Patient acceptability of 3D printed medicines

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Abstract

Patient-centric medicine is a derivative term for personalised medicine, whereby the pharmaceutical product provides the best overall benefit by meeting the comprehensive needs of the individual; considering the end-user from the beginning of the formulation design process right through development to an end product is a must. One way in which to obtain personalised medicines, on-site and on-demand is by three-dimensional printing (3DP). The aim of this study was to investigate the influence of the shape, size and colour of different placebo 3D printed tablets (Printlets™) manufactured by fused deposition modeling (FDM) 3DP on end-user acceptability regarding picking and swallowing. Ten different printlet shapes were prepared by 3DP for an open-label, randomised, exploratory pilot study with 50 participants. Participant-reported outcome (PRO) and researcher reported outcome (RRO) were collected after picking and swallowing of selected printlet geometries including sphere, torus, disc, capsule and tilted diamond shapes. The torus printlet received the highest PRO cores for ease of swallowing and ease of picking. Printlets with a similar appearance to conventional formulations (capsule and disc shape) were also found to be easy to swallow and pick which demonstrates that familiarity is a critical acceptability attribute for end-users. RRO scores were in agreement with the PRO scores. The sphere was not perceived to be an appropriate way of administering an oral solid medicine. Smaller sizes of printlets were found to be preferable; however it was found that the perception of size was driven by the type of the shape. Printlet colour was also found to affect the perception of the end-user. Our study is the first to guide the pharmaceutical industry towards developing patient-centric medicine in different geometries via 3DP. Overall, the highest acceptability scores for torus printlets indicates that FDM 3DP is a promising fabrication technology towards increasing patient acceptability of solid oral medicines.

1. Introduction

The pharmaceutical industry has shifted towards tailoring the drug product to the individual. The pharmaceutical term often used is `patient centric medicine` as a derivative term for personalised medicine. The objective of a patient centric drug product is to provide the best overall benefit by meeting the comprehensive needs of the individual (Drumond et al., 2017). One way to obtain personalised doses, on-site and on-demand is by three-dimensional printing (3DP) (Alomari et al., 2015; Goyanes et al., 2014). The added value of 3DP is also to ensure patient centricity using a robust process which is a critical requirement for providing medicine of appropriate quality (Wilson et al., 2016). End-user acceptability, defined as the ability and willingness of the end-user to take the drug product as intended, has been considered critical for the success of patient centric drug products. Any type of modification to the dosage form (e.g. crushing; splitting) could result in under or over dosing the therapeutic agent by altering the bioavailability. In this context the type of dosage form strongly contributes to the patient acceptability hence the therapeutic outcome of the drug product. In particular vulnerable patients require individualised medicine design to overcome the medicine related difficulties such as dysphagia, manual dexterity and poor hand coordination ability. In relation to orally administered dosage forms, the effect of palatability and size of the drug product on patient acceptability have been studied in recent years (Liu et al., 2016; Mittal, 2017). However, the end-user`s ability and willingness to take different shapes of tablets have not been explored thoroughly. The available data is only limited to the fact that patients' preference of tablet shape is associated with its size (Liu et al., 2015).

3DP is a computer controlled additive manufacturing process that creates solid objects layer by layer, whereby computer aided design is used to readily produce any design or model (Goyanes et al., 2015b). 3DP encompasses a range of different printing technologies. For instance, powder bed inkjet printing, which was developed in the 90s (Wu et al., 1996), is used in the manufacture of the first successful licensed 3D printed medicine (Spritam) (Aprecia_Pharmaceuticals, 2015). Selective laser sintering (SLS), which is a more recent 3DP powder bed approach that uses a laser beam to sinter and merge the particles of powder into a solid structure, has been used to manufacture 3D printed tablets (Printlets™) with different drug release properties (Fina et al., 2017). An alternative technology, stereolithography (SLA), has been evaluated to manufacture oral dosage forms (Wang et al., 2016) as well as personalized facial masks for topical drug delivery (Goyanes et al., 2016a). A further 3DP technology, gel extrusion has been also evaluated for the preparation of 3D printed medicines (Khaled et al., 2014; Khaled et al., 2015).

Of all of the 3DP technologies, fused deposition modelling (FDM) 3DP however, offers immediate production of printlets on demand, and therefore is the most suitable type of 3DP to be used in production of patient centric pharmaceuticals. In FDM 3DP a polymer filament is passed through a heated nozzle and the molten polymer is deposited onto a build plate creating the layers of the object to be printed (Goyanes et al., 2014). FDM can be used with a wide a range of different pharmaceutical grade excipients, both soluble (Goyanes et al., 2017; Melocchi et al., 2016; Sadia et al., 2016) and insoluble (Hollander et al., 2016); for this reason FDM has been shown to be extremely versatile in the development of drug delivery systems, especially personalised oral medicines (Goyanes et al., 2015a; Goyanes et al., 2016b; Skowyra et al., 2015), delivery systems for nanocapsules (Beck et al., 2017), medical devices (Genina et al., 2015) and wound dressings (Muwaffak et al., 2017).

Most of the reports about 3D printed medicines assess *in vitro* drug release characteristics based on the constituent materials (Goyanes et al., 2017; Melocchi et al., 2016) and design (Goyanes et al., 2015b; Goyanes et al., 2015c; Markl et al., 2017), but there are no reports evaluating probably one of the biggest advantages of this computer controlled technology, that is the possibility of creating many innovative shapes or designs to improve patient acceptability (Cleave, 1965). The shape design and the size of the formulations can potentially affect the ease of swallowing and can minimise risk of oesophageal damage (Hey et al., 1983). The shape can also affect the picking process in target populations (Dombrower et al., 1998). The shape and size of the formulations can, hence, have an impact on patient`s ability and willingness to take medicine, however the relevant data is limited to conventional geometries such as oval and round shapes (FDA, 2015).

The study of which shapes are best received by patients both in terms of ease of picking and intake and of aesthetics can improve patient's acceptability and therefore compliance (Buckalew and Coffield, 1982; Jacobs and Nordan, 1979). The aim of this study was to investigate the influence of the shape of different placebo printlets manufactured by FDM 3DP on end-user acceptability regarding picking and swallowing. The effect of the size and the colour of the printlets on their acceptability was also evaluated. To author´s knowledge, this is the first study investigating the effect of the shape of 3D printed tablets on human perception.

2. Materials and Methods

2.1. Materials

Hydroxypropylcellulose (Klucel ELF) was chosen as main polymer for the study (Ashland Pharmaceuticals, UK). Mannitol was added as plasticizer and magnesium stearate as

lubricant to facilitate the extrusion and 3D printing; both were purchased from Guinama, Spain. Candurin Orange Amber and Gold Sheen were obtained from Merck Performance Materials, UK. Essential Waitrose Green, Black and Blue food colouring and Dr. Oetker green and blue food colouring gels were purchased from Waitrose, UK.

2.2. Preparation of the extruded filaments

Hot melt extrusion (HME) was used to manufacture the filaments used in FDM printing. The filaments were prepared in 40g batches of a mixture a polymer (hydroxypropylcellulose, 73.75% w/w), plasticiser (mannitol, 21.25%) and lubricant (magnesium stearate, 5% w/w). The materials were mixed using a mortar and pestle until no agglomerated particles were observed. The mixture was extruded using a single-screw hot melt extruder (Noztec Pro hot melt extruder, Noztec, UK) to obtain the filaments (extrusion temperature 130°C, nozzle diameter 1.75 mm, screw speed 15 rpm). The extruded filaments were stored in plastic bags until printing. To avoid diameter variations of the filament 5 batches of 40g mixture were extruded in a continuous process in order to obtain enough filament for the preparation of the Printlets™.

Coloured filaments were produced that could then be used to print coloured printlets. Pharmaceutical grade colouring (Candurin Orange Amber and Candurin Gold Sheen) 1%w/w or food colouring 5%w/w were added before extrusion in the mixture using a mortar and pestle. The mixed powders were then extruded as normal.

2.3. FDM 3D printing

The printlets were manufactured using the filaments created by hot melt extrusion using a fused-deposition modelling 3D printer (MakerBot Replicator 2X, MakerBot Inc, USA). The printlet design templates were delineated with 123D design (Autodesk Inc. USA) and exported as a stereolithography file into the 3D printer software (Makerware v3.10.0.1725). The .stl format contains only the object surface data, and all the other parameters need to be defined from the MakerBot software in order to print the desired object. The print settings were defined as follows: standard resolution (layer height 0.20mm) with no raft, supports for sphere and titled printlet, printing temperature 140°C, speed while extruding 90mm/s, speed while travelling 150mm/s, infill 100% and number of shells 2.

The shapes selected for the study were: disc, torus, sphere, tilted diamond, capsule, pentagon, heart, diamond, triangle and cube (Figure 1).

The disc and the capsule were chosen as examples of traditional formulations. The sphere and the torus were chosen for their potential drug release properties that have been evaluated in previous studies (Cheng et al., 1999; Goyanes et al., 2015b). The tilted diamond was picked due to existence of shapes of a similar design coming to market and because of its potential for easy picking (Tovey, 1983). The cube was chosen as an example of extreme geometry. The unconventional shapes including pentagon, triangle, diamond and heart and were chosen as being discussed in FDA Guidance for Industry (FDA, 2015).

For the swallowing study, the size and weight of the printlets were selected by 3D printing a disc with the same dimensions as a standard 500mg paracetamol tablets purchased from Boots (Boots UK, UK). The sizes of the other geometries were adapted in size to match the weight of the printed disc (488mg). The capsule shape resulted similar in dimensions to a size 2 capsule (18mm x 6.35mm).

To obtain printlets of different sizes (so also different weights), capsule printlets were manufactured using the same filament at different sizes, capsule size 0 (21.7mm x 7.65mm), size 1 (19.4mm x 6.91mm) and size 3 (15.9mm x 5.82mm). Capsule shapes were all printed twice. The average weight of the two capsule shapes were taken and used as the reference weight for that size. Then the other shapes were all scaled up or down as appropriate, to match the weights of the different sizes capsules, on the Makerbot software.

2.4. Determination of printlet morphology

Images of the printlets alongside a ruler for scaling were taken using a Nikon CoolpixS6150, with the macro option enabled.

2.5. Acceptability testing

The acceptability study was a single site, open label trial using placebo printlets. Study samples were prepared under strict quality measures. The study participants were 50 adults aged 18 to 45 years. Each participant was presented with coded and randomised samples. During the study session, the acceptability data was collected via Participant Reported Outcome (PRO) and Researcher Reported Outcome (RRO) measures. Ethical approval was granted by the UCL Research Ethics Committee (REC 8249/003).

For the recruitment the study advert was circulated to all University College London (UCL) students and staff via myUCL newsletter and via UCL School of Pharmacy mailing lists. The participants interested in taking part in the study were invited to contact the research team directly using the contact details included in the advert and to select their preferred day/time slots. Upon their contact, the research team sent invitations for the study and provided the participant information sheet including a clear statement explaining the data obtained during the study used exclusively for research purposes. The participants were given until one week before the study to evaluate whether to take part and were invited to ask questions or obtain further information. The participants were then contacted once again asking them to confirm their participation or to opt out if they wish. On the day of the study, a member of the research team verbally explained the study sessions. The participants signed the consent form only after having read and understood the information sheet previously provided, and after having asked any questions they may have to the research team. The consent form was provided in two copies to be signed: one copy to be kept by the participant and another copy to be retained by the research team.

The study involved three brief sessions to: 1. Explore the participants` willingness to take printlets prior to the study tasks (pre-swallowing session) 2. Explore the participants` ability to pick and swallow different shapes of printlets (picking and swallowing sessions, respectively) 3. Explore the participants` opinion about modification of the printlets in terms of size and colour (semi-structured interview session).

During the picking session, participants were asked to pick ten different 3D printlets (Figure 1) (one sample presented at a time) and place them in a container approximately 30 cm above the table level to mimic the average height between the table and the mouth. After this task, PRO was obtained by asking participants to rate their acceptability using a five point facial hedonic scale anchored to statements about their experience of picking the 3D printlet, ranging from extremely uncomfortable to extremely comfortable on a computerised questionnaire (Qualtrics, Provo, US).

During the swallowing session, participants were presented five different 3D printlets (sphere, torus, disc, capsule, tilted diamond) (Figure 1) (one sample presented at a time) and asked to swallow with aid of water if they were willing to do so. Only five different 3D printlets were selected for swallowing session to minimise the burden on participants. After this task, PRO was obtained by asking participants to rate their acceptability using a five point facial hedonic scale anchored to statements about their experience of swallowing the 3D printlet, ranging

from extremely uncomfortable to extremely comfortable on a computerised questionnaire (Qualtrics, Provo, US). The volume of water swallowed for each sample was also measured.

During both picking and swallowing sessions, RRO was also obtained. One researcher observed and scored the participants` facial expression and performance for sample picking and swallowing. The scale for facial expression measured one behavioural item ranging from signs of distress to positive face/other signs of approval in a two point score system. The scale for performance ranged from unsuccessful attempt to successful completion of the task (picking or swallowing) in a two point score system (Figure 2).

At the end of picking and swallowing sessions, participants were invited to participate in a brief semi-structured interview in which they were asked whether they would be willing to take the sample printlet every day for several years and how they would change the sample according to their preferences. In addition, participants were presented ten different shaped 3D printlets in their different sizes (Figure 3) and were asked to point out the maximum size that they were willing to swallow. The participants were also shown nine different colours of capsule shaped printlet (Figure 4) and asked to point out their most preferable colour.

2.6. Statistical analysis

The acceptability for picking and swallowing the printlet was evaluated separately. PROs obtained from the five points hedonic facial scale were converted into numerical values (1 = extremely uncomfortable, 5 = extremely comfortable), as reported in Granato et al. (2012). The sample was considered acceptable if the median PRO score was 3 or above. Score values were then analysed using Friedman analysis of variance followed by Dunn's post hoc test (Prism 7, GraphPad Software Inc.) (Lawless and Heymann, 2010). RRO scores obtained from the samples related to the picking and swallowing tasks were summed separately, and differences between the total RRO scores of each samples were calculated using Friedman's test and Dunn's post hoc test for multiple comparisons (Prism 7, GraphPad Software Inc.) (Lawless and Heymann, 2010). The sample was considered acceptable if the total median RRO score was 2 or above. Differences were considered significant if $p < 0.05$.

3. Results and discussion

3.1. FDM 3D printing

The ten selected shapes were repeatedly printed with the filaments prepared by hot melt extrusion to obtain sufficient samples for the study. Over 350 printlets were produced, 50 samples of disc, torus, sphere, tilted diamond and capsule, and 15 samples of pentagon, heart, diamond, triangle and cube. The printlets were consistent in size, shape and appearance. The quantity produced highlighted the ability of FDM to enable mass customization in a robust manner, quickly printing many items of the same design. Production of these atypical shapes by conventional technologies would be challenging in the extreme, which highlights the potential applications of FDM 3DP in pharmaceutical industry to produce innovative geometries. FDM 3DP showed excellent reproducibility as printlets were successfully prepared at reference weight of 488mg ± 5%, based on the disc shape, with small variations in weight: disc 488 ±13mg, torus 487 ±14mg, sphere 495 ±15mg, tilted diamond 491 ±17mg, capsule 510 ±11mg, pentagon 500 ±18mg, heart 498 ±15mg, diamond 481 ±15mg, triangle 503 ±20mg and cube 490 ±11mg. The capsule shape printlets of this weight were equivalent in size to a size 2 capsule.

Additionally, each geometry was printed in four different sizes as seen in Figure 3, allowing collecting acceptability data not just based on the shape, but on the size of the printlet as well.

Size 2 capsule-shaped printlets were also prepared with the colour filaments obtained using both powdered and liquid colourants (Figure 4). The characteristics of the filaments were not affected by the addition of the colorants and the tablets showed similar size and shape characteristics to the white capsule printlet

3.2. Acceptability testing

In total fifty participants (average age: 24.6 years ± 5.2) were recruited for the human panel study, of which 30% were male. All participants completed the online questionnaire about their willingness and ability to pick and swallow different shapes of printlets as well as their opinion about modification of the printlets in terms of shape, size and colour. The results of the picking and swallowing of printlets were used to assess the end user`s ability and willingness to take the 3DP printed medicine. Despite the increasing research interest in the acceptability testing of oral dosage forms, there is still a limited number of studies defining the limit of acceptability as stated in a recent review paper (Mistry and Batchelor, 2017). In this respect, the limits for acceptability of printlets were set as described in the Section 2.6 of this paper.

Overall, the torus shape received the highest PRO and RRO scores for the picking and swallowing (Table 1). This shape is a new design which is only achievable through 3DP,

therefore the benefit of novel fabrication technologies for developing patient-centric formulations. Capsule and disc shapes were also scored high by the participants during the human panel (Table 1). This result was attributed to the similarity of geometries to the conventional solid dosage forms such as compressed tablets and gelatine capsules hence repeated exposure of the participants to similar designs.

3.2.1. Picking session

All studied printlet shapes received high scores in picking up, as shown by most printlets receiving a median score of over 4 which is the second highest score corresponding to somewhat comfortable (Table 1, Figure 5). The torus shape was found significantly easier to pick than the tilted diamond ($p < 0.05$). The disc was also evaluated easier to pick in comparison with the tilted diamond and with the pentagon ($p < 0.05$). The capsule was found to be easier to pick than the tilted diamond ($p < 0.05$). Interestingly, the spherical shape was not evaluated easier to pick than any other shape. This suggests that the absence of sharp edges in combination with the prevalence of one dimension over the others could positively influence the ability to pick the shape.

None of the printlets was scored as extremely uncomfortable to pick up which was reassuring, but the fact that every shape received a minimum PRO score of 4 was surprising. PRO high scores were confirmed by RRO median scores of 3 in all the shapes analysed. This included traditional capsule and disc shapes. Older people have been reported to have poorer fine hand motoric skills due to advanced age and potential diseases causing changes in hand function ability (Notenboom et al., 2014; Stegemann et al., 2010).. Tilted diamond was designed similar to the marketed Tiltab tablets (Tovey, 1983), where most stable position on a horizontal flat surface is a tilted position for easy picking, showing potential benefit to tackle dexterity and increase patient compliance. Surprisingly despite being specifically designed for ease of picking, tilted diamond scored the lowest on median with the widest interquartile range.

3.2.2. Swallowing session
In relation to swallowing printlets, the participant`s willingness to swallow all the printlets samples was explored at pre-swallowing stage. At the pre-swallowing stage of the panel, the printlets pentagon, heart, diamond, triangle, cube received the lowest acceptability scores along with tilted diamond (data not shown). PRO scores showed the positive perception of participants towards traditional shapes of disc and capsule both at pre- and post-swallowing of printlet samples (Figure 6).

The participant´s ability to swallow printlets was evaluated after the pre-swallowing task for only five out the ten shapes (disc, torus, sphere, tilted diamond and capsule). At swallowing

stage of the panel, the capsule shape printlet was predictably scored minimum 4 (somewhat comfortable) or above with over half of the volunteers scored 5 (extremely comfortable) in accordance with its high ratings received at pre-swallowing stage (Figure 6). The capsule shape was also confirmed as acceptable by a median RRO score of 3. Although this might be attributed to the participant`s familiarity of the shape, the printlet was designed to be 3D printed with rounder edges compared to caplets manufactured by conventional methods. The hypothesis of familiarity was also supported with the finding that 49 (98%) participants reported to be willing to swallow capsule shaped printlet every day (Figure 7).

The torus was also well received with a median PRO acceptability score of 5 (IQR=1), and a median RRO acceptability score of 3 at swallowing stage of the human panel, indicating its potential for as a 3DP patient centric medicine. As the PRO measure for the willingness to take torus shape was lower at pre-swallowing stage (4; IQR=2), it was attributed to the fact that torus was not regarded a medicine shape at initial look in comparison to well-known capsule and disc shapes. Torus pre-swallowing PROs were significantly higher ($p < 0.05$) than those of the tilted diamond, pentagon, diamond, triangle, and cube, whereas no significant differences were found between torus and sphere, disc, capsule, and heart. However torus shape printlet received higher PRO score than disc shape (4; IQR=1) after swallowing ($p < 0.05$) demonstrating the influence of the experience on perception (Figure 6, Table 1). Torus also received higher PROs after swallowing compared to the tilted diamond (4; IQR=0) ($p < 0.05$).

While the tilted diamond was expected to score low based on results from the picking and pre-swallowing stages, it surprisingly scored 4 (median value; IQR = 0) for the swallowing PRO acceptability, and 3 (median value; IQR = 0) for the swallowing RRO acceptability (Figure 6). Although this finding may show that the tilted diamond is much more acceptable to swallow than it appears, still a high number of participants (18 out of 50) refused to swallow it. Moreover the feedback received during semi-structured interview claimed tilted diamond to be too sharp warranting consideration into rounding off the protrusions. The participants still suggested remaining the feature of flatness for ease of picking but reducing the edges to prevent difficulty in swallowing. Similar comments were received for the triangle shape suggesting rounding off the edges of the printlet.

The sphere shape printlet received lowest acceptance from the panel (Figure 6). Although the initial perception about ease of swallowing was positive at pre-swallowing, it scored the lowest of all the shapes that were swallowed (Figure 1), with a median PRO score of 3 (IQR = 2) representing neither comfortable nor uncomfortable, and a RRO score of 2 (IQR = 2). Another interesting finding was the noticeably higher volume of water consumed to swallow sphere

printlet (mean: 53 mL) compared to other four printlet shapes (mean volume ranged between 40 to 44 mL). Further data obtained during the semi-structured interview phase recorded some views around the perception of sphere as a confectionary shape rather than a medicine shape. In accordance sphere was found to be the shape that smallest number of participants would swallow every day out of the swallowed shapes, as well as the diamond and the triangle (Figure 7).

Among the shapes being investigated only in regards to participant`s willingness to swallow at pre-swallowing stage, the highest PRO measure was received for heart shape with a median of 3.5 (IQR=2). Other interesting finding was the wider interquartile ranges obtained for the swallowing acceptability of printlets only explored at pre-swallowing stage. This was explained by the novelty of geometries achieved by 3DP hence less familiarity as a medicine shape. Hence the ease of picking and swallowing were not seemed the only parameter driving the printlet acceptability although shape has been suggested to be determined to be functional (Naeve, 2010).

Despite receiving higher pre-swallowing score than the diamond, the pentagon was much more poorly received with fewer people being willing to swallow it every day as seen in Figure 7. This was explained with the flat and pointed geometry of the pentagon shape printlet. However it was not possible to make a general statement about the pointed geometry because the heart, despite not being too rounded, was scored the best out of the printlet shapes only explored at pre-swallowing stage. This was associated to the appealing feature of the heart shape potentially associated with cardiovascular diseases as reported in semi-structured interviews. The diamond shape did not score much higher than the sharper tilted diamond in the pre-swallow test, which may indicate that people are not willing to swallow diamond shapes in general in agreement with previous studies explored the preference with visual testing (Wan et al., 2015). However, it should be stressed that, despite a low pre-swallowing score of 2.5 for the tilted diamond, this was affected by quite a few refusals to swallow. Overall these findings indicated the importance of the initial impression as well as the repeated exposure to a certain shape of medicine paving the way for further studies towards optimising the design of solid oral dosage forms. Moreover rounder shaped objects were reported to be preferred over more angular ones (Bar and Neta, 2007) due to latter potentially to be perceived threatening (Larson et al., 2009). For instance it might be considered to round off the edges of diamond shape to improve acceptability.

The cube shape was very poorly received with a pre-swallow score of 2 (IQR=3), the lowest of all the geometries tested. Most people were concerned it would lodge in the throat. It was

also the lowest scoring shape in whether people would swallow it every day. A good picking score of 4.5 (IQR=2), means that perhaps people might be willing to use it as a sub-lingual or buccal formulation.

3.2.3. Effect of printlet size

Regarding the size of the formulations, if a printlet was poorly received at size presented to participants (size 2), then instead of removing the shape from consideration, presenting a printlet version that was smaller in size and weight might improve users´ opinion of it. On the other hand, if a shape was well received, it was also important to see if people were willing to swallow a larger version of it. It is necessary to test the effect of printlet size as low potency medications often have to be formulated as a larger printlet in order to deliver the therapeutic dose. As shown in Figure 8, majority of the participants reported to be willing to swallow larger sizes of sphere, torus and capsule among other printlet shapes presented to participants during the swallowing session. PROs obtained during semi-structured interview session reported torus and disc shapes to be considered as swallowing acceptable at bigger sizers compared to other printlet shapes. This data also supported the overall acceptability of torus as a novel 3DP printlet shape. In accordance with the PROs measured at pre-swallowing session, most of novel shapes were found to be more acceptable at smaller sizes.

3.2.4 Effect of printlet colour

Regarding the coloured printlets shown as in Figure 4, there is a great variety of opinions, with thirty seven people out of the fifty said they were an improvement. Among the participants perceived colour as an improvement feature for printlets, turquoise was deemed to be the best favourable colour likely being associated with tranquillising effect (de Craen et al., 1996). Black and dark green were deemed the least favourable colours, and were the only ones were claimed to decrease the acceptability of printlets. Seven people elected white as their favourite colour who did say colour was an improvement, contradicting previous studies (Overgaard et al., 2001). Finally one person said pink was an improvement, and no-one said it was detrimental so here it was found to be rather neutral opinion about this specific colour. Colour of medicine has potential impact on end-user acceptability. Having said the effect of different colour on patient adherence has not been fully understood. In some reports darker colours were associated with evening medicine or white colour with safety (Contract_Pharma). As vibrant colours have been used more in oral solid dosage forms, in particular with the expansion in generic drug market, further studies are required to investigate the additive effect of colour on patient acceptability.

3.2.5 Effect of printlet shape

Shape has been reported to be one of the critical acceptability attributes for monolithic dosage forms to be swallowed intact (Jagani et al., 2016). Overall this study demonstrated the influence of shape on the acceptability of medicine to end-user. Previous focus was more towards investigating the effect of surface and size of tablets in regards to patient`s safety during swallowing (Yamamoto et al., 2014). One reason was the availability of techniques (e.g. film-coating) only for improving the surface characteristics of tablets (Capsugel; Colorcon). In the current pharmaceutical market, patient needs drive pharmaceutical product design. Potential benefit of variety of tablet shapes has been more recognised. It is also important to note that changing the shape of medicines can affect their drug release profiles (Goyanes et al., 2015b), this can be used to their advantage, as it allows medicines to be altered to fast and slow release without the addition of more excipients or alteration of the formulation.

The advancements in fabrication technologies enable mass customization, manufacturing the improved design of tablets by changing the shape of tablets. In this respect pharmaceutical industry should consider the impact of shape on acceptability to various patient groups particularly in anticipation of the ageing population (Ogata et al., 2008). Moreover further studies should explore the contribution of the shape aspect to overall acceptability of a solid oral dosage form besides other sensory attributes including size, taste, texture and colour.

4. Conclusion

FDM 3D printing was shown to be effective in producing printlets of varying geometries, sizes and colours. The human panel study showed a variety in PRO in regards to swallowing and picking acceptability of different printlet shapes. While capsule and disc shaped printlets were found to be acceptable in relation to their familiar geometry associated with conventional medicines, the torus printlet was found to be an acceptable novel shape indicating its potential as a 3DP patient centric medicine. The sphere and tilted diamond shapes were reported to receive changing perception about the swallowing acceptability between pre-swallowing and post-swallowing stages. Surprisingly, the tilted diamond received the lowest PRO measured for picking acceptability. Coloured printlets which are still yet to be fully explored are possible and may increase the willingness of people to swallow these formulations. Our study has been the first study to guide the pharmaceutical industry towards developing patient centric medicine in different shapes via 3DP. The advancements in 3DP is expected to increase the familiarity and repeated exposure to the medicine in novel shapes hence bringing the potential to manufacture a wider range of patient centric medicine forms.

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Figure captions

Figure 1. 3D representation of the prepared printlets: A) top view B) side view; from left to right: 1 disc, 2 torus, 3 sphere, 4 tilted diamond, 5 capsule, 6 pentagon, 7 heart, 8 diamond, 9 triangle and 10 cube.

Figure 2. A) An example PRO scoring for swallowing task and B) An example of RRO scoring for picking task which were collected during human panel study

Figure 3. Image demonstrating fabricated geometries presented in four different sizes. For each row: corresponding to weights of 3D printed A) size 0 capsule, B) size 1 capsule, C) size 2 capsule and D) size 3 capsule. From left to right: disc, torus, sphere, tilted diamond, capsule, pentagon, heart, diamond, triangle and cube (units are cm).

Figure 4. Capsule-shaped printlets in different colours. From left to right: black, dark green, turquoise, pink, orange, dark yellow, yellow, light yellow and white (right printlet does not incorporate colorant). Units are cm.

Figure 5. PRO scores for willingness and ability to pick printlet samples (n=50)

Figure 6. PRO scores for willingness to swallow printlet samples (pre-swallowing) (All shapes n=50) and ability to swallow printlet samples (post-swallowing) (sphere n=39; torus n=42; disc n=42; tilted diamond n=32; capsule n=48)

Figure 7. PRO scores for willingness to take printlet samples every day

Figure 8. PRO scores for willingness to swallow printlet samples in different sizes corresponding to weights of 3D printed size 0, size 1, size 2 and size 3 capsule