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Combination of FDM 3D Printing and Compressed Tablet for Preparation of Baclofen as Gastro-Floating Drug Delivery System (Conference Paper)#

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Abstract

This study aimed to develop an oral drug delivery system for gastro-retentive sustained drug release of baclofen by using a 3D printed capsular device since baclofen has a short half-life of 2.5 to 4 hr and has a narrow absorption window. Firstly sustained-release tablets of baclofen were formulated through the hot-melt extrusion of various thermoplastic polymers and direct compression of the extrudate, then a capsular device was designed and 3D printed to contain two air pockets to enable floating of the device and has four windows for drug release. 3D printing of the capsular device was done by an FDM printer using biodegradable polylactic acid (PLA) filament, and the sustained release tablets were inserted into the device to allow the medicine to be released into the stomach over a longer period. An in vitro buoyance test and an in vitro dissolution test were used to examine the buoyancy and sustained-release features of the formulated gastro-floating system.

Five sustained release formulas were developed using different thermoplastic polymers in hot-melt extrusion. Produced tablets were assayed for drug content, hardness, and friability while a DSC study was done on the selected formula. F 5 which contains 20% baclofen, 55% Eudragit RS-100, 20% ethylcellulose, and 5% PEG 4000 showed sustained release where the complete dissolution of the drug occurred in 12 hr, and the gastro-floating device remained floating all the time.

This method has a great potential for developing various floating drug delivery systems with the required release profile.

Keywords: Sustained-release, 3D printing, Hot-melt extrusion, Gastro-floating device, Baclofen.

الجمع بين الطباعة ثلاثية الابعاد و الحبوب المضغوطة لتحضير دواء الباكلوفين كجرعة دوائية طائفة (بحث مؤتمر)#

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الخلاصة

هدفت هذه الدراسة إلى تطوير التحرر الدوائي المستمر لدواء الباكلوفين من خلال استخدام كبسولة مطبوعة بطابعة ثلاثية الأبعاد لتمكن حبوب الباكلوفين للطفو والبقاء في المعده لأن الباكلوفين يتراوح عمره النصفي من ٢,٥ إلى ٤ ساعات واكثر الدواء يكون امتصاصه من الجزء العلوي للجهاز الهضمي. اولا تمت صياغة حبوب الباكلوفين ذات التحرير المستمر من خلال البثق بالذوبان الساخن باستخدام العديد من البوليمرات المتميعة بالحرارة ثم كبس المنبثق الناتج على شكل حبوب، بعد ذلك تم تصميم كبسوله و طباعتها باستخدام خيوط قابلة للتحلل بالطابعة ثلاثية الابعاد بشكل يحتوي على اثنين من الجيوب الهوائية التي تساعد على طفو الكبسوله ولها أربع نوافذ لإطلاق الدواء.

تم استخدام الطباعة ثلاثية الأبعاد لطباعة جهاز كبسولي باستخدام خيوط PLA القابلة للتحلل ، وتم إدخال أقراص الباكلوفين ذات التحررالدوئي المستمر في الكبسولة للسماح بتحرير الدواء في المعدة على مدى فترة أطول. تم استخدام اختبار الطفو في المختبرواختبارالذوبان في المختبر لفحص ميزات الطفو والتحرير المستمر لنظام العوم المعدي المصمم.

تم تطوير خمس صيغ ذات تحرر دوائي مستمر باستخدام بوليمرات مختلفه المتميعة بالحرارة في البثق بالذوبان الساخن. . تم تقييم الأقراص المنتجة من حيث محتوى الدواء والصلابة والتفتت بينما أجريت دراسة DSC على الصيغة المختارة. أظهر F 5 الذي يحتوي على ٢٠٪ باكلوفين ، و ٥٥٪ Eudragit RS-100 ، و ٢٠٪ إيثيل سلولوز ، و ٥٪ PEG 4000إطلاقًا مستدامًا حيث حدث انحلال كامل للدواء خلال ١٢ ساعة ، وظل الجهاز المعدي عائمًا طوال الوقت..

تتمتع الطابعه ثلاثية الابعاد بإمكانية كبيرة لتطوير أنظمة مختلفة لتحريرالدواء على مدى طويل طافيا في المعدة.

الكلمات المفتاحية: تحرر دوائي مستمر، طباعة ثلاثية الأبعاد ،قذف بالذوبان الساخن، جهاز عائم معدي، باكلوفين

Introduction

Gastroretentive (GR) systems are meant to keep medication formulations in the stomach for longer periods of time, increasing the oral bioavailability of pharmaceuticals with a restricted gastrointestinal tract absorption window. GR systems can also help medications that have low stability in the lower gastrointestinal tract or treatments that operate locally within the stomach [(1)].

The gastroretentive drug delivery systems can be retained in the stomach and help with the oral sustained delivery of medications with a specific absorption window in the gastrointestinal tract. These systems aid in the continual release of the medicine, resulting in maximum bioavailability [(2)].

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Drugs with a narrow absorption window are those that are absorbed primarily in certain regions of the gastrointestinal tract (GIT), such as baclofen, which is absorbed preferentially in the upper part of the GIT [(1)]. Reformulation of these medications into sustained-release forms confronts significant hurdles, as while the dosage form must deliver prolonged drug release, it must also keep the drug in close proximity to the absorption site [(3)].

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 γ-aminobutyric acid (GABA), and it works by activating (or agonizing) GABA receptors, specifically GABAB receptors [(4)]. Baclofen is rapidly and extensively absorbed and eliminated. The half-life of the drug is ~2.5 to 4 hr in plasma [(5)]. Baclofen has a narrow absorption window in the upper gastrointestinal system, resulting in limited bioavailability [(6)]. Baclofen is challenging to manufacture into sustained-release dosage forms since its absorption is reduced or non-existent once it reaches the colon (or even before).

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. HME characteristics such as die geometry, feeding rate, temperature, barrel design, shearing force, and screw rotating speed should all be considered. Researchers can contribute to the development of a desirable final product with a preferred drug release profile and uniformity of size, shape, and drug content by optimizing these parameters. 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 [(7)]. HME offers the advantage of being environmentally safe, and cost-effective technology when compared to other pharmaceutical manufacturing techniques. Furthermore, by generating solid dispersions and solid solutions, HME enhances bioavailability. This is important for pharmaceutically insoluble compounds, which are common among newly discovered compounds [(8)]. HME was utilized to make sustained-release tablets, pellets, and granules, among other pharmaceutical drug delivery systems [(9)]. The type of polymer plays an important role in manufacturing the type of drug delivery system such as ethylcellulose was applied for the melt extrusion of sustained-release mini-matrices [(10)], and other thermolabile polymers such as Eudragit RL-100, Eudragit RS-100, and polyethylene oxide can be used for the sustained release dosage forms.

Fused Deposition Modelling (FDM) is a 3D printing technique that relies on the extrusion of thermoplastic filament through a high-temperature printing head with a nozzle that moves on the X and Y axis, thereafter solidification of the melted filament on a platform that moves in the Z-axis. The 3D structure will be formed from the deposition of the melted filament in a layer by layer so as the first layer solidify immediately after extrusion, the next layer will be extruded above till the 3D structure is complete according to the digitally designed object [(11)]. Due to the utilization of comparatively simpler and less expensive equipment, a varied selection of excipients, and the simplicity of generating dosage forms, even with complicated geometries, that have acceptable patient acceptability, FDM is the most commonly assessed 3D printing approach in the pharmaceutical sciences [(12)].

In this work, a gastro-floating system for baclofen was developed using 3D printing technology for oral delivery with sustained release, allowing plasma baclofen concentration to be maintained for an extended length of time. Rapid prototyping, which is a versatile tool for developing unique pharmaceutical dose formulations with different and complex geometry, is one of the key advantages of 3D printing technology. As a result, we set out to create a gastro-floating device using 3D printing technology and insert a baclofen sustained-release tablet made using hot-melt extrusion into it. The air pockets inside the device, which were manufactured using an FDM 3D printer, were credited with the device's capacity to float. The baclofen formulation inserted into the floating device allowed for sustained release of the drug.

Materials and Method

Materials

Baclofen, Ethylcellulose, and Polyethylene Oxide 600 K (PEO Mw 600,000) were purchased from Baoji Guokang Bio-Technology Co Ltd (Baoji, China). Eudragit® RL-100, and RS-100 were 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

The formulations' composition is shown in Table 1. As granules, Eudragit RS-100 and Eudragit RL-100 were crushed by a miller before extrusion. Baclofen and other excipients were mixed for 15 minutes in 30 gram batches with a mortar and pestle to ensure a uniform mixture. 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 [(13)].

A miller crushed the extrudate before sieving it 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.

Table 1.Formulations composition for HME tablets (%w/w)

Formula	Baclofen	Ethyl cellulose	PVP K30	PEG 4000	PEO 600K	Eudragit RL-100	Eudragit RS-100
F1	20	20	55	5	-	-	-
F2	20	30	45	5	-	-	-
F3	20	20	-	5	55	-	-
F4	20	20	-	5	-	55	-
F5	20	20	-	5	-	-	55

3D Printing of the gastro-floating device

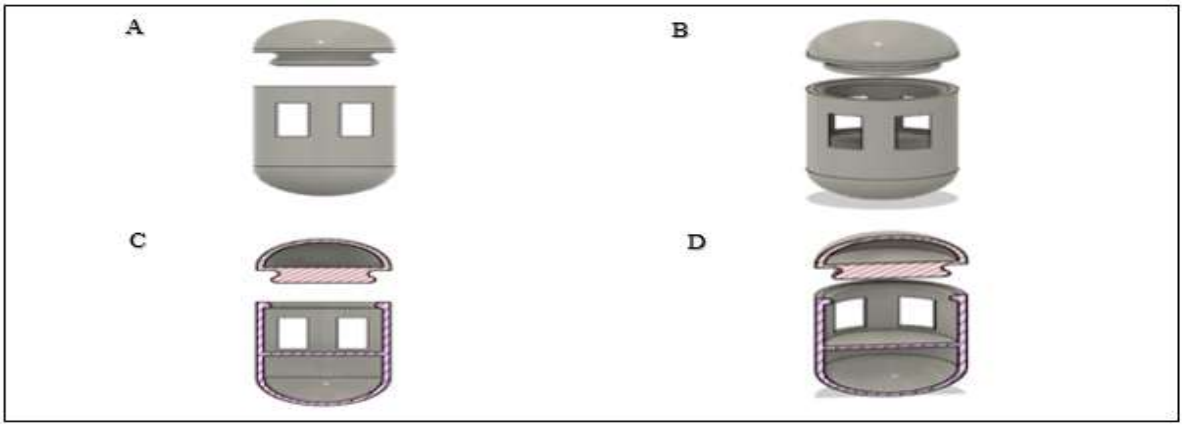

Figure 1. 3D design of the gastro-floating device, (A) Front view, (B) Side view, (C) Front sectional view, and (D) Side sectional view.

Drug content determination

The drug content in all prepared formulas was determined spectrophotometrically, where 100 mg of the sieved ground extrudate was dissolved in 100 ml of 0.1N HCl and kept for 12 hr under stirring then filtered. Then 1 ml of the filtrate was diluted to 10 ml with 0.1N HCl and spectrophotometric absorbance was taken at λmax of 220 nm and drug content was calculated accordingly [(14)].

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 device (n = 3) was 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 [(15)].

In-vitro dissolution studies

The in vitro release rates of baclofen were determined by inserting a tablet from each formula into the 3D printed gastro-floating device 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 [(14)].

Characterization of the selected formula

Tablet hardness

The crushing strength of three tablets from each selected formula was measured using a YD-1 tablet hardness tester (Huanghua Faithful Instrument Co., China), whereby an increasing force was applied to the tablet until it was fractured [(16)].

Friability test

An Erweka friability tester TA3R (Erweka GmbH, Heusenstamm, Germany) was used to determine the friability of the compressed tablets of the produced formulations. Twenty tablets from each formula were weighed and placed in the drum, which was rotated at 25 rpm for four minutes, after which the tablets were reweighed and the weight differences were calculated and shown as a percentage [(17)].

Weight variation

Twenty tablets were weighed each one separately; later, the average weight was measured. If the weights of no more than two of the tablets are outside the % limit and no tablet differs in weight by more than double that percentage, the conditions are met [18].

Differential scanning calorimetry (DSC)

Thermodynamic analysis of pure Baclofen, as well as the extrudate of a selected formula (F5), were determined using a DSC 60 (Shimadzu, Japan). The samples (5-6 mg) were placed in an aluminum pan and heated at a rate of 10°C/min between 25°C and 300°C under a dry nitrogen purge. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale, while an empty aluminum pan served as the reference [19].

Results and Discussion

Drug content

The chemical integrity of baclofen in the extrudate was analyzed using a UV–vis spectrophotometer. Drug content was in the range of 98.9% to 101% as shown in (Fig. 2) indicating no significant drug loss occurred during HME since extrusion temperature were lower than the melting point of baclofen which is 208°C [5].

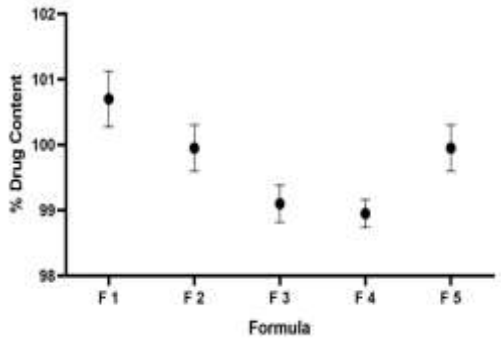

Figure 2. Drug content of sustained-release tablets (mean SD, n=3).

In-Vitro buoyance studies

In vitro floating ability of the gastro-floating device with baclofen tablet incorporated inside it was evaluated where the floating lag time was relatively zero as the device floated at the surface immediately after being immersed in the medium for all the formulas, while the total floating time was more than 12 hr for all the formulas since the device remained floating until 12 hr after the start of the experiment.

In-Vitro dissolution Studies

In the present study, the combination of HME and FDM 3D printing was successfully employed to prepare a sustained-release tablet and gastro-floating device to increase the residence time of baclofen at or above the absorption window.

Different polymers were tested which are PVP K30, PEO 600K, Eudragit RL-100, Eudragit RS-100, and ethylcellulose, in addition to PEG 4000 was added as a plasticizer to reduce the extrusion temperature. The gastro-floating device was floating from the start of the study until the end after 12 hr (Fig. 3). The release profile of the developed formulas is shown in Figure 4.

F 1 showed the fastest release among other formulas since PVP K30 is a hydrophilic polymer and used for solubility enhancement and immediate release dosage forms but the addition of ethylcellulose slowed the release since it's a water-insoluble polymer and used for modified release dosage forms [20,21].

Increasing the percentage of ethylcellulose to 30% in F2 reduced the dissolution rate to 85% in 12 hr because of the retardation effect of ethylcellulose [10].

Replacing PVP K30 in F 1 with PEO 600K in F 3 resulted in a slower release of baclofen since PEO is used for extending the drug release depending on the molecular weight, although its hydrophilic polymer but the interaction of the polymer with water causes the hydration and swelling that develops a hydrogel layer and this drives the entry of water within the matrix which regulates the controlled release behavior of drugs from the system [22].

F 4 and F 5 which have Eudragit RL-100 and Eudragit RS-100 respectively as a sustained-release polymer in addition to ethylcellulose showed relatively similar dissolution profiles with similarity factor (f2) equal to 73.1 and reaches complete release in 12 hr. F 5 released more than 50% of the drug after 3 hr while F 3 released 47% of the drug after 3 hr and this is related to the specification of the polymers where the sustained release effect was more obvious after 3 hr. Since the aim of this work was to develop a sustained release tablet of baclofen that can release the drug over 12 hr, so F 5 which released 99% of the drug in 12 hr was selected for further characterization to study the effect of hot-melt extrusion and other tableting processes.

Figure 3. Gastro-floating device with F5 sustained-release tablet inside it.

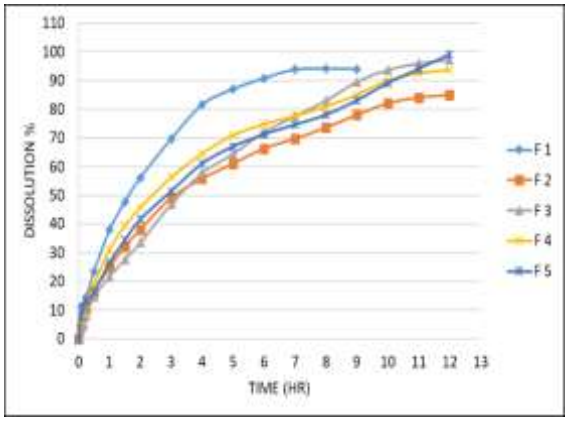

Figure 4. *In-Vitro* drug release of baclofen tablet incorporated into a gastro-floating device

Tablet hardness

The hardness of the prepared tablets was within the acceptable limit [23] (equal to or more than 4 Kg), so that means they can withstand and resist breaking during handling and packaging as shown in Table 2.

Friability test

A Friability test was performed to investigate the capacity of the tablets to resist chippings and abrasion that happened during handling, packaging, and shipping. All the prepared tablets were non-friable and the percent of friability for all prepared tablets is below one (Table 2).

Weight variation

The weight variation of tablets is shown in Table 2, the result was found in the range of 149 ±1 to 150 ±1 from all the formulations. This fulfills the USP requirements in the limit of ±7.5% of the average weight. That means no large difference is observed in the weight of individual tablets from the labeled weight due to good mixing and no particle aggregation or fluidity that may cause differences in the die filling and difference weight of the tablet and strength [24].

Table 4. Physical properties of HME tablets

Formula	Tablet Hardness (KG)	Friability %	Weight variation (mg) ± SD
F1	8.6 ± 0.1	0.06	149.9 ± 0.15
F2	8.1 ± 0.2	0.06	150.1 ± 0.26
F3	7.2 ± 0.31	0.09	150 ± 0.38
F4	8.1 ± 0.5	0.05	150.1 ± 0.2
F5	8.5 ± 0.15	0.03	150 ± 0.12

Differential scanning calorimetry (DSC)

The thermal behavior of pure Baclofen showed a sharp endothermic peak at 209.92°C corresponding to baclofen melting temperature with the onset of a peak at 200 °C and end set at 220 °C which indicates that the drug is present in a pure crystalline state as shown in Figure 5, this DSC study was in agreement with the reported one [25].

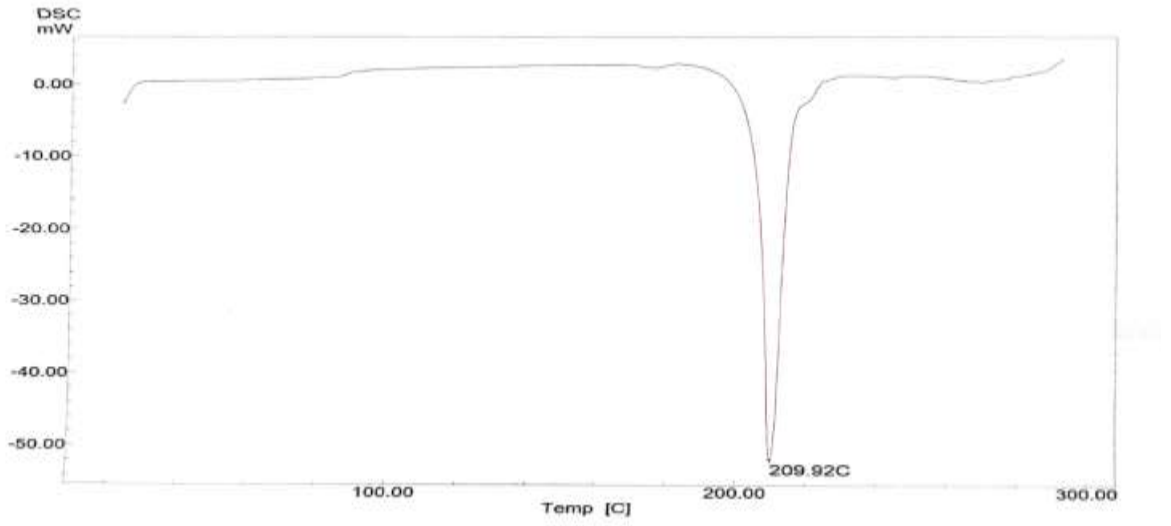

Figure 5. DSC thermogram of pure baclofen.

The thermogram of the extrudate of F 5 which contains baclofen, Eudragit RS-100, ethylcellulose, and PEG 4000, is shown in Figure 6. PEG 4000 has shown a peak at 57.09 °C that is attributed to the glass transition temperature of the polymer [26], the sharp endothermic peak of baclofen has been disappeared and this may be attributed to the conversion of baclofen from the crystalline state to the amorphous state and also due to the dilution

of baclofen concentration as its added in 20% of the total weight of the formula. The endothermic peak at 187.54 °C is belong to the ethylcellulose after processing in HME [21].

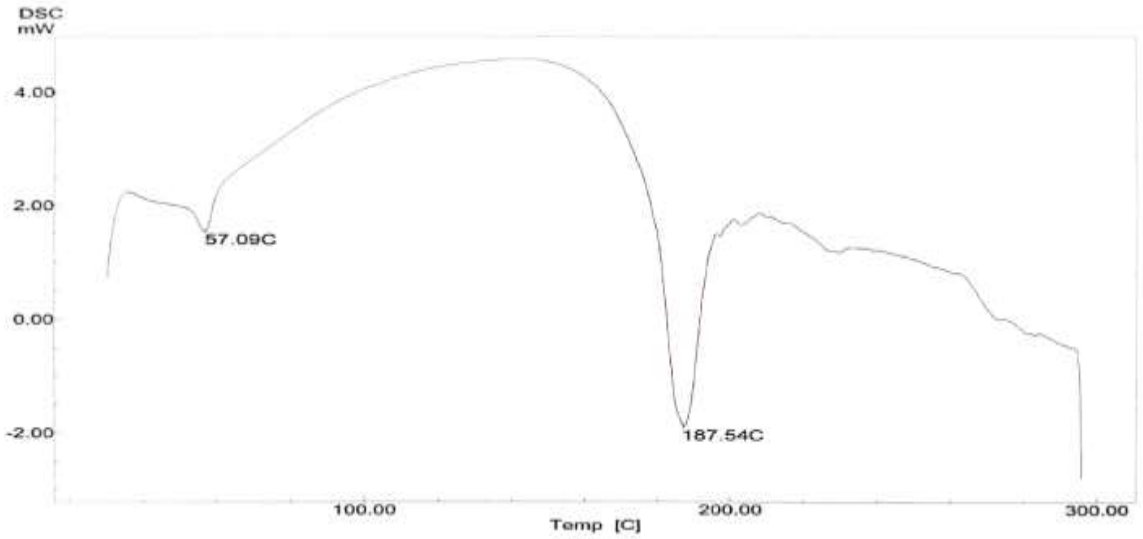

Figure 6.DSC thermogram of F 5 extrudate.

Conclusion

Formulation of baclofen sustained-release tablets was successfully done through hot-melt extrusion where the selection of thermoplastic polymers and their concentration were crucial to obtain the required release profile.

The incorporation of 3D printing in the formulation of capsule shells and the ability to create complex designs allowed the manufacturing of gastro-floating capsule shell that remains floating for more than 12 hr and this can be an advantage of converting any dosage form into a floating system with the required release profile.

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