing enables to adjust doses according to the pharmacokinetic and pharmacodynamic differences between different paediatric subgroups and can include a very variable dose interval, since very low doses (20). *In vitro* drug delivery studies with fluorescein demonstrated that 3D printed dosage forms allow to create with accuracy dosage forms with API content as low as 10^{-12} mole per tablet (37). FDM 3D printing system is able to overcome the limitations of the traditional techniques and to produce tailored tablets or capsules to each individual with a high accuracy and several geometric devices with immediate or/and controlled drug release characteristics and also with a good reproducibility (20,31). Goyanes, A. et al., revealed a dependency between drug release profiles and infill percentage printing settings: less infill percentage tablets correspond a faster drug release; in opposite, tablets with higher infill percentage present extended release profiles. For infill percentages below 20%, tablets overall density decreases in such way that promotes floating effect which can increases time drug release due to gastroretention phenomenon, especially useful for weakly basic APIs (21,38). Pietrzak, K. et al., concluded that tablets release profile and size may be directly proportional (19). Goyanes, A. et al., in a study performed in 3D printed PVA caplets with paracetamol or caffeine, demonstrated that there is not a relation between microstructure and drug release profile. They suggest that it can be explained by that the fact of the swelling layer of the PVA difficult permeation through pores and the API dissolution process is controlled by diffusion or erosion (23).

FDM bridged with a HME loading drug system, is an advantageous sequential method to implement in hospitals pharmaceutical services since is rapid and has significantly low costs (23,39). A HME system incorporated upstream from the printer nozzle can be an alternative to accomplish it (40). The reduction in costs can be reflected in the simplicity and the effective costs of these systems but also, in the fact that 3D printing must reduce costs inherents to the production of complex products by reducing the number of unit operations

and having the capacity of control the preciseness of the drug release (35). Also, 3D printers systems occupy relatively little space and it may possible to control remotely these systems by using computer software and network (8). Another important aspect is the safety for the healthcare professional as the pharmacist, since these systems does not require organic solvents and is much easier to contain the dust created during the blending and extrusion processes, making unnecessary to have expensive gowning requirements and dust controls (35). In addition, FDM can be the most adequate printing system to unit dose fabrication allowing 3D printer to work as a mini-dispenser (8,23).

4.1 Conjuction HME-FDM

Before to print by FDM, the APIs have to be loaded into the polymeric filament. This maybe done by impregnation or extrusion (15,31). Impregnation is based on passive diffusion of the drug into filament matrix by soaking filament in a high-concentration solution of the pretended drug for a period of 24h with agitation. Finally, occur a drying process to ensure drug entrapment within the polymer matrix. Usually, is employed a non solvent for the polymer such as ethanol or methanol (31). In impregnation the risk of the degradation of the API is limited (29). Also, the diameter of the polymer filament remains the same so the printer will not have difficulties to print it (21). However, this method is time-consuming, expensive and inefficient since it demands high concentrations of drug solution to incorporate relatively few amounts of API and is limitated only to APIs molecules that can be trapped into the polymer matrix by passive diffusion (29,31). To study the ability of ellipse shaped printed tablet by FDM to contain a given dose of API and control its release, Skowyra et al. reached a PVA filament loading about only 1.9% (w/w). Also, they verified that prednisolone may have lost its plasticity during incubation in methanol (41). In another study, Goyanes et al., achieved a drug loading of only 0.29% (w/w) of fluorescein into commercial PVA filament (21). Goyanes et al. realized analogous impregnation assays with 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA), obtaining also, low drug loadings of 0.24% and 0.06% (w/w), respectively, but HME probably will not be a suitable solution to increase drug loading because of the heat since both 4-ASA and 5-ASA suffered some degradation when in contact with the heated extruder of the printer (29).

Initially, in 1930's, HME appeared with industrial application. Nowadays, is one of the processing technologies widely used in the plastic, rubber and food industries. Due to its

potential its application is spreading to the healthcare field (4). Moreover, HME is generally used to manufacture filaments for FDM. Similar to what happens in FDM, also in HME the temperature is a critical parameter. Here, there is a fundamental concept: Residence Time Distribution (RTD) which indicates the time that APIs, polymers and excipients stay in the screw. This factor gains special attention for thermolabile molecules because how higher is RTD, higher risk of degradation of materials (30). Generally, RTD varies from 5 seconds to 10 minutes depending of the L/D ratio (expresses dimensions of the screw by dividing lenght by the diameter of the screw), extruder type and screw design (42). The barrel section temperatures must be optimized, so that, the melt acquires the adequate viscosity that allows its conveying and accurate mixing. Still, is crucial to keep temperature low enough to avoid thermal degradation of the components (4). Others critical parameters are: feeding rate, shear and screw rotating speed which may be adjusted according to the final size, shape and content pretended (43). Thus, HME consists into force the materials to pass in a rotating screw at elevated temperatures before being extruded, creating the filament with the intended characteristics. In this step it may possible to include in the blend APIs and other excipients (23,31). Extrusion begins with weighing and mixing necessary amounts of the polymer, APIs and excipients to form a homogeneous powder mixture, paying attention to their rheologic behaviour: several small APIs molecules soluble in the polymeric excipients can act as plasticizers, decreasing viscosity of the melt but, contrary, to APIs concentrations beyond the solubility limit, molecules are suspended as solid material, increasing viscosity. Then, the powder blend will be sheded into the hopper, flowing into the extruder's barrel where it will be submitted to a combination of elevated heat and pressure, melting. Generally, the temperature is 15–60°C above the melting point of semi-crystalline polymers or the Tg in case of amorphous polymers. To finish process, the rotating screw helps to push out of a metallic nozzle the molten material, step which may be facilitated with lubricants aid such as magnesium stearate or glyceryl monostearate (thermal lubrificant). Then, filaments will be appropriate packaged and stored in a vacuum desiccator to remove any water's residue (38,42,44). In the end, it may be obtained a solid dispersion (APIs and polymer originate two phases) or a solid solution (APIs and polymer molecularly dispersed originating only one phase with one Tg). The solid dispersions formed can be classified in crystalline solid dispersions and amorphous solid dispersions. By producing amorphous solid dispersions, HME reveals potential to be an option to solve problems associated to solubility and bioavailability of poorly water soluble APIs and to immediate release formulations. However, the state in which the API is dispersed in the polymer impacts the stability and the

bioavailability of the filament: formation of hydrogen, ionic, Van der Waals bonds and hydrophobic interactions between the API and the polymer increase APIs Tg and consequently, restraining crystallization (30,45).

HME equipment consists on an extruder that is a barrel divided into three sections along its lenght: feeding, melting or compression and metering which may contain one or two rotating screws that transport material down the barrel to the die. Die determines extrudate final physical form (4,42). Depending on the number of screws, there are single and twin screw extruders. Twin screw extruders are the most suitable since that these allow to obtain a homogeneous and a consistent mixing of the polymers with APIs and others excipients because the presence of two screws optimize mixing and conveying conditions at different zones inside the barrel and also have less tendency to overheating and shorter transit time. However, if the screws rotate in the same direction there is a co-rotating extruder; if the screws rotate in opposite directions there is a counter-rotating extruder. Co-rotating twin screw extruders demonstrate to be more advantageous since there is not air entrapment risk or requirement of high energy, high pressure and screw speed as it occurs in counter-rotating (4,42). HME has the advantage of being able to incorporate at the end of the system a pelletizer or through appropriate extrudates cut processes to the formation of solid pharmaceutical forms (46).

To produce caplets for oral administration by FDM, Goyanes et al., produced four different filaments of PVA containing paracetamol or caffeine using HME method. They were obtained 4.3% and 8.2% for paracetamol filaments loading. For caffeine was obtained filaments with a drug loading of 4.7% and 9.5%. HME shown to be more efficient to produce drug-loaded 3D printable filaments with higher percentage of drug (23). Besides HME allow to obtain a higher drug loading, this technique is solvent-free, it is a continuous process, demanding few steps and there is not compression. Nevertheless, it requires a higher energy input and it should not be applied to termolabile materials without adjust some parameters, allowing their stability during time required to process complete (42,43).

The choice between impregnation and HME is not effortless. Impregnation conduct to a very small amount of drug loading however, if is used a higher drug/polymer ratio in HME system, it may concern the initial thermoplastic properties of the polymer and in that way, the capacity to print a dosage form with high drug loading may be compromised (29).

5 Polymers safer and wider used in FDM

In FDM systems thermoplastic polymers have as main function act as drug loading filaments (31). Thermoplastic polymers that are suitable for use in FDM are: acrylo-nitrile butadiene styrene (ABS), polylactic acid (PLA), polycaprolactone (PCL), ethylene vinyl acetate (EVA), poly methyl methacrylate (PMMA) and polyvinyl alcohol (PVA) (31). The last one, has been largely used as an extended release matrix for oral delivery (18).

Despite of being one of the earliest thermoplastic polymers employed in FDM, ABS, synthesised starting from three monomeric chemicals (acrylonitrile, butadiene and styrene), is not suitable for medical or pharmaceutical aims because of its toxicity and poorly biocompatibility (31).

EVA is a thermoplastic copolymer of ethylene and vinyl acetate (VA). The VA proportion may modify EVA properties as crystallinity, stiffness, softening and melting temperature which are inversely proportional to VA content. For that reason, EVA is suitable for FDM technique when mixed with thermo-setting polymer PDMS, being commonly used with PDMS in implantable controlled release devices. EVA is a biocompatible, insoluble, non-toxic and was approved by FDA. In addition, EVA-based devices products are available on the market as for example the contraceptive IVR Nuvaring® (31,47).

PMMA has had an important role in the reconstructive materials field such as: dental implants, craniofacial reconstructions, bone implants and ocular prostheses (31). PMMA includes copolymers as the known Eudragit (31). Pietrzak et al., printed tablets by FDM with immediate and extended release profiles of theophylline by loading the drug by HME into three types of Eudragit polymers (Eudragit RL, RS and E) (19).

PCL is suitable for tissue engineering, wounds dressings, or drug delivery systems once it can not be degradated in vivo, due to the lack of the enzymes responsible for its biodegradation in human body. However, PCL is bioresorbable begin with hydrolitic degradation, making it suitable for long-time degradation devices (3).

Having been recognized as safe by FDA, PLA has been employed in tissue engineering and regenerative medicine, due to the fact that PLA is not toxic and does not induce human carcinogenic effects because of its biodegradability. From its hydrolysis results alfa-hydroxy acid that will enter into the tricarboxylic acid cycle being then excreted. However, PLA has

been successfully used in medical field using 3D printing techniques such as FDM. PLA demonstrates to have a low cell affinity because of its hydrophobicity, which can cause an inflammatory response when in contact direct with biological fluids (3). None the less, properties of PLA are dependent of the variable ratio of the L and DL isomeric forms. That ratio influences crystallinity level which are essential to control hardness, melting point, stiffness, and tensile strength of PLA. For a ratio L/DL higher, a greater level of crystallinity is achieved (3,48).

Nevertheless, between the polymers that are adequate to apply in FDM technique, the major focus has been polyvinyl alcohol (PVA). This synthetic polymer is largely used since the early 1930s in several areas since industrial, commercial, medical to food applications (49). PVA has an optimal biocompatibility and biodegradability with very few adverse effects making it appropriate for pharmaceutical and medical uses (10,21) . Also, its greater solubility in water although is low soluble in ethanol and insoluble in several organic solvents constitutes also an advantage (3) . PVA is poorly absorbed at gastrointestinal level being classified as non-toxic. This is reinforced by its high oral LD50 (from 15 to 20 g/kg) and this polymer does not accumulate in the body when administered orally, being mostly excreted in feces (studies carried out in rats detected 98% and only 0.02% after 48 hours of oral administration of 0.01 mg/ kg ^{14}C-labeled PVA in feces and urine, respectively). These characteristics add to the others mentioned above make PVA adequate to pharmaceutical forms for oral administration since it is relatively harmless when oral administered (3,49).

From a toxicological point of view, according to Hodge and Sterner, the results of acute toxicity studies indicate that orally administered of PVA would be set in the category of least concern, ‘‘relatively harmless’’. Demerlis et al. summarized data obtained relatively to studies of subacute and subchronic toxicity (see A3). With regard to chronic studies, PVA does not shown to have any carcinogenic, mutagenic or clastogenic effects nor any negative effects on reproducity (49). Nevertheless, studies conduced in male and female rats present NOAELs for PVA administered orally of 5000 mg/ kg body weight/ day in the 90-day dietary study and 5000 mg/kg body weight/ day in the two-generation reproduction study which was the highest dose tested (49).

This thermoplastic polymer is synthesized by either partial or full hydrolysis of polyvinyl acetate by removing the acetate groups. The hydrolysis degree of the acetate groups has a huge influence on PVA melting point (Tm) that varies from 180 ºC (partially hydrolyzed) to 220 ºC (fully hydrolized) (10,21) . Also, PVA viscosity scale of the polymer differs from 3.4

to 52 mPa.s for (partially hydrolized) to 4 to 60 mPa.s (fully hydrolized). The lower the degree of hydrolysis and polymerization of PVA, the higher its solubility in water and the easier its crystallization and the molecular weight of the polymer (3).

PVA has been proved its suitability in FDM, showing a drug loading to hang around almost 10% (23). According to Goyanes et al., excipients such as plasticizers could aid to obtain considerably drug loading percentages over than 10% (50). Also, since APIs and polymers interact mostly through hydrogen bonding, the differences in the interaction between APIs (depending on groups on their structures capable to stablish hydrogen bonds) and PVA (this one has –OH groups) could explain the differences in the physical form of the APIs (amorphous or crystalline) after process (50) .

Studies defend that PVA may not be so adapted for immediate release profiles formulations, required for approximately 70% of oral dosage formulations. For that, materials as Eudragit E and hydroxypropyl cellulose (HPC) for example, may be more suitable. Is nedeed more research in polymer filaments development suitable to extrude and to print at lower temperatures with thermolabile materials for immediate release profiles but that are able and safer orally administered in children (33).

To work around APIs thermal degradation disadvantage, Kempin et al. investigated other polymers, besides those described in literature, that could be printed at temperatures below 100°C. PEGs demonstrated to be a good way forward and even PVP attending to the right plasticizer at the approppriate amount (51). PEG is a hydrophilic polymer formed of repeating units of hydrophilic ethylene oxide (—CH2—CH2—O—) monomers. It was approved by FDA and it is frequently employed in the biomedical engineering field. It has been a target of interest to create hydrogels that may be utilized in extrusion-based 3D printing. Its capacity of PEGylation, even at low concentrations, allows through covalent bonding, to transform toxic molecules in non-toxic molecules and also, hydrophobic molecules in more soluble molecules at certain ratios (52–55).

6 Excipients suitable for paediatry and for HME-FDM conjuction

6.1 Excipients that can be advantageous in FDM

In any manufacturing process, even in 3D printing processes, excipients are fundamental to achieve the desirable physicochemical characteristics of the dosage forms and the intended drug-release profiles (Table 6.1.1). Moreover, the appearance and the therapeutic performance can be tailored by adjusting the size and shape of the printed form and by incorporating functional excipients as: drug release modifying agents, colorants, taste masking agents and others (20). However, formulation of medicines can envolve several problems as solubility and stability. Excipients may have an important role to solve them (56). However, adult and paediatric populations have different susceptibility to excipients toxicity. Additionally, toxicity of excipients employed may vary across paediatric subgroups, since excipients are metabolized differently by children of different age. The selection of acceptable excipients for use in paediatric population must be subjected to even more rigorous specifications than for availibility in adults (5,56,57). Similar to what happens to APIs, excipients respect risk-benefit relations and so, excipients must be accurately selected and employed only just the quantity as much as needed, respecting their limits of exposure. This is particullary important in children, especially in neonates which are considered more vulnerable to toxicity caused by some excipients as benzyl alcohol (5,56,58).

Table 6.1.1 Inside each group there was an excipients selection attending to safety for children and suitability for HME-FDM.

Crystallization Inhibitors				
Excipient	**Function**	**Suitable for pediatry**	**Adverse effects**	**Observations**
Polycarbophil	They have been shown to avoid or reduce a common physical instability phenomenon as the	- Its use is safe and effective, being supported by extensive toxicological studies (59).	-	- Prolonged exposure to excessive temperatures may reduce coloration and stability but can induce plasticization effect (59).
PVP/ Povidone		- ADI temporary ≤ 25 mg/kg (WHO). - Nontoxic (oral route).	-	- Softens at 150 ºC (59).

	recrystallization of crystalline APIs which are first converted to an amorphous state in HME process but tend to recrystallize during their storage (43).	- It is not absorbed from the gastrointestinal tract or mucous membranes (59).		
HPMC		- NOAEL (rats): 5000 mg/kg. - TDI: 5 mg/kg/day (60).	- Were reported laxative and constipation effects at high doses. - Lack of evidence that modified celluloses have mutagenic, carcinogenic or teratogenic effects, nor that they affect development (60).	- When used in matrix, due to its hydrophilicity, it has capacity to slow API release due to the water retention and consequently gel formation (17).

Disintegrants				
Excipient	**Function**	**Suitable for pediatry**	**Adverse effects**	**Observations**
PVP/ Povidone	These excipients may be employed to disintegrate tablets when exposed to water and quickly release APIs (17).	- ADI temporary ≤ 25 mg/kg (WHO). - Nontoxic (oral route). - It is not absorbed from the gastrointestinal tract or mucous membranes (59).	-	- Softens at 150 ºC (59).
Sodium starch glycolate		- Widely used in oral formulations. - Nontoxic and nonirritant (59).	- Ingestion of large quantities may be harmful (59).	- It does not melt. - It confers highly stability. - It is very hygroscopic (59).
Croscarmellose sodium		- WHO did not specify an ADI. - Nontoxic and nonirritant (59).	- Laxative effect (59).	
Colloidal silicon dioxide		- Widely used to oral formulation. - Safe (59).	-	- Highly Tm: 1600 ºC. - Can act as a thermal stabilizer (59).
Crospovidone		- Without data available about ADI in humans by WHO (59).	-	- Tm ~ 150 ºC. - Water-insoluble disintegrant. - Larger particles provide a faster disintegration than smaller particles. - It has been studied as a superdisintegrant (59).
Microcrystalline cellulose		- Widely used in oral formulations. - Little toxic potential.		- Also has lubrificant properties.

		- It is not absorbed systemically after oral administration (59).		- Tm ~ 260 ºC (59).

Colourants				
Excipient	**Function**	**Suitable for pediatry**	**Adverse effects**	**Observations**
Tartrazine; Allura red AC; Ponceau 4R	Colourants may transform 3D printing medicines more visually appelative.	- They are not appropriate to children use (12,59).	- Behaviour issues. - Allergic reactions (59).	-
Indigo carmine		- Due to its toxic effects it can not be safety used in paediatric medicines (61).	- Hypotension. - Bradycardia. - Hypersensitivity reactions (61).	-
Titanium dioxide		- Nonirritant and nontoxic excipient. - Studies in rat showed that its particles in the 500 nm range concentrated in all major body organs after oral administration (59).	- Possible carcinogenic. - Skin irritant. - Fibrinogenic (61).	- Very high Tm. - Also can act as coating agent (59).

Plasticizers				
Excipient	**Function**	**Suitable for pediatry**	**Adverse effects**	**Observations**
Triacetin	These excipients have an important role during HME. By establishing intermolecular secondary valence forces with the polymers, plasticizers allow to soft polymers, making them more flexible. Also, these compounds decrease polymers Tg and their melt viscosity by increasing the free volume between polymer chains. They may also improve physical and mechanical properties of the final dosage form by influencing the product's tensile strength and elastic modulus. In addition, these excipients	- Nontoxic and nonirritant at the levels employed as an excipient (59). LD_{50} (mouse, oral): 1.1 g/kg LD_{50} (rat, oral): 3 g/kg (59).	-	- Hydrophilic plasticizer (59).
Citrate esters		- Considered as relativelly nontoxic (59).	- In large quantities they may be harmful (59).	- As triethyl citrate, tributyl citrate, acetyltributyl citrate and acetyltriethyl citrate (59).
Vitamin E TPGS		- NOAEL (rats): 1000 mg/kg/day (59).	-	- May enhance drug absoption. - Antioxidant activity (59).
Methyl paraben		- Estimated total ADI for parabens ≤ 10 mg/kg (WHO) (59).	- Nonmutagenic, nonteratogenic, and noncarcinogenic with rare risk of sensibilization (59).	- Chuanbin et al., demonstrated that methylparaben can be employed as a solid-state plasticizer in polymeric extrudates (62).
Surfactants		- Surfactants should be carefully used in children to avoid their potential toxic effects (61,63). - In general, they have a low	- Polysorbate 80 may cause E-Ferol syndrome in neonates (61).	-

	may lower HME energy input, temperature and torque required, decreasing materials degradation. Yet, when is used PVA as a carrier, a higher drug loading may compromise filaments quality. Thus, has been demonstrated that plasticizers may allow to obtain a higher drug loading without commitment of quality. Also, plasticizers may improve semi-crystalline polymers fusion (20,42,43).	oral acute toxicity (animal studies). - Studies in rats showed absorption from gastrointestinal tract after oral administration and a quickly elimination through the urine, faeces, and expired air. - Cationic surfactants showed an irritating effect on gastrointestinal tract stronger than anionic and non-ionic ones (63).		
Low-molecular-mass PEGs		- Toxicity relatively low. - ADI ≤10 mg/kg (59).	- Laxative effect. - Adverse reactions have been reported, mostly with glycols of low molecular weight (59).	-
Sebacate esters		- Considered nontoxic. - After oral administration is metabolized as fats (59).	-	- As dibutyl sebacate. - Used at concentrations of 10–30% by weight of polymer. - Used as a synthetic and adjuvant flavour (59).
Phthalate esters		- They should be avoid (64).	- They may have a negative impact on the fetal and children normal growth and development (64).	- As dibutyl phthalate (DBP) and diethyl phthalate (DEP) (64).
Glycol derivatives		- Propyleneglycol is not appropriate to children, mainly <4 years old and neonates (12).	- Contact dermatitis. - Laxative effect. - Seizures. - Neurotoxicity. - CNS depression (59).	-

Antimicrobial preservatives				
Excipient	**Function**	**Suitable for pediatry/ Toxicity**	**Adverse effects**	**Observations**
Propyleneglycol	Useful to inhibit microbial development, growth and contamination.	- Contraindicated in children <4 years old (12).	- Contact dermatitis. - Laxative effect. - Seizures. - Neurotoxicity. - CNS depression (59).	-

Propylparaben and methylparaben		- Estimated total ADI for parabens ≤ 10 mg/kg (WHO) (59).	- Nonmutagenic, nonteratogenic, and noncarcinogenic with rare risk of sensibilization (59).	- Tm ~ 125–128 ºC (methylparaben). - Tm ~ 95-98 ºC (propylparaben) (59).

Some formulations may even require antioxidants. These excipients may be classified as preventive antioxidants such as ascorbic acid, EDTA and citric acid and as chain-breaking antioxidants such as hindered phenols and aromatic amines, which inhbit free radical chain reactions through reactions with their groups hydroxyl and amine (42).

6.2 Improving organoleptic characteristics: Palatability

The importance of palatability has been recognised by regulatory authorities, including EMA, and is defined by organoleptic properties such as smell, taste, aftertaste and texture or mouthfeel of a medicine, mainly administered by oral route being a concept deeply associated to the concept of acceptability (57). Before 5 years old, children seem to not have an emotional response to a pleasant or unpleasant odours, but after 6 years old, the adult pattern may be observed. Children are able to recognize sweetness and saltiness sensations and to asess the strength or degree of each one from an early age. They are even capable to distinguish sweet taste in mixtures. Thus, children show to prefer higher levels of sweetness than adults (13). That is why children prefer sweet-tasting and they reject bitter-tasting (57). Thus, to increase therapeutic compliance is important to improve palatability masking taste and smell, adding excipients accountable for add appelative flavors and colors which may be more acceptable for children (5,56,65,66). Studies have found that compliance rates in children may vary from 11 to 93%, with major factors attributed to formulation and palatability (57).

6.2.1 Taste masking methods

Since several APIs have aversive taste, it becomes crucial to get strategies to mask their unpleasant taste. Selection of taste masking approach needs to be done attending to each case and to the API organoleptic properties and physical and chemical features. More than one

taste masking technique can be used. Each one has advantages and disadvantages thereby, during development phase its selection has to be well thought out and tested (57).

6.2.1.1 Sweeteners and flavouring systems

There are bulk sweeteners (which afford body and texture) and intense sweeteners (at very low concentrations these sweeteners provide an intense sweet taste) (Table 6.2.1.1.1). Different sweeteners have a variable spectrum of sweetness that must match to the taste profiles of APIs to mask them (57). However, FDA and other entities considered noncaloric sweeteners unsafe in children below 2 years old and it consume should be minimal or completely restricted during pregnancy and lactation (67). Furthermore, intense sweeteners have several advantages: a low calorific burden, little or no glycemic response and they are non or less cariogenic (57). Otherwise, risks associated to the use of cariogenic sweeteners may be minimized depending by the duration of the treatment and gravity of disease or establishing oral hygiene practices after oral administration. Also, the use of fructose, glucose or sucrose which have potential to raise plasma glucose should be strictly limited or possibly totally avoided in diabetic individuals. In these cases, if the medicine is for long term use sugar free alternatives should be recommended (14,57).

Table 6.2.1.1.1 Non or less cariogenic sweeteners compared with sugars suitable for paediatric use and HME-FDM (57,59).

	Toxicity	Contraindications	Adverse effects	Observations
Sugar alcohols/ polyols: **- Hydrogenated monosaccharides** (erythritol, xylitol, sorbitol, mannitol) **- Disaccharides**	- All have ADI classified as 'not specified' by WHO because is considered that they are not used in quantities able to produce toxicity (however for xylitol a 0,5–1,0 g/kg are generally well tolerated by most individuals) (59). - LD_{50} (rat, oral):> 13 g/kg (erythritol); LD_{50} (mouse, oral):> 23 g/kg, LD_{50} (rat,	- Rare hereditary fructose intolerance: should avoid medicinal products containing fructose, sucrose, lactitol, maltitol (4-O-α-glucopyranosyl- D-sorbitol), or sorbitol (57).	- Gastrointestinal disorders (except erythritol) (14,57,59): - Abdominal discomfort - Flatulence - Bloating - Laxative effect - Sorbitol: more irritating than mannitol and better tolerated by diabetics than sucrose but is not completely safe for	Erythritol: 119–122ºC. Xylitol: 92–96ºC. Sorbitol: 110–112ºC (anhydrous form). Mannitol: 166–168ºC. Isomalt: ~ 160ºC. Lactitol: ~ 146ºC.

(isomalt, lactitol, maltitol)	oral): 30 g/kg (lactitol); LD_{50} (mouse, oral): 22 g/kg, LD_{50} (rat, oral): 13,5 g/kg (mannitol); LD_{50} (mouse, oral): 17,8 g/kg (sorbitol); LD_{50} (mouse, oral): 12,5 g/kg, LD_{50} (rat, oral): 17,3 g/kg, LD_{50} (rabbit, oral): 16,5 g/kg (xylitol) (59).		them (59).	Maltitol: 148–151 ºC (59).
Aspartame	- ADI≤ 40 mg/kg (WHO) (59).	- Phenylketonuria (57). - May occur cross-reactivity with sulphonamides (12). - Bitter aftertaste (13).	- Hyperactivity (still inconclusive) (57) . - Recent studies in children age 3-15 years old associated its consume with migraine (67).	- Tm ~ 246-247ºC. - It must be treated at high temperatures for a short time to avoid degradation (59).
Neotame	- ADI≤ 2 mg/kg (EFSA; WHO). - Derivative of aspartame not metabolised to phenylalanine (57).	- Reported as safe for use by children and diabetics and during pregnancy and lactation (59).	- Studies demonstrated that it is fairly nontoxic, nonteratogenic and noncarcinogenic (59).	- Tm ~ 80-83 ºC (59).
Cyclamate	- It should be avoided (67). - ADI for sodium and calcium cyclamate, expressed as cyclamic acid: ≤ 11 mg/kg (WHO). - In Europe, a temporary ADI has been set at ≤ 1,5 mg/kg (59). LD_{50} (mouse, oral): 17 g/kg LD_{50} (rat, oral): 15,25 g/kg (59).	- "Sulfa allergy" (sulphonamide allergy) (57).	- Were reported photosensitive dermatitis cases. - Extensive long-term animal studies and epidemiological studies in humans have failed to show any evidence that its metabolite cyclohexylamine is carcinogenic or mutagenic (59).	- Tm ~ 169–170 ºC (Cyclamic acid) (59).
Saccharin	- It should be avoided (67). - Saccharin: ADI ≤ 2,5 mg/kg (WHO) (59). LD_{50} (mouse, oral): 17,5 g/kg LD_{50} (rat, oral): 14,2 g/kg (59).	- "Sulfa allergy" (sulphonamide allergy) (57). - Sodium saccharine can cause a bitter aftertaste (13).	- Saccharin can change gut microbiota, inducing glucose intolerance, contributing to obesity and diabetes (67). - Few cases of urticaria and photosensitization reactions (59).	- Tm ~ 226-230 ºC (59).

The binary mixtures of sweeteners employed synergistically, can be complemented with supporting flavours for aroma and taste (Table 6.2.1.1.2). Natural flavours have better

palatability than artificial, but latter are chemically more stable and easier to characterize. Further, flavours are often complex mixtures and their exact composition is commonly unknown which may cause serious problems associated to the compatibility with other components existent in the formulation and also related to safety such as possible risk of toxicity, allergies and sensibilization. Another concern is the fact of some flavours available may contain ethanol or propylene glycol that even in very small quantities could have negative effects in children (13,57). However, addition of the flavours may affect products compatibility, safety and efficacy so this can also constitute a barrier to use some flavours in some formulations (57).

Table 6.2.1.1.2 Flavours used to mask certain basic flavours of APIs (13).

Basic sensation	Flavour to cover this taste
Acid	Cherry, lemon, lime, mandarin, orange, strawberry
Alkaline	Banana, caramel, cherry, liquorice, passion-fruit, peach
Bitter	Cherry, chocolate, grapefruit, liquorice, strawberry, peach, raspberry, tutti-frutti
Salty	Caramel, grapefruit, lemon, orange, vanilla
Sweet	Banana, caramel, cream, chocolate, grape, vanilla

6.2.1.2 Bitter blockers and taste modifiers

This group interferes directly with the taste receptor or taste transduction mechanism. Bitter receptor antagonists are often tasteless and must be close structurally analogues of known bitter compounds to bind competitivelly to the same receptor, blocking G-protein release, gustducin. However, this is 'trial and error' approach due to the strong genetic component present. Taste transduction cascade blockers are presently under development but show to be more potent since they involve taste transduction pathway blockage. The ion channel, specifically Transient Receptor Potential cation channel sub-family Member 5 (TRPM5), is a key-component of this cascade and so, if its activity be controlled it is thought that unpleasant tastes can be atenuated or even disappear. Nevertheless, the transduction mechanism subjacent to bitter taste perception and the exact mechanism of action of bitter blockers are not yet fully understood leading to empirical approaches with a limited probability of success and involving risks that are still mainly unknown either in adults or children. Notwithstanding, there are several questions from point of view toxicological, safety and regulatory that need to be answered but it is anticipated that will still to remain a challenge

because of the genetic component and the several receptors and multiple transduction pathways responsible for bitter perception (57).

6.2.1.3 Modification of API solubility

Avoiding to put the API in solution is possible to prevent is aversive taste because, only in solution the API is capable to interact with the taste receptors in oral cavity. This can be possible by keeping the API unionised (by adding pH modifiers and suitable only to ionisable pH-dependent solubility behaviour APIs) or using an alternative solid form such as a salt, cocrystal or polymorph, with low solubility in the formulation vehicle or slower dissolution rate. The benefit of these taste masking methods in children is not clear and bioavailability and others pharmacokinetic parameters can be compromised (57).

6.2.1.4 Creation of a 'molecular' barrier around the API by complexation

This strategy includes ion exchange resins (IER) and cyclodextrins (CD) which are little absorbed by gastrointestinal tract due to its size and apparently do not cause toxic effects. On one hand, IER act by binding at molecular level to the API, avoiding its interaction with the taste receptors. API–resin complexes or "resonates" can be used in suspensions, directly compressed into conventional tablets or even in ODTs (orally disintegrating tablet). Moreover, IER may act as superdisintegrants for tablet formulations. However, API and IER should have opposite charges to succeed an anion–cation interaction and the resinate should be stable in the formulation to ensure taste masking. On the other hand, CD are water soluble cyclic oligosaccharides apt to form inclusion complexes with other molecules, in aqueous solutions or solid state. The inner cavity of CDs tends to be relatively polar and is therefore hydrophobic, while its exterior side is hydrophilic. While α CD is used mainly in parenteral formulations, β CD is mainly used in oral formulations. Although not yet determined the maximum tolerated dose of CDs for paediatric population, is known that in large doses they may have gastrointestinal disorders, as diarrhea (57).

6.2.1.5 Lipidic barrier system

Besides their utility to afford controlled or/ and delayed release properties, lipidic excipients (glycerides, esters of glycerol and fatty acids) used alone, in combinations or mixed with

other excipients may be a less expensive alternative to polymeric coatings to mask efficiently salty or bitter tasting APIs since the quantity of lipidic excipients necessary to the process is generally less compared to polymers. Also, lipidic coatings appears to be safer not having ADI restrictions and more efficient than other systems since they do not require solvents for evaporation or dilution, allowing a higher, faster and more uniform application even in powders with a very high specific surface. Also, being a water-free taste masking system, lipidic coatings are suitable for humidity sensitive APIs reducing also the risk of microbial contamination. However, these excipients may have a negative effect on API bioavailability and the influence of storage conditions specially extreme conditions on physico-chemical properties still requires to be deepen due to the particular characteristics of lipids (57).

6.2.1.6 Application of a physical 'barrier' on the API or the dosage form

This technique is especially suitable for pharmaceutical forms with reduced dimensions such as pellets or mini tablets and consists on masking unpleasant taste by applying coating. The polymeric coating excipient acts as an insoluble barrier at pH of saliva (pH 6–7) but it should dissolve at enteric pH (pH 5), avoiding interaction with the taste buds on the tongue (Table 6.2.1.6.1). Coating process can be done by using conventional coating processes operated in fluidized bed systems or in a drum coater, by microencapsulation, granulation-spheronisation or spray drying. The two last ones are not at all the first choice for paediatric population because both employ solvents that may leave residuals in the final product that may be toxic to them. However, microencapsulation demonstrated to be useful to solve some gaps in taste masking API particles because this method showed to be able in keeping coating intact without undergoing fusion or rupturing during tableting, ensuring the taste masking (57,68).

Table 6.2.1.6.1 Polymeric coating excipients suitable for paediatry and HME-FDM.

Excipient	Suitable for pediatry/ Toxicity	Adverse effects	Observations
Eudragits	- ADI~2–200 mg/kg. - Depending on the grade of Eudragit may be considered as safe in humans (based on chronic oral toxicity studies in rats) (59).	-	- Eudragit RS may delay more API release than Eudragit RL since it has less quaternary ammonium groups which increase macromolecular matrix hydrophilicity through water interactions leading to higher permeability (19). - Eudragits may be used according to the profile release pretended (59): - E: soluble in gastric fluid < pH 5. - L, S, FS: enteric coating agents; L is soluble at pH > 6; S and FS are soluble at pH > 7. - RL, RS, NE 30D, NE 40D, NM30D: to water-insoluble film coats for sustained-release.
PVP/ Povidone	- ADI temporary ≤ 25 mg/kg (WHO). - Nontoxic (oral route). - It is not absorbed from the gastrointestinal tract or mucous membranes (59).	-	- Softens at 150 ºC (59).
HPMC	- NOAEL (rats): 5000 mg/kg. - TDI: 5 mg/kg/day (60).	- Laxative and constipation effects at high doses. - Lack of evidence that modified celluloses have mutagenic, carcinogenic or teratogenic effects, nor that they affect development (60).	- When used in matrix, due to its hydrophilicity, it has capacity to slow API release due to the water retention and consequently gel formation (17). - Used as coating agent for extended-release tablet matrix (60).
HPC	ADI ≤ 1500 mg/kg (WHO). - Nontoxic and nonirritant (oral route). - It is not absorbed from the gastrointestinal tract (59).	- Laxative effects (59).	-
Methylcellulose	- ADI 'not specified' by WHO. - Nontoxic, nonallergenic, and nonirritant (by oral route is not digested or absorbed) (59).	- Gastrointestinal disorders. - Compromise normal absorption of some minerals. - If swallowed with an	- High viscosity grades may act as a disintegrant (59).

		insufficient quantity of liquid, esophageal obstruction may occur (59).	
Ethylcellulose	- Nontoxic, nonallergenic and nonirritating. - Without an ADI specified since it is not considered to be a health hazard (59).	-	- Hydrophobic coating agent that also can act as a flavoring agent or to improve stability by reducing oxidation.
Isomalt, maltitol, xylitol	See table 6.2.1.1.1.	See table 6.2.1.1.1.	- Additionally, they supply sweet-taste masking. Xylitol provides a durable hard coating (12,59) .

6.3 Conclusion about the better masking process in 3D printed medicines for paediatric use

Sweeteners and flavours are frequently the first approach due to their wide range available. Moreover, this approach does not require special manufacturing technologies or equipment and it does not affect bioavailability. Unfavorably, they have to be add during extrusion and so their physical and chemical features should be studied attending to the HME and FDM process parameters to make sure that these excipients are not degraded during filaments manufacturing and during 3D printing. Further, in some cases, only adding sweeteners and flavours is not enough to mask highly aversive with an intense lingering aftertaste APIs. Thus, other methods need to be add in a complement or in alternative. Polymeric and lipidic coatings are considered to be the most powerful techniques for taste masking but they may have some impact on the bioavailability. By itself, 3D printing of solid dosage forms facilitate masking of unpleasant flavour of APIs by using film or sugar-coated however coatings may have an impact on the bioavailability of the paediatric medicines (57). Some polymers often used for coating such as Eudragits have been successfully incorporated into extruded polymeric filaments by HME to achieve the desirable release profile and then, printed into capsules by FDM. On the other hand, this pharmaceutical dosage form alone is capable to cover inside unpleasant taste APIs (68).

Walsh et al. proposed a scheme (see A2) to help to select which masking technique or system and even the pharmaceutical form can be adjusted for each age and child. This scheme prentends to be merely empirical and not a guidance, since there are several factors to take into account besides safety, efficacy and easiness of administration and others (57).

7 Quality control

WHO defined quality control as the set of measures taken, including the setting of specifications, sampling, testing and analytical clearance, that assures that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics (69). Each pharmaceutical product must be submitted to quality control which guarantees safety, efficacy and quality of the pharmaceutical final product. HME-FDM requires two steps of quality control: firstly, to assess filaments quality and finally, to the final product.

7.1 Filaments quality control

Since filaments act as feedstock to FDM printing, is fundamental to establish quality control measures to assure their best quality to proceed to FDM printing with reliability (Table 7.1.1).

Table 7.1.1 Filaments quality control.

Test	Methods	Specifications	Observations	References
Drug identification	- Raman and IR spectroscopic techniques. - According to Ph. Eur. 9 monography.	- Dependent of the API.	-	(70,71)
Filaments drug-loading	- HPLC - Raman and IR spectroscopic techniques.	- [85%,115%] - [75%,125%].	- Small samples must be taken from constant lengths along the complete filament length.	(23,45,51,70)
Consistent drug distribution along filament	- Raman and IR spectroscopic techniques - Confocal Raman Microscopy (CRM) - Microscopic techniques.	- Consistent distribution.	- Small samples must be taken from constant lengths along the complete filament length.	(45,51,71–73)
Diameter	- Laser micrometers or ultrasonic gauges (both at production place)	- 1.75-3.00 mm.	- It must be compatible with print head.	(21,38,74)
Diameter uniformity	- Visual inspection of each filament portion	- Consistent diameter.	-	(15,74)

	- Digital caliper			
Stiffness	- Dynamical mechanical analysis (DMA) - Universal tester (tensile, flexural, and torsion) - Texture analyzer	- Fuenmayor et al., estimated that filament stiffness should not exceed 1000 N/m.		(74,75)
Brittleness	- Dynamical mechanical analysis (DMA)	~ 0,15–0,2 %Pa (10^4)	-	(38,74)
Softness	- Shore durometer.	- Depending of the final aim.	- It depends of the plasticizer amount and polymers behaviour and characteristics.	(74)
Surface morphology/ cross-sectional morphology	- SEM.	- Depending of the final aim.	- Skowyra, J. et al., defend that it is the space between the deposited material layers after printing that originates a porous structure. Is intended a smooth structure; rough structures or with irregular porous may be due to rapid evaporation of water or degradation by the high temperature.	(18,23)
Porosity (pore size distribution; microstructure)	- Mercury intrusion porosimetry.	-	- Goyanes et al., concluded that there is not a relation between microstructure and release profile.	(23)
Crystallinity	- Thermal analysis (DSC) - X-ray powder diffraction (XRPD) - Solid state nuclear magnetic resonance (SSNMR) spectroscopy - IR spectroscopy - Raman spectroscopy	- Crystallinity and amorphous states need to be such as to promote bioavailability.	- DSC is useful to study quantitative detection of transitions such as Tm and Tg. - XRPD may characterize crystalline properties (diffraction pattern is like a fingerprint). SSNMR is similar, probing crystallinity materials.	(18,33,42,45, 75,76)
Thermal properties of materials/	- Thermal analysis (DSC) - Thermogravimetric analysis - IR spectroscopy	- Depending of the final aim.	- TGA allows to conclude about materials thermodegradation.	(18,33,42,45, 75,76)

miscibility	- Raman spectroscopy - Hot stage microscopy		- DSC and Hot stage microscopy are useful to determine experimentally miscibility.	
Dissolution studies (Ph. Eur. 9 2.9.3)	- Depending on release profile, each of one of next methods may be applied with appropriate dissolution environment and at 37±0.5°C (2.9.3 Ph. Eur. 9th Ed.): 1. System with hamper 2. System with agitator blade 3. Pistons system 4. Continuous flow system - Assays must be performed with conditions which mimetize saliva, stomach and enteric pH of children: pH saliva= 6-7; pH stomach=1-2,5; pH enteric=5-8.	- Quantity Q of an API, expressed as a percentage of the indicated on the label, which dissolves in a prescribed time interval (Ph. Eur. 9). - Depending of the therapeutic aim, APIs and dosage form.	- Small samples must be taken from constant lengths along the complete filament length.	(51,70,77,78)

7.2 Final product control

Attending to the quality control tests described in the Ph. Eur. 9 to which solid pharmaceutical forms must be subjected to be approved, was created the following table, taking into account the adjustment of the tests to the production techniques in question: HME and FDM since in 3D printing does not occur compression, for example, excluding assays as friability and toughness associated to mechanical resistance (Table 7.2.1) (70).

Table 7.2.1 Final product quality control.

Test	Method	Specifications	Observations	References
Organoleptic characters (colour, smell, appearance, texture)	- Macroscopic.	- Dependent of the intended final characteristics.	-	(70)
Drug identification (Ph. Eur. 9)	- According to Ph. Eur. 9 monography.	- Dependent of method used.	-	(70)
Uniformity of	- According to Ph. Eur. 9	- [85%,115%]		(70)

content (Ph. Eur. 9 2.9.6)	monography.	- [75%,125%]	-	
Mass uniformity (Ph. Eur. 9 2.9.5) (If average mass ≤ 40 mg: 2.9.6)	- Weighing in analytical balance	- Up to 80 mg of average mass: 10% - [80; 250[mg of average mass: 7,5% - ≥ 250 mg of average mass: 5%	-	(70)
Dissolution (Ph. Eur. 9 2.9.3)	- Depending on release profile, each of one of next methods may be applied with appropriate dissolution environment and at 37±0,5°C (2.9.3 Ph. Eur. 9): 1. System with hamper 2. System with agitator blade 3. Pistons system 4. Continuous flow system - Assays must be performed with conditions which mimetize saliva, stomach and enteric pH of children: pH saliva= 6-7; pH stomach=1-2,5; pH enteric=5-8.	- Quantity Q of an API, expressed as a percentage of the indicated on the label, which dissolves in a prescribed time interval. - Depending of the therapeutic aim, APIs and dosage form.	-	(70,77,78)
Disaggregation (Ph. Eur. 9 2.9.1)	- According to Ph. Eur. 9, disaggregation device A is used to tablets whose size does not exceed 18 mm and disaggregation device B is used to larger tablets.	- Time dependent on therapeutic aim.	-	(70)
Surface morphology/ cross-sectional morphology	- SEM.	-	- Skowyra, J. et al., defend that it is the space between the deposited material layers after printing that originates a porous structure. Is intended a smooth structure; rough structures or with irregular porous may be due	(18,75)

			to rapid evaporation of water or degradation by the high temperature.	
Porosity (pore size distribution; microstructure)	- Mercury intrusion porosimetry	-	- Goyanes et al., concluded that there is not a relation between microstructure and release profile.	(23)
Determination of 3D printed tablet morphology: Diameter and thickness	- Digital calliper.	- Consistent.	-	(21)
Crystallinity	- DSC. - XRPD. - SSNMR spectroscopy - IR spectroscopy and Raman spectroscopic techniques.	- Crystallinity and amorphous states need to be such as to promote bioavailability.	- Quantitative detection of transitions such as Tm and Tg: DSC. - To characterize crystalline properties (diffraction pattern is like a fingerprint): SSNMR and XRPD.	(18,33,42,45,75, 76)
Thermal properties of materials	- TGA - Raman and IR spectroscopic techniques	-	- TGA allows to conclude about materials thermodegradation.	(18,33,42,45,75, 76)
Microbiological control (Ph. Eur. 9 2.6.12)	- According to Ph. Eur. 9 monography.	A maximum of 10^3 bacteria and 10^2 yeasts per gram or per mL. Default of Escherichia coli (1 g or 1 mL).	-	(70)

7.3 Process Analytical Technology (PAT)

Since 2004, regulatory authorities as FDA have been encouraging PAT tools application to guarantee safety and final product quality (79). Several techniques can be applied but their choice depends on their suitability and capacity to fulfill analysis purpose (45). Raman spectroscopy and NIR spectroscopy have been show a great potential as in-line and on-line PAT tools in HME to optimize design, analysis and control within the manufacturing process. They are spectroscopic techniques based on the molecules vibrational transitions which ask for spectral analysis and methods to support analysis of the complex data acquired such as chemometric methods and MVA (Multivariate data analysis) (43,72,76,80,81). They afford: chemical composition, molecular structure, reliable quantitative analysis, polymorph

identification, real-time release assays and even polymers processing analysis. Raman demonstrated to be helpful to monitorize critical process parameters such as pressure, temperature, and feed rate. It provides also, privileged knowledge about blend components interactions, miscibility and their spatial phase distribution. This is possible due to thermoresistant probes that can be put directly into three spots: in the extruder barrel, in the extruder die nozzle or in the final extrusion part. Tg also can be monitorized by Raman spectroscopy (82). The possibility of corrections in real-time assure safety, efficacy and quality of the final product (45,72,76,83). NIR and Raman spectroscopies already demonstrated to be useful to assess at real-time coating and active coating processes by strategically positioned special probes, allowing the coating process to proceed without interruption for adjustments (71,84). The following tables resume advantages and disadvantages of both methods (Tables 7.3.1 and 7.3.2).

Table 7.3.1 Advantages and disadvantages of Raman (30,45,71,72,83).

Advantages	Disadvantages
Non-destructive.	Impurities or colour variations of the sample may cause fluorescence which requires a longer excitation wavelength (NIR λ= 785 or 830 nm). CARS technique also can be an alternative to minimize these interferences.
Wide range of Raman-based tools: since miniaturized and tunable lasers, microprocessor control and even fibre optics Raman. These allow a process-compatible, remote and without contact analysis and turn possible to have less expensive, smaller and faster alternatives.	
Versatility; allows transparent, translucent, opaque and coloured samples analysis and even different dosage forms since solids and semi-solids to suspensions and solutions (water is a weak Raman scatterer).	Raman scattering also can occurs in the presence optical scattering and optical absorbance (named Rayleigh scattering caused by elastic collisions).
One scan can collect spectral data in the range of 4000-40 cm^{-1}. Low frequency/ IR region (400-40 cm^{-1}) includes some of the relevant vibration modes to the different solid states identification.	Handheld Raman tools requires reliable calibration and relative intensity correction.
	Risk of subsampling due to the small spot size of the laser. This can be prevented by using TRS or WAI techniques. WAI must be combined with sample rotation during spectral acquisition and the temporal and spatial averagings of the acquired data.
Minor or no sample preparation required.	Low signal intensity.
	Requires variation in the molecule's polarisability induced by the irradiated monochromatic laser light to be detected.

Table 7.3.2 Advantages and disadvantages of NIR (45,72,76,85).

Advantages	Disadvantages
Non-invasive and non-destructive; fast, continuous, on-line and in-line analysis.	Unlike Raman spectroscopy, NIR requires a reference light route.
Minor or no sample preparation required (spectra can be obtained directly from solid samples).	Chemical composition and physical properties of samples can affect NIR signal.
Enables several measurement installations including transmittance and reflectance setups.	Demands rhythmical variations in the molecule's dipole moment to occur absorbance.
Sensitivity to changes in hydrogen bonding and rearrangements in the crystal structure may provides knowledge about molecular interactions; extremely sensitive to water and hydrogen bonding.	
Fibre optic probes available which allows a remote and portable analysis.	

Saerens L., et al., were the first to validate in-line Raman spectroscopy for API quantification during HME (86). Savolainen, M. et al., to investigate polymorphic variations at molecular level in indomethacin used several techniques such as MIR, NIR and Raman spectroscopy. The last one was most sensitive to degradation products and to polymorphic variations induced by preparation techniques (87). Wahl P. et al., looked into for the most favorable probe positioning in the extruder during HME using in-line NIR spectroscopy (88). Also, Saerens L., et al., integrated a Raman probe in each section of the barrel to improve knowledge about material behavior during HME to optimize critical parameters preponderant on it (89). In a study carried out by Saerens L., et al., they demonstrated the potential of Raman spectroscopy as an in-line PAT tool to API real-time quantitative analysis and to assess polymer and API solid state during HME, detecting amorphous and crystalline states throughout the process (90). Kelly, A. et al., concluded that a single NIR spectroscopy technique is able to follow two different materials by assembled a high temperature reflectance NIR probe in the extruder die directly opposed to a highly reflective surface to simultaneously measure API and plasticizer contents during HME (91).

Notwithstanding, due to their similiar analysis speed and the possibility of single sampling configuration, is in development the possibility to integrate Raman systems with IR systems providing further advantages when compared to individual techniques. They may act as complementar techniques due to their different fundamentals, taking different sensitivities to different signals (71,72,87).

Conclusion

Paediatric population is a challenge from the pharmacotherapeutic point of view. 3D printing technologies are increasingly show potential in healthcare field to embrace that challenge. Notwithstanding, focus should be placed on FDM and HME since these techniques together demonstrate feasibility to be implemented in hospitals pharmaceutical services to give answer to the lack of personalisation and flexibility, consequence of the heterogeneity of this population. However, although its huge potential, pharmaceutical field is quite demanding having high standards of quality imposing regulatory, legislative, safety, quality control and validation procedures obstacles to the emerging technologies.

Furthermore, also excipients, fundamental to assure stability and performance of medicines, was studied. Children are susceptible to suffer toxicity effects due to their pharmacocynetic and pharmacodynamic fragilities attributed to gradual maturation of these systems. So, excipients must be employed taking into account benefit risk balance, searching as much as possible more tolerable alternative excipients and limiting their concentrations.

Each product must be submitted to assays to test and assure that the triad efficacy, quality and safety is obeyed. In HME-FDM, these assays must be performed in two phases: to control extruded filaments as feedstock to FDM and in the final pharmaceutical product. HME-FDM have crucial and critical parameters that must be rigorously controlled to optimize the process and to avoid materials degradation. Several studies have been demonstrating the suitability of implement in-line PAT tools as vibrational spectroscopic techniques as Raman spectroscopy and NIR.

Although 3D printing technologies are approved and used to manufacture medical products, it is still early to the possibility to print other pharmaceutical products but there are space to these technologies be employed in medicines manufacturing in a near future. Nevertheless, for now, several barriers as legislative, regulatory, safety and quality aspects (quality control garantee, stability of drugs and excipients during processes and critical parameters adjustment) need to be overcome before widespread of 3D printing technologies in healthcare services.

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Attachments

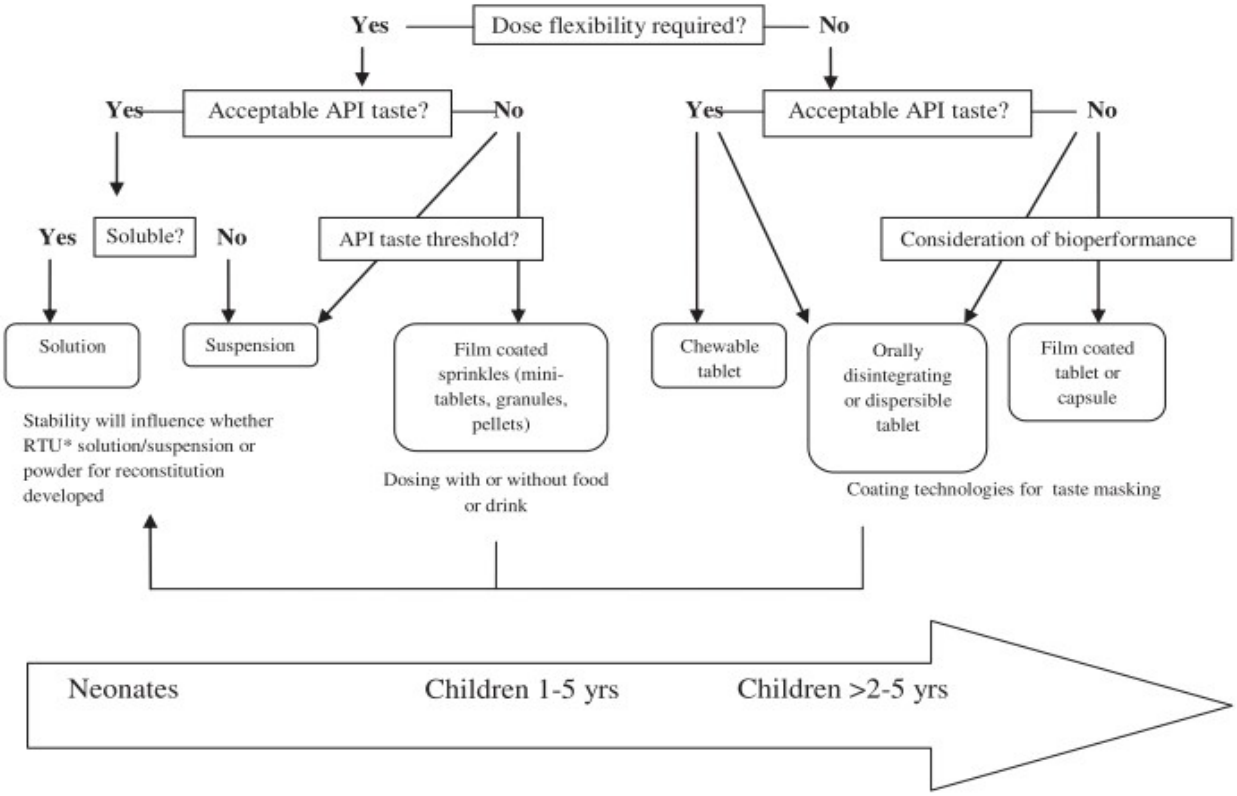
A1. Matrix: Route of administration /dosage form vs. Age (13).

Route / Dosage Form	*Preterm newborn infants*	*Term newborn infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (pre school) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Peroral						
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent DF*	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersable DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5
Nasal						
Solution	3	4	4	4	4	4
Semisolid DF	2	3	3	4	4	4
Rectal						
Suppositories	4	5	5	4	3	2
Rectal Enema	5	4	4	3	3	2
Rectal capsules	2	3	4	4	4	3
Topical/ transdermal						
Ointment, Cream, Gel	4	4	4	5	5	5
Liquid DF	4	4	4	5	4	4
Transdermal Patch	1	2	2	4	4	5
Parenteral						
i.v. Solution	5	4	4	4	4	3
i.m.	3	3	3	4	4	3
s.c.	4	4	4	4	4	3
Pump system	5	4	4	4	4	3
Pulmonary						
Nebuliser	2	3	4	5	4	3
MDI / Spacer	1	3	4	5	4	4
DPI	1	1	3	4	5	5
Ocular						
Eye drops	3	4	4	4	5	5
Semisolid DF	2	3	4	4	4	4

*DF: Dosage Forms

Source: EMA. Reflection paper: Formulation of Choice for the Paediatric Population (EMEA/CHMP/PEG/194810/2005).

A2. Scheme proposed by Walsh et al. to aid to select the most suitable masking system (57).



Source: Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R, et al. Playing hide and seek with poorly tasting paediatric medicines : Do not forget the excipients. Adv Drug Deliv Rev. 2014;73:14–33.

A3. Repeated oral dose studies with PVA (49).

Specie	Dose	Results	References
Mouse	100−1500 mg/kg	One mouse in 1500 mg/kg dose group died. No other mortalities or abnormalities.	JSCI, 1968
Mouse	500 mg/kg/day for 20 days	No mortalities or abnormalities.	JSCI, 1968
Mouse	100, 500, 1000 mg/kg/day for 26 weeks	No mortalities or abnormalities.	JSCI, 1968
Rat	2200−4400 mg/kg for 2−4 weeks	No gross changes. Hepatic hydropic changes eosinophilic infiltrations of gastric submucosa and myeloid marrow.	Hueper, 1939
Rat	0.5% PVA for 8 weeks (~500 mg/kg/day)	Two mortalities prior to end of test period. Five surviving rats showed inflammatory lesions of the lungs.	DuPont Chemical, 1936
Cat	0.5, 1.0 g/kg/day for 8 weeks	No abnormalities during test period; autopsy revealed vacuolar degeneration in liver and renal tubular epithelium.	DuPont Chemical, 1936
Dog	? mg/kg for 20 days[a]	HNEL (NOAEL)=10,000 mg/kg. No effects reported.	Clydesdale, 1997b
Dog	? mg/kg for 180 days[a]	LEL (LOAEL)=800 mg/kg. Diarrhea, emesis	Clydesdale, 1997c

a- Details not provided.

Source: Demerlis CC, Schoneker DR. Review of the oral toxicity of polyvinyl alcohol (PVA). 2003;41:319–26.