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Development of Gastro-floating Drug Delivery System by 3D Printing: Impact of Formulation and Design on the Release Profile of Baclofen

Nuha Mohammed Abdulkhaleq*, Mowafaq M. Ghareeb

Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
*Correspondence to: Nuha Mohammed Abdulkhaleq (E-mail: pharmacyone@gmail.com)
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Abstract

Objectives: Baclofen is a skeletal muscle relaxant with a short half-life and a narrow absorption window in the upper part of the gastrointestinal tract, and this study aims to formulate a sustained-release tablet of baclofen and 3D printing of gastro-floating device and study the effect of various polymers and device design on the release profile of baclofen.

Method: Firstly, four formulas were produced through the hot-melt extrusion and direct compression of the extrudate to produce 30 mg baclofen tablets, then four gastro-floating devices (A, B, C, and D) were designed with two air pockets to enable the floating of the device and have drug-releasing windows with total surface area 4, 10, 20, and 40 mm^2 respectively, for drug release. 3D printing of the devices was done by an FDM printer and the tablets were inserted into each device and test it for drug release.

Results: Decreasing the surface area of the drug releasing windows revealed a significant reduction in the dissolution of baclofen irrespective of the type of polymers and useful for sustained release formulation but may be associated with lag time. Devices with one and two releasing windows (Device B and C respectively) sometimes revealed similar dissolution profiles and this related to the position of the window regarding the surface of the dissolution media. Device D with four windows and a 40 mm^2 surface area was found to produce more reliable results. F3 which contains Eudragit RS-100 as the main polymer showed sustained release in device D where the complete dissolution of the drug occurred in 12 hours, and the gastro-floating device remained floating all the time and was assayed for drug content, FT-IR, and DSC study.

Conclusion: Hot-melt extrusion was successfully employed to produce sustained release tablets of baclofen. FDM 3D printers are considered a potential tool to produce gastro-floating devices with the required design and release profile.

Keywords: Baclofen, printing, three-dimensional, gastro-floating device, sustained-release, fused deposition modelling

Introduction

In recent years, the health sciences and pharmaceutical industries have conducted an extensive study into the additive manufacturing technology known as three-dimensional (3D) printing. The term "3D printing" refers to a wide range of 3D printing methods that make use of a wide range of printer technologies and a wide range of materials, all printed at varying resolutions and speeds.[1] Ink-jet (IJ), nozzle, and laser-based 3D printing technologies are the main types and are currently the most widely used in pharmaceutical research.[2] Each main 3D printing type has a variety of sub-types. Fused deposition modeling (FDM), pressure-aided microsyringes (PAM), stereolithography (SLA), and selective laser sintering (SLS) are some of the most prevalent sub-types in the pharmaceutical area.[3] FDM is the 3D printing method that uses heat to melt a thermoplastic filament and extrude it in successive layers to create a 3D object from a digital design. It's considered a cost-effective method for building products with complicated geometry or of virtually of shapes or sizes. Designing and printing devices for specific patients is considered a potential advantage of this type.[4]

Extemporaneous synthesis of unit dosage forms of any dose, customized to the patient, is likely to be the future of medication design and manufacture, moving away from mass production of tablets/capsules with a limited dose range.[5] The development of low-dose drugs with narrow therapeutic indices (such as immunosuppressants and/or blood thinners), increased awareness and importance of pharmacogenomics, and the need to formulate drug combinations are all factors driving this change so the pharmaceutical business must analyze and accept emerging manufacturing technologies to meet this issue and 3D printing is one technology that has such promise.[6]

HME (hot-melt extrusion) is a method that involves driving raw materials through a die at a high temperature to give them a uniform shape and density. HME is a widely used method that can be used to make a variety of pharmaceutical preparations, particularly solid dispersions.[7] Compared to other approaches, HME has a few advantages, for example, it's a one-step, solvent-free, continuous-operation method, as well as a scalable process and is environmentally safe, and cost-effective technology when compared to other pharmaceutical manufacturing techniques.[8] HME has been usually used in pharmaceutical manufacturing with various dosage forms, such as sustained-release tablets, pellets, transmucosal/transdermal films,[9] and implants[10] BSA. HME is a simpler way of continually preparing sustained-release tablets than existing methods.[11]

Oral drug delivery is the most convenient, patient-friendly, cost-effective, and secure way to treat a variety of disorders. Traditional oral formulations have significant drawbacks, including poor targeting ability, short gastrointestinal (GI) tract retention time, and low bioavailability.[12] To solve the problem of traditional oral formulations, gastro-retentive (GR) drug delivery systems were introduced to the pharmaceutical industry.[13] Since the GR system was introduced almost three decades ago, various approaches have been applied to extend the gastric residence time of GR systems, including low-density (floating), high-density (sinking), expandable (swelling), and mucoadhesive systems.[14] Innovative approaches, such as

magnetic field-assisted GR systems, plug-type swelling systems, and floating systems with or without effervescence, have also been applied to prolong gastric retention time.[15] The physiological conditions of the stomach and gastric retention and emptying time are highly variable. The main challenge is to maintain the drug delivery system in the stomach for a sufficient time until all the drugs are released at a predetermined rate in a dynamic physiological condition.[16]

The GR drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems help in continuously releasing the drug, thus ensuring optimal bioavailability.[17]

Recently, research groups have successfully developed a floating capsule-in-3D-printed device (FPD) for the incorporation of a commercial amoxicillin capsule. This device was produced from polyvinyl alcohol (PVA), followed by a crosslinking process to extend the floating time and obtain a sustained release. A longer floating time of the device was achieved as the device was crosslinked for a longer time and at a higher temperature; however, dark color of FPD was obtained.[18]

Previously, the design of devices for GR drug delivery systems has been studied, and it was found that the release lag time can be reduced by creating pores or channels on the devices. The devices can be loaded with both tablets[16,19] or capsules [18] for GR drug delivery systems. Fu et al. invented a tablet-in-device (TiD) system with polylactic acid (PLA) to contain riboflavin sustained-release (SR) tablets. This system was built with two chambers; one contains a tablet, and the other is an air chamber to provide buoyancy. Although this TiD was able to float in the stomach of a rabbit for more than three days, it remained in a position beyond this period and did not leave the stomach.[19]

Baclofen is a centrally acting skeletal muscle relaxant used to treat spasticity. In some clinical trials, it has also been demonstrated to be an effective treatment for alcohol and cocaine addiction. Baclofen is a chemical derivative of the neurotransmitter-aminobutyric acid (GABA), and it works by activating (or agonizing) GABA receptors, specifically, GABAB receptors.[20]

The commercially existing baclofen tablets provide immediate drug release and are associated with dizziness, drowsiness, insomnia, nausea, and a sudden decrease in arterial blood pressure. These unwanted effects are explained by the fast absorption of the drug and elevated plasma levels (plasma levels peaking) after oral administration. Moreover, the drug needs to be taken three or four times daily due to its very short half-life (approximately 2.5 h) which increases the incidence of these side effects, and also it's considered a narrow absorption window drug. Dose titration is needed at the beginning of therapy to reduce the above-mentioned side effects.[21]

This study aims to first formulate sustained-release tablets of baclofen (optimized to release the drug over 12 hr) by HME to be incorporated into the floating device and study the impact of formulation composition on the release profile, the second aim is to develop floating devices by FDM 3D printing using PLA filament (which is safe, biodegradable, and has been widely used in 3D printing[16]) and study the effect of the design of the floating device on drug release by varying the surface areas of the drug releasing windows.

Materials and Methods

Materials

Baclofen and Ethylcellulose were purchased from Baoji Guokang Bio-Technology Co. Ltd. (Baoji, China), Eudragit® RS-100 was donated by Evonik (Darmstadt, Germany). Kollidon® 30 (Polyvinylpyrrolidone K30) was donated by BASF Co. (Ludwigshafen, Germany). PEG 4000 (Polyethylene glycol) was purchased from Himedia Laboratories Co. Ltd. (Mumbai, India). Polylactic acid filament (PLA filament, 1.75 mm in diameter) was purchased from Prusa Research (Prague, Czech Republic).

Preparation of Hot-Melt Extruded Tablets

Baclofen and other excipients were mixed for 15 minutes in 30 gram batches with a mortar and pestle to ensure a uniform mixture. As granules, Eudragit RS-100 was ground using an electric coffee grinder before extrusion. The formulations' composition is shown in Table 1. For all of the formulas, the mixture was extruded using a single-screw Noztek Pro Filament Extruder (Noztek, Shoreham, UK) with a 3 mm nozzle at a screw speed of 15 rpm and an extrusion temperature of 140°C.[22]

The resulting extrudate was ground using an electric coffee grinder then it was sieved through a size #35 USP mesh to eliminate any aggregated or agglomerated particles. Direct compression of the sieved extrudate with a 6 mm round concave punch produced 150 mg tablets equivalent to 30 mg baclofen.

3D Printing of the Gastro-Floating Device

The software Autodesk® Fusion 360 (V. 2.0.10244) was used in the design of the floating devices. The structure of the devices was intended to be quite analogous to that of a capsule. The devices were made to include two air pockets; one in the body and the other in the cap. Additionally, the body of the device has a hollow section where the tablet can be placed. Around this hollow section, windows for drug release were designed where four devices were designed with a different number or dimensions of drug releasing windows as shown in Table 2.

All the devices have a height of 20 millimeters, an interior diameter of 8 millimeters, and a thickness of 0.5 millimeters. Using a Prusa i3 MK3S FDM 3D printer (Prusa Research, Prague, Czech Republic) equipped with a 0.4 mm nozzle and a commercial PLA filament, the gastro-floating devices were printed. The temperature of the extruder was set to 200°C, while the temperature of the platform was set to 70°C. The following is the configuration of the printing system: Infill percentage is 100%, layer height is 0.1 mm, and printing speed is 50 mm/sec. After the devices had been constructed, the baclofen tablet that had been prepared was inserted into the

Table 1. **Formulations composition (%w/w)**

Formula	Baclofen	PVP K30	PEG 4000	Eudragit RS-100	Ethyl cellulose
F1	20	75	5	-	-
F2	20	50	5	25	-
F3	20	25	5	50	-
F4	20	65	5	-	10

Table 2. **Illustrative design of the floating devices**

Device	A	B	C	D
Front view				
Slice view				
No. of windows	1	1	2	4
Windows size	2 × 2 mm	2 × 5 mm	2 × 5 mm	2 × 5 mm
Total windows surface area	4 mm^2	10 mm^2	20 mm^2	40 mm^2

center compartment of the body, and the cap was then locked to form the entire gastro-floating system.

Drug Content Determination

The drug content of all prepared formulations was measured spectrophotometrically by dissolving 100 mg of sieved ground extrudate of each formula in 100 ml of 0.1N HCl and kept for 12 hr under stirring before filtering it, then 1 ml of the filtrate was diluted to 10 ml with 0.1N HCl, absorbance was measured spectrophotometrically at λmax 220 nm, and drug content was determined accordingly.[21]

In vitro Buoyancy Studies

The *in vitro* buoyancy was calculated using the Roy et al. method where floating lag time and total floating time were calculated. The gastro-floating devices ($n = 3$) were submerged in 100 ml of 0.1 N HCl with a tablet inside the capsular device. Floating lag time is the time it takes for the device to rise to the surface and float. The total floating time was calculated as the amount of time the dosage form remained on the surface at all times.[23]

In-Vitro Dissolution

The *in vitro* release rates of baclofen were determined by inserting a tablet from each formula into the four 3D printed gastro-floating devices (A, B, C, D) respectively and placing it in 900 ml of 0.1 N hydrochloric acid (pH 1.2) as a dissolution medium at 37 ± 0.5°C. Drug release was performed using USP dissolution apparatus type II (paddle type) at 50 rpm for 12 hr. Aliquots of 5 ml were withdrawn at the following time intervals: 5, 10, 15, 30, 60, 90, 120 min then every hour until 12 hr. The samples were filtered and the medium was replenished with a similar volume of fresh medium. Using the dissolving liquid as a blank, the quantity of baclofen was measured using spectrophotometry at 220 nm, and the percentage of drug release in total was computed. The outcome was calculated as the average of three runs.[21]

Characterization of the Selected Formula

Differential Scanning Calorimetry (DSC)

A DSC 60 (Shimadzu, Japan) was used to measure the thermodynamic properties of pure Baclofen and the selected formula (F3). It was heated at a rate of 10°C/min between 25°C and 300°C in an aluminum pan under a dry nitrogen purge. An empty aluminum pan was utilized as a reference to calibrate the DSC temperature and enthalpy scales using indium/zinc standards.[24]

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pure Baclofen and selected formula (F3) were obtained by using an FTIR spectrophotometer (Lambda scientific 8300, Australia). Samples were ground and mixed with dry potassium bromide then pressed in the form of discs using a hydraulic press. The samples were analyzed at wave numbers (4000–500 cm^{-1}).[25]

Results and Discussion

Drug Content Determination

The content of Baclofen in the formulas was analyzed using a UV–Visible spectrophotometer. Drug content was in the range of 98.8 to 100.4% as shown in Figure 1 indicating no significant drug loss occurred during HME since extrusion temperature was lower than the melting point of baclofen.[26]

In vitro Buoyancy Studies

The *in vitro* floating ability of the gastro-floating device that had a baclofen tablet incorporated inside of it was evaluated. The floating lag time was relatively zero because the device floated at the surface immediately after being immersed in the medium for all of the formulas. On the other hand, the total

floating time was more than 12 hours for all of the formulas because the device remained floating until 12 hours after the beginning of the experiment.

In-vitro Dissolution

The drug release of each formula was tested in the four devices (A, B, C, and D) so the release of the F1 tablet in device (A) was donated as F1A and so on for the other formulas and devices.

Dissolution curves of F1, F2, F3, and F4 in the four devices are shown in Figures 2-5 respectively.

Since the aim of this work was to produce sustained release tablets that release the drug over 12 hr, F3 was selected as the optimized formula as F3D released 96% of the drug over 12 hr and was selected for further characterization.

Characterization of the Selected Formula

Differential Scanning Calorimetry (DSC)

The thermal behavior of pure Baclofen showed a sharp endothermic peak at 209.9°C as shown in Figure 6, corresponding

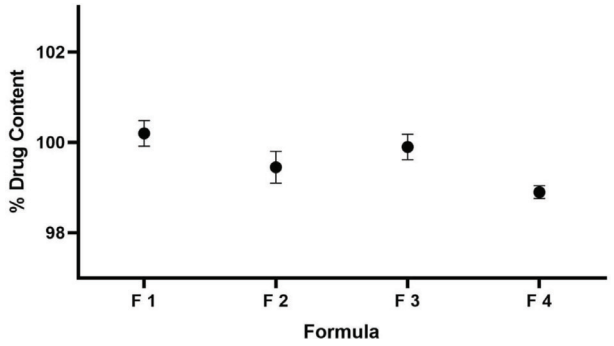

Fig. 1 **Drug content of sustained-release tablets (mean ± SD, *n* = 3).**

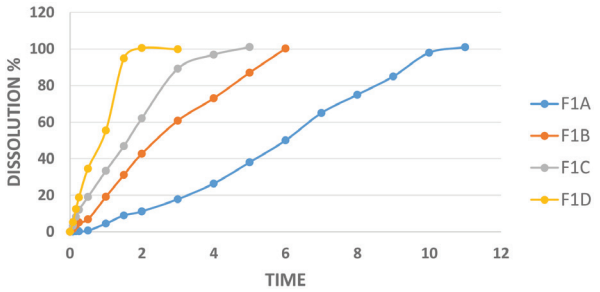

Fig. 2 **The dissolution profile of F1 tablets in devices A, B, C, and D.**

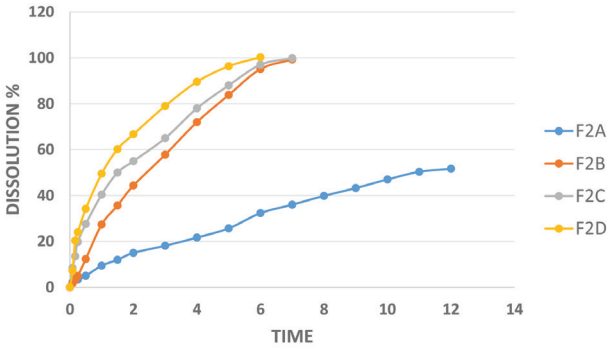

Fig. 3 **The dissolution profile of F2 tablets in devices A, B, C, and D.**

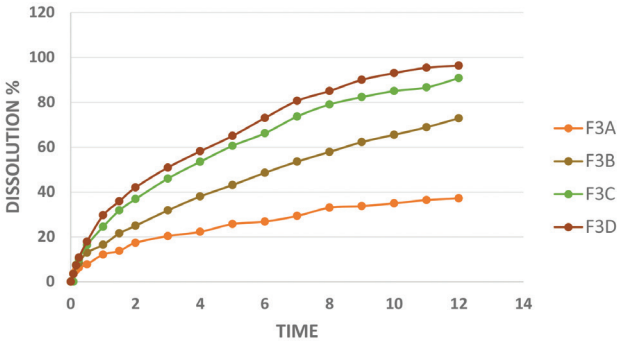

Fig. 4 **The dissolution profile of F3 tablets in devices A, B, C, and D.**

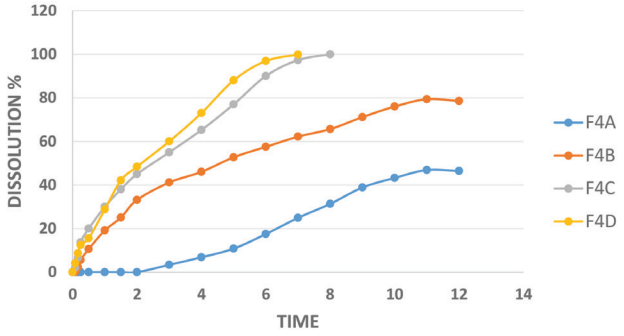

Fig. 5 **The dissolution profile of F4 tablets in devices A, B, C, and D.**

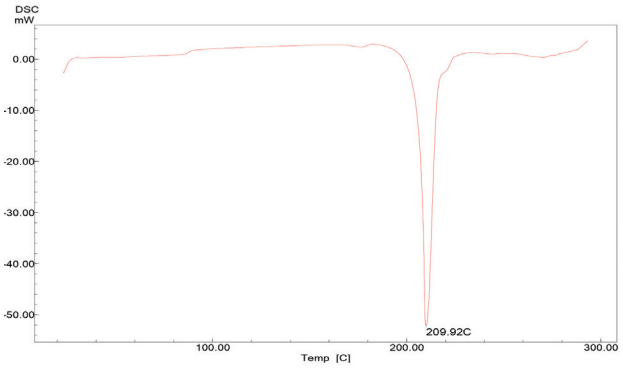

Fig. 6 **DSC thermogram of pure baclofen.**

to baclofen melting temperature, with the onset of a peak at 200°C and end set at 220°C, indicating that the drug is present in a crystalline state.[27]

The thermogram of the extrudate of F3 containing baclofen, Eudragit RS-100, PVP K30, and PEG 4000 is shown in Figure 7. The polymer PEG 4000 exhibits a peak at 58.25°C, which corresponds to its glass transition temperature.[28] The disappearance of the sharp endothermic peak of baclofen can be attributed to the conversion of baclofen from the crystalline state to the amorphous state as well as the dilution of baclofen concentration as it consists of 20% of the total weight of the formula. The endothermic peak at 185.81°C is belong to the Eudragit RS-100.[29]

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectroscopy has been used to investigate possible interactions between the drug and polymers in solid dispersion systems. The crystalline baclofen shows the primary amide N-H stretching vibration band at 3407 cm^{-1} (Figure 8).

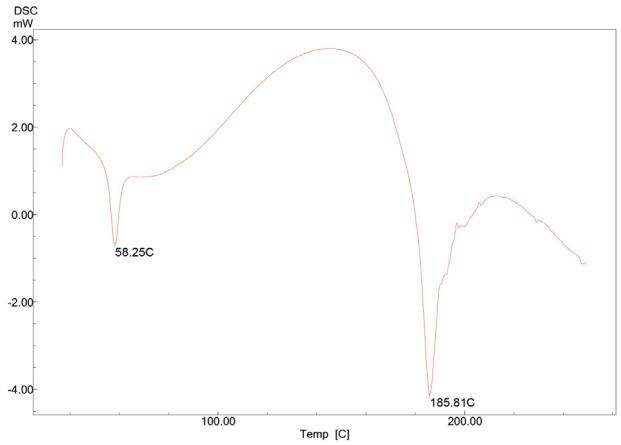

Fig. 7 **DSC thermogram of F3 extrudate.**

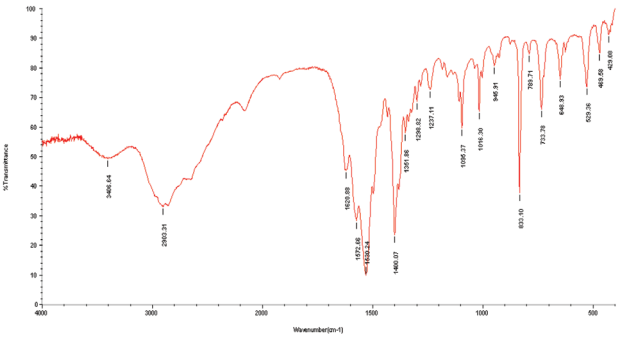

Fig. 8 **FTIR of pure baclofen.**

A strong band of C=O stretching was seen at 1621.84 cm^{-1}, for the O-H group of acid exhibited stretching frequencies at 2904 cm^{-1}. The bands occurring in the 734 cm^{-1} were assigned for C-Cl stretching. The presence of C=C in the aromatic ring was seen in 1573 cm^{-1}.[30]

The spectrum of the ground extrudate of F3 selected formulas showed no significant differences from pure Baclofen (Figure 9), which indicated that no new chemical bonds were created during the formation of solid dispersion and proved there was good compatibility between the drug and excipients.

Discussion

The baclofen tablet used in this study actually was different from the marketed immediate release baclofen tablets. Hot-melt extrusion was used to formulate baclofen tablets with various releasing properties where immediate release and sustained release polymers were used to study the effect of polymers and device design on the release properties. The gastro-floating system aimed to achieve long-term release of baclofen in the stomach so that the loaded tablet had to always be limited in the floating device and the formula which gives sustained release of baclofen over 12 hours (F3D) was selected for further characterization.

F1 was composed of PVP K30 as an immediate release polymer and PEG 4000 as a plasticizer and the release profile of F1 tablets in the four devices is shown in Figure 2. F1A showed sustained release of baclofen despite using immediate release polymers where the complete release of the drug

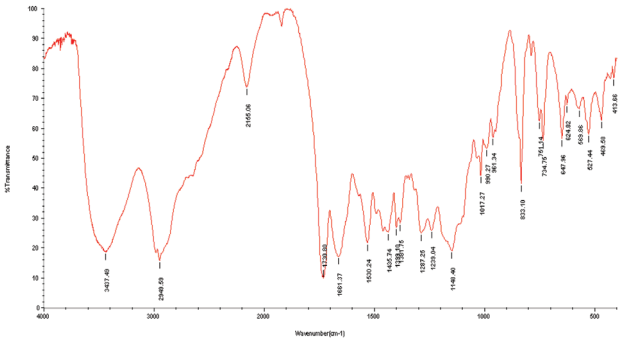

Fig. 9 **FTIR of F3 extrudate.**

occurred after 10 hrs and this was attributed to the small drug releasing windows surface area (4 mm^2) that restricts dissolution media entry inside the hollow section of the capsular device thereby slows drug release.[14] Increasing the surface area of the drug releasing windows to 10 mm^2 and 20 mm^2 in F1B and F1C significantly enhanced the dissolution rate where complete drug release occurred after 5 and 6 hrs respectively. F1D with the largest windows surface area (20 mm^2) showed the fastest release where the complete release of the drug occurred after 2 hrs.

The addition of Eudragit RS-100 in F2 while reducing PVP K30 concentration significantly reduced the dissolution rate of baclofen since Eudragit RS-100 is a sustained release polymer and used for a customized release profile.[31] Release profile of F2 in the four gastro-floating devices is shown in Figure 3.

F2A significantly retained the dissolution of baclofen where about 50% of the drug was released after 12 hrs compared to F2D where the complete release of the drug occurred after 6 hrs. It's worth noting that sometimes the release profile of devices B and C are quite similar as in F2 where the similarity factor (f2) between F2B and F2C is 50.7 and this may be attributed to the position of the device in the dissolution jar since it's positioned horizontally and in the device (C) one of the windows is immersed inside the dissolution media and the other window which is against it is above the dissolution media so media entry into the device is relatively done through one window and this is similar to the device (B) which have only one window.

Increasing the concentration of Eudragit RS-100 to 50% in F3 compared to 25% in F2 results in further retardation of baclofen dissolution (Figure 4) as its insoluble polymer and drug release is mainly occurs by diffusion suggesting that the matrix with higher insoluble polymer content provides a more tortuous pathway, and/or a less porous tablet was formed.[26] Also in F3 we can notice that there is no significant difference between the dissolution profile of F3C and F3D where the similarity factor (f2) was 63.2, and this may be due to the insoluble nature of Eudragit RS-100 which requires a time for media entry into the device and drug diffusion and doubling the windows surface area does not significantly affect the dissolution rate, and another cause is the position of the device, specifically the position of the windows towards the surface of the dissolution media, which affect media entry into the device.[32]

The addition of 10% ethyl cellulose in F4 instead of PVP K30 in F1 also results in extending the dissolution rate as it's an insoluble polymer and has been used in the formulation of

sustained-release dosage forms.[33] Dissolution profile of F4 in the four gastro-floating devices is shown in Figure 5. F4A started the release of the drug after 2 hr from the start of the experiment and this is due to the position of the drug releasing window where it was above the surface of the dissolution media when placed in the dissolution jar at the start of the experiment and after 2 hr the device flipped and the entry of the dissolution media into the hollow section of the device started and thus tablet dissolution started, this fact is considered a disadvantage of this device design although it can be used for altering the release profile into sustained release but it may be associated with an unintended lag time. F4C and F4D also have similar dissolution profiles where the similarity factor (f2) was 64.7 as seen in F3.

In conclusion, HME is considered a good option in the formulation of sustained release tablets with the ability to modify the release profile depending on the type of polymers used. FDM 3D printers are considered a potential tool to produce gastro-floating devices with the required design and release profile. Although manipulation in the number and size of the drug releasing windows results in changing the release profile where decreasing the total surface area of the drug releasing windows revealed a significant reduction in the dissolution rate, but its not always predicted as either a lag time occurs as seen in device A or a relatively similar dissolution profile may occurs as seen in device B and C. Increasing the number of drug releasing windows thus total surface area ensure suffient dissolution media entry into the hollow section of the device and tablet immersion while keeping the tablet floating and produce a more reliable dissolution profile that depends mainly on the composition and the type of the tablet inside the device. The introduction of gastro-floating devices into the pharmaceutical industry will make feasible of altering any tablet into a floating tablet.

Further *in vivo* investigations are recommended to study and efficacy of the 3D printed gastro-floating devices.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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