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Research Article

Formulation Development and Evaluation of Biodegradable Stent of Atorvastatin and Clopidogrel for Treatment of Atherosclerosis

Vishvesh Kanabar*, Vipul Patel

Department of Pharmaceutics, School of Pharmacy, RK University, Rajkot, Gujarat, India

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ABSTRACT

This study aimed to create, develop, and optimize a biodegradable stent made of polylactic-co-glycolic acid (PLGA) that contained clopidogrel and atorvastatin for the management of asthma. Solvent casting was used to create biodegradable stents. In particular, PLGA 75:25 polymer films were used to create stents using the solution-casting method. The base material was created by dissolving the polymer in isopropyl alcohol and adding PEG 400 as a plasticizer. Clopidogrel and atorvastatin were used as the active pharmaceutical ingredients in the stents. The resulting mixture was homogenized to avoid air bubbles before being poured onto metal pans and allowed to gently evaporate in a refrigerator. The polymer films were then cut into strips, wound around cylindrical rods to form helical stents, and baked in an oven to guarantee that all of the isopropyl alcohol had evaporated. The biodegradable polylactic acid stents that included clopidogrel and atorvastatin demonstrated an impressive 99.34 ± 0.44% encapsulation efficiency. Differential scanning calorimetry (DSC) analysis revealed that there were no chemical interactions between the stent's component parts. Significant water absorption over 80% was seen over a period of 8 days, which is remarkable. A thorough effect on disrupting plaque was seen at day 21, and on day 22, the stent began to biodegrade. Over the course of 20 days, the cumulative medication release percentage rose to 99.92%. According to the study's findings, treating atherosclerosis with an optimized biodegradable polymeric stent made of PLGA and combining atorvastatin and clopidogrel is a novel and promising treatment option.

Introduction

As the primary cause of death and morbidity, cardiovascular diseases—of which atherosclerosis is at the forefront—continue to have a substantial negative impact on world health. Atherosclerosis is a complicated and multifaceted problem that is defined by the gradual buildup of lipid-rich plaques inside artery walls. Although there has been progress with traditional methods such as medication therapy and lifestyle changes, novel strategies that directly address the underlying pathophysiology are still desperately needed.

In this regard, biodegradable stents have surfaced as a viable approach to address the complex problems related to atherosclerosis. These stents have the potential to completely change the way atherosclerosis is managed because they are specifically made for the controlled delivery of lipid-lowering medications.[1] The fascinating field of biodegradable stent technology is examined in this article, along with how it can improve patient outcomes by lowering restenosis, improving site-specific medication delivery, and more.[2]

We begin the complex process of bringing this innovative therapeutic strategy from the lab to clinical practice by exploring the broad formulation development and evaluation field. The next parts will clarify the fundamental ideas, approaches, and most current developments in this field, providing insightful information on the direction that cardiovascular medicine is headed.[3]

These cutting-edge stents offer a distinct advantage by precisely targeting the diseased location, effectively minimizing potential systemic side effects, and maximizing

***Corresponding Author:** Mr. Vishvesh Kanabar

Address: Department of Pharmaceutics, School of Pharmacy, RK University, Rajkot, Gujarat, India

Email ✉**:** vishvesh.kanabar@rku.ac.in

Tel.: +91-7433900011

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medication concentrations at the lesion. Their slow deterioration over time also solves the permanent drawbacks of metallic stents, namely the possibility of late-stage restenosis and the requirement for ongoing antiplatelet medication.[4]

This study gives a comprehensive idea of the changing field regarding biodegradable stents as a therapeutic platform for managing atherosclerosis. Focusing on the finer points of formulation creation and thorough assessment, we want to reveal this cutting-edge technology's revolutionary potential for cardiovascular therapy.[5] We will explore basic concepts, different formulation approaches, drug release kinetics mechanisms, and the difficulties in transferring this technology from lab to clinical settings in the sections that follow. We will also discuss important aspects of the design of biodegradable stents, including as mechanical characteristics, drug-polymer interactions, and biocompatibility.[6] Our objective is to offer a thorough understanding of the potential and difficulties associated with biodegradable stents in the management of atherosclerosis by illuminating these crucial aspects, thereby advancing the field of cardiovascular healthcare. The intersection of pharmacology, material science, and medical device engineering presents tremendous promise for improved therapy modalities for atherosclerosis; this paper aims to clarify the way forward.[7]

This innovation is unique compared to previous work since it has several benefits over conventional metallic stents. First of all, because they progressively break down and are absorbed by the body, they remove the requirement for long-term foreign material inside the vessel.[8] This feature lowers the chance of long-term problems with metallic stents, like in-stent restenosis or thrombosis, because the biodegradable stent entirely degrades and the vessel returns to its original state. Furthermore, compared to inflexible metallic stents, biodegradable stents offer a more flexible option for more natural artery movement and lower vessel injury.[9] Moreover, the long-term medication management required for metallic stents can be avoided by developing biodegradable stents intended to elute medications to prevent restenosis.[10] Targeted therapy is another way that this adaptable medication delivery technology might be used to treat underlying diseases like inflammation. All things considered, biodegradable stents are a promising development in interventional cardiology that may help patients achieve better results and experience fewer long-term problems than those connected with metallic stents.[11]

This endeavor aimed to develop biodegradable polymeric stent structures with the ability to release active medication ingredients. In particular, because of their capacity to reduce cholesterol and inhibit platelets, atorvastatin and clopidogrel were utilized as model drugs.[6] They might be put to film-based polymeric biodegradable stents to allow for regulated local release during the mechanical support phase because they were water insoluble.[12,13]

When compared to conventional metallic stents, this innovation has several advantages. First, because they do not stay in the channel permanently, their slow deterioration over time lowers the likelihood of extended duration problems such as thrombosis or restenosis within the stent. This feature facilitates the healing process of the vessel naturally, enabling it to revert to its initial state in the absence of any foreign objects. Furthermore, as opposed to inflexible metallic stents, biodegradable stents offer a more flexible option that can improve patient comfort and lower the chance of vascular injury. Moreover, after the stent has completely disintegrated, some biodegradable stents are made to elute medications to prevent restenosis, which removes the need for ongoing medication therapy.[14] Targeted therapy is another way that this adaptable medication delivery technology might be used to treat underlying diseases like inflammation. In comparison to metallic stents, biodegradable stents may also make access easier for upcoming procedures or treatments and may lessen inflammation and allergic reactions. All things considered, biodegradable stents are a promising development in interventional cardiology that may help patients achieve better results and experience fewer long-term problems than those connected with metallic stents.[15]

Materials and Methods

Materials

A complimentary sample of both clopidogrel and atorvastatin was given by Cadila Pharmaceuticals, Dholka, Ahmedabad. The supplier of the polylactic glycolic acid polymer was Nomisma Healthcare Private Limited in Vadodara. We bought isopropyl alcohol and HPMC E50 LV from Loba Chemie in Maharastra. We bought PEG 400 and castor oil from Oxford Fine Chem in Maharastra. For the study, pharmacopoeial and analytical grade reagents and solvents were all used.

A magnetic stirrer (made by Remi Equipments Pvt. Ltd.), FTIR spectroscopy (made by Shimadzu, 8400S, Japan), differential scanning calorimetry (made by Shimadzu, DSC-60), an ultrasonicator (made by Selectdtc 5033, Japan), UV-visible double beam spectroscopy (made by Shimadzu 2450, Japan), a Brookfield Viscometer (made by Brookfield LDV II+Pro), a digital pH meter (made by TOSHCON Industries, pH meter CL 54+) were among the instruments utilized.

Infrared Fourier Transform Spectroscopy (FTIR)

FTIR spectroscopy allowed for qualitative identification of the molecule and gave adequate details on its constituent groups. A perkin elmer fourier transform Infrared spectrophotometer (FTIR) was used for the infrared investigation.[16]

Preparation of Biodegradable Stents

PLGA 75:25 polymer films were used to create the stents by the solution-casting method. PLGA 75:25 was first dissolved in isopropyl alcohol to a final 25% (w/v) concentration. After the polymer had dissolved in the organic phase, 0.2 mL of PEG 400 plasticizer was added. Atorvastatin and clopidogrel were added to the polymer solution of stents that were loaded with medication at amounts of 3.73 and 27.99 mg per stent, respectively. For two hours, at room temperature, the mixture was continually mixed in order to achieve homogeneity. The polymer solution was then poured onto aluminum pans, filling a 3 by 2 cm area. After that, these pans were placed in a 4°C refrigerator to allow for a controlled and gradual evaporation of the isopropyl alcohol, it stopped air bubbles from forming in the polymer sheets.

As shown in Figs 1 and 2, the films were sliced in 1.5 x 0.4 cm strips after evaporation, and they were then wound around cylindrical rods to form helical shapes. In order to guarantee that the isopropyl alcohol evaporated completely, these rods were placed in a oven set at 40°C. At last, stents were taken out of the rods.[17-20]

DSC Studies

Differential scanning calorimetry (DSC) was used to conduct studies on the glass transition temperatures (Tg) of PLGA as well as the thermal behavior of the polymeric system. This was accomplished by weighing and placing distinct PLGA 75:25, pure medicine, and stent compositions into aluminum hermetic pans. These pans were sealed and then put inside a TA Instruments, USA Q100 DSC analyzer. To obtain the DSC data, the samples were heated at a rate of 10°C/min from 25 to 300°C, and then they were cooled back down to the initial temperature.[21,22]

Water Uptake Studies of the Polymeric Stents

Before starting the water absorption trials, accurate weight measurements of the biodegradable stents were obtained in order to evaluate the swelling properties. The vials holding the samples were kept at 37°C after the stents were submerged in 10 mL of 7.4-pH phosphate-buffered saline (PBS). The stents were carefully taken out of the solution at predetermined intervals (2, 3, 4, 5, 6, 8, 12, and 15 days). The stents were promptly weighed once again after any excess water droplets were removed from their surfaces.

The following formula was used to determine water uptake:

Water Uptake (%) = (A-B)/B x 100 where A is the weight of the stent originally and B is its weight following water swelling.[23,24]

Determining Plaque Buster Time

The in-house plaque buster model was used to measure the plaque buster time. The drug-eluting biodegradable stent, gravel filter, flow regulator, accumulated fat, and phosphate buffer 7.4 comprise the construction of the model. The buffer was permitted to flow from the stent through the model channel using an under-gravel filter. The flow was regulated to keep it at 250 mL/min. Once more, the descending buffer was gathered in a reservoir

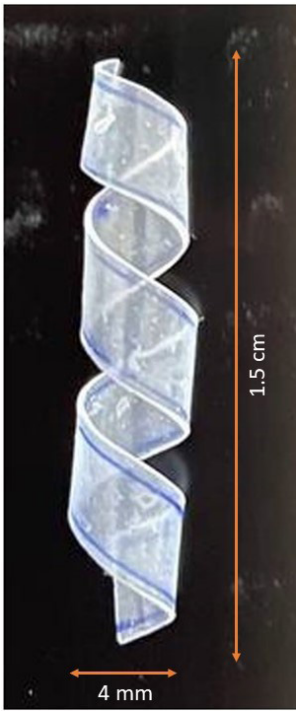

Fig. 1 : Dimension of Stent

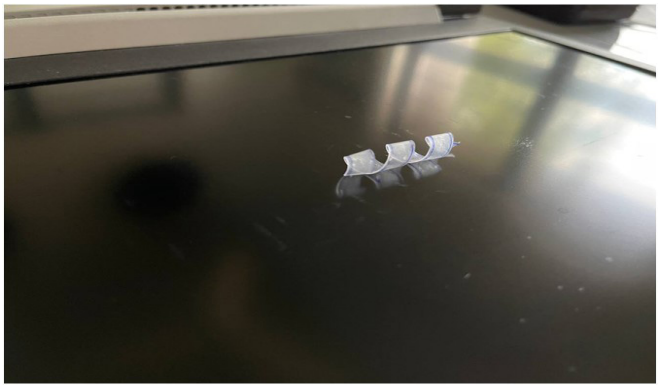

Fig. 2: Digital image of stent

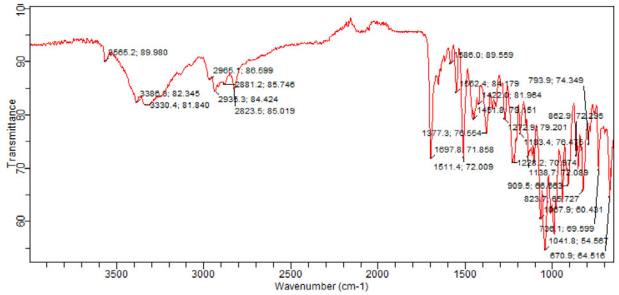

Fig. 3: FTIR study of aatorvastatin

and circulated through the channel. Fat was first placed beneath the gravel filter and then moved to the footpath. Fat was broken down and removed from the gathered area. Days were counted in order to determine if all fat was removed from the passage and placed beneath the gravel filter.[25,26]

Stent Biodegradation Time Measurement

The same in-house model that was used in the plaque buster study was employed to measure the stain biodegradation time. Using a flow regulator, the buffer was continuously circulated at rate of 250 mL/min. Within few days, the stent began to biodegrade by this circulation. Days were tracked to determine when 100% of the stent biodegraded in the bloodstream.[27,28]

In-vitro Drug Release Studies

Drug release *in-vitro* was studied using the paddle over disc approach. Dry films of defined thicknesses were weighed, cut into circles, and then adhered with adhesive on a glass plate. Then, the device was maintained at 37 ± 0.5°C, and the plate was submerged in a 500 mL phosphate buffer solution with a pH of 7.4. The paddle was adjusted to run at 50 revolutions per minute and positioned 2.5 cm away from the glass panel. A UV-visible double-beam spectrophotometer was used to analyze samples (5 mL aliquots) for drug content at predetermined intervals up to 28 days. Three duplicates of the experiment were conducted, and the mean value was computed for analysis.[29,30]

Results

Fourier Transform Infrared Spectroscopy

The characteristics peak for PLGA polymer, pure drugs atorvastatin and clopidogrel, and both were noted, as illustrated in Figs 3, 4, and 5.

The pressed pellet and liquid sample techniques were used to collect the spectra of standard atorvastatin in order to detect the distinctive absorption peaks that corresponded to the N-H group's stretching vibrations. The first background spectrum for the liquid sampling approach was obtained using chloroform. In order to quantify the medicine, the FTIR spectrum of atorvastatin calcium in chloroform was examined for a variety of functional group peaks. Due to the absorption of the N-H group, the compound presented a strong, crisp signal between 3400 and 3600 cm^{-1} without interference. This signal showed a distinct, powerful peak that grew linearly with concentration. This attribute was chosen for the atorvastatin quantitative analysis.

Pure clopidogrel's FTIR spectra revealed a prominent absorption band at 1752 cm^{-1} from C=O stretching vibrations and around 3012 cm^{-1} from O–H stretching of the hydrogen sulfate molecule. The band at 3121 cm^{-1} is caused by aromatic C–H stretching vibrations. The

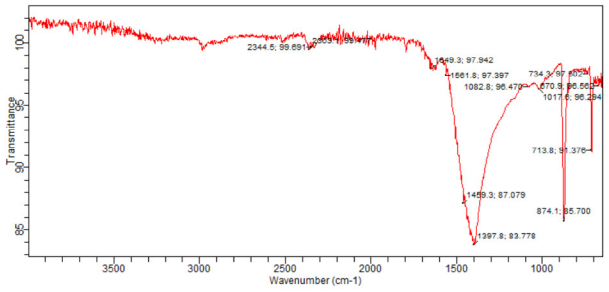

Fig. 4: FTIR study of clopidogrel

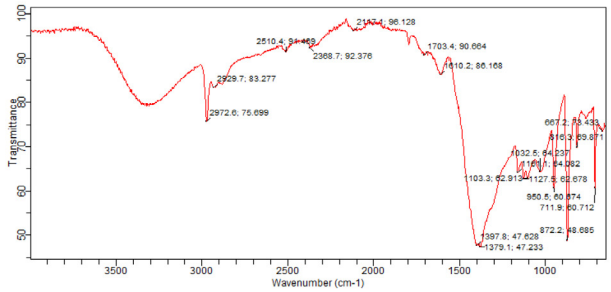

Fig. 5: FTIR study of PLGA

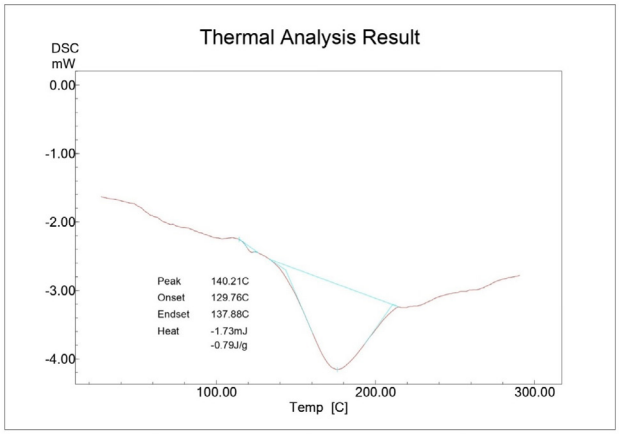

Fig. 6: DSC study of atorvastatin

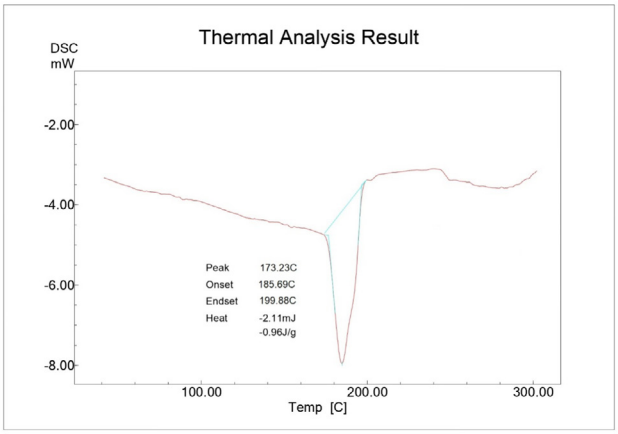

Fig. 7: DSC study of clopidogrel

Table 1: Formulation of all batches

Material	*Quantity per petri plate*							
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
Atorvastatin (mg)	300	300	300	300	300	300	300	300
Clopidogrel (gm)	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
PLGA (gm)	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00 g
PEG 400 (mL)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Isopropyl alcohol (mL)	Upto 20	Upto 20	Upto 20	Upto 20	Upto 20	Upto 20	Upto 20	Upto 20

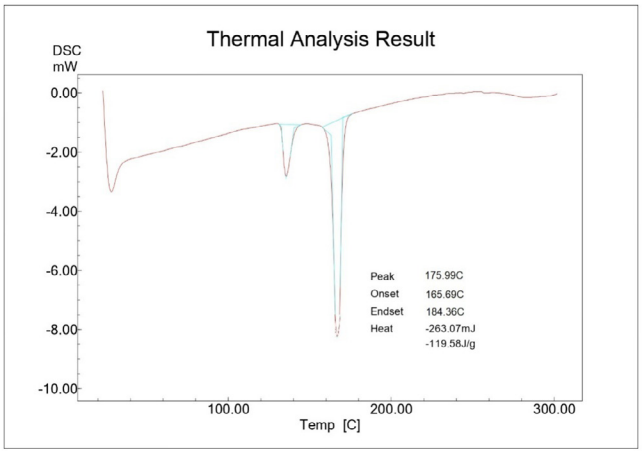

Fig. 8: DSC study of PLGA

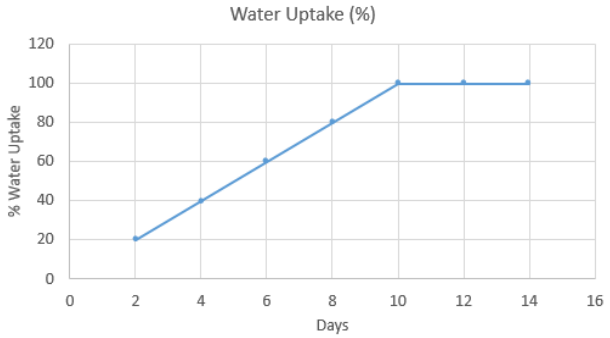

Fig. 9: Water uptake study

FTIR spectrum also saw a large absorbance band at 2505 cm^{-1}. This band is thought to be caused by the stretching vibrations of bound N–H that arise from the salt formation between the –OH of hydrogen sulfate and the quaternary nitrogen of clopidogrel. The C-O stretching band was visible at 1062, 1155, and 1186 cm^{-1}.

Strong peaks at 3,503 and 1,763 cm^{-1}, which were indicative of PLGA pure, were visible in the FTIR spectra of BSA-loaded PLGA. The 1,686 cm^{-1} peak of the amide bond verified the conjugation of PLGA, which was also observed in blank PLGA. Bovine serum albumin (BSA)-loaded poly (lactic-co-glycolic acid) (PLGA) was subjected to fourier-transform infrared (FTIR) spectra analysis. The results

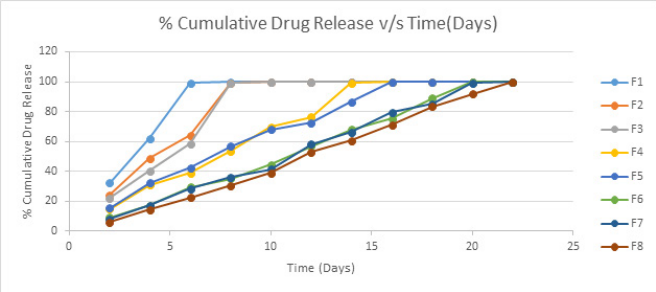

Fig. 10: Graph of % CDR *vs* time in days for drug release

showed two unique peaks at 3,503 and 1,763 cm^{-1}, which are representative of the peaks associated with pure PLGA. These peaks line up with particular functional groups in the structure of the PLGA. The stretching vibration of hydroxyl (OH) groups is responsible for the peak at 3,503 cm^{-1}, whereas the stretching vibration of carbonyl (C=O) groups is responsible for the peak at 1,763 cm^{-1}. These results support the structural integrity of the polymer by indicating the existence of PLGA in the BSA-loaded sample.

Biodegradable Polymeric Stent Preparation

Atorvastatin and clopidogrel, the APIs, were combined with excipients such as PLGA, PEG 400, and isopropyl alcohol to create stents. All batch formulations are displayed in Table 1.

Differential Scanning Calorimetry Studies

Figs 6 and 7 shows that the characteristics peak of the pure drugs clopidogrel and atorvastatin was observed in that order. According to data, the melting points of pure drugs, clopidogrel and atorvastatin, were determined to be 185 and 175°C, respectively. DSC studies revealed that the melting point of PLGA polymer is 176°C (Fig. 8).

Water Uptake Studies of the Polymeric Stents

As seen in Fig. 9, the PLGA 75:25 polymers showed a notable water uptake, reaching over 80% of their starting weight. This high and quick absorption of water is expected to quicken the stent's breakdown in the *in-vitro* release medium. Because of their greater propensity to swell and absorb water, swelled PLGA 75:50 stents showed enhanced brittleness and deformation after just 10 days.

Measurement of Plaque Buster Time and Stent Biodegradation Time

The in-house plaque buster model was used to measure the plaque buster time and the stent biodegradation time. The study's data are displayed in the Table 2.

In-vitro drug release studies

In-vitro drug release studies were carried out using the paddle-over-disc method. The results for this study are shown as in Table 3 and Fig. 10.

Discussion

About 4 mm diameter and 150 mm length stent formulations are widely used in cardiac interventions and are representative of common dimensions in clinical practice. These stents are helical in shape and are carefully designed to provide just the right amount of mechanical support for the artery wall and flexibility for vessel navigation while guaranteeing easy breakability when needed. PEG 400, a plasticizer, is added to the stents to increase their mechanical strength for scaffolding while preserving the requisite flexibility for arterial travel. This plasticization action makes stent inflation possible, which prevents the polymer matrix from visibly cracking.

The biodegradable polymer films' thickness closely satisfies the requirements for cardiovascular stents with helical geometries, and the resultant stents exhibit good mechanical strength. The helical design works well for mechanical scaffolding and reduces the possibility of restenosis. Additionally, this design increases the drug-loading capacity and gives the stents a bigger surface area. During angioplasty, the smooth and rounded polymeric struts help to minimize vessel wall damage and reduce irritation.

To determine the condition of the integrated medications in the polymer phase, DSC analysis is used. For PLGA, clopidogrel, and atorvastatin, peaks in the DSC thermogram at particular temperatures offer important information about their molecular states and guarantee accurate formulation characterization.

Given that water uptake is a critical characteristic that impacts medication release and stent integrity, it is shown that the PLGA 75:25 polymers absorb over 80% of their starting weight. On the other hand, quick absorption of water may cause the stent to deteriorate more quickly, which could cause brittleness and deformation after 12 days.

Plaque buster time analysis indicates that a PLGA concentration above 1.00 gm/stent is optimal for maintaining the stent's ability to remove plaque for over 18 days. Table 2 clarifies this relationship, showing that a higher polymer content is associated with a longer biodegradation time—a critical factor in attaining the best possible plaque clearance. Drug release experiments using paddle over disc approach involving atorvastatin and clopidogrel-loaded PLGA 75:25 stents show a release period ranging from 6 to 22 days depending on the formulation design. According to the results, a longer cumulative drug release is correlated with a higher concentration of PLGA polymer% (Fig. 10).

Table 2: Plaque buster time and stent biodegradation time along with PLGA concentration

Batch	*Plaque buster time (Days)*	*PLGA concentration*	*Stent biodegradation time (Days)*
B1	Not done 100 % due to stent biodegradation done earlier	0.25 GM	2
B2		0.50 GM	5
B3		0.75 GM	12
B4		1.00 GM	18
B5	21	1.25 GM	22
B6	22	1.50 GM	32
B7	23	1.75 GM	38
B8	21	2.00 GM	42

Table 3: %Cumulative drug release *v/s* time (Days)

Days	*%Drug Release as per different formulation batches*							
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
2	32.23	24.25	22.12	14.82	15.36	9.23	8.23	6.12
4	62.12	48.58	40.23	30.73	32.25	17.34	17.28	14.23
6	99.11	64.21	58.35	38.83	42.26	29.36	28.36	22.33
8	-	99.25	99.15	53.65	56.89	35.15	36.15	30.53
10	-	-	-	69.56	68.12	44.58	41.19	38.83
12	-	-	-	76.40	72.36	56.69	58.23	52.75
14	-	-	-	99.12	86.69	68.08	66.29	60.69
16	-	-	-	-	99.89	75.45	79.69	71.15
18	-	-	-	-	-	88.96	84.99	83.49
20	-	-	-	-	-	99.92	99.14	91.69
22	-	-	-	-	-	-	-	99.80

To sum up, PLGA 75:25 stents retain their radial strength and morphologies, which are critical factors in avoiding restenosis. This particular formulation demonstrates its potential efficacy in cardiac therapies by providing the required mechanical support throughout the study.

Conclusion

PLGA 75:25 was used as the biodegradable polymer, and PEG 400 and isopropyl alcohol were added as the plasticizer and carrier, respectively, to create and improve biodegradable stents loaded with atorvastatin and clopidogrel through carefully planned controlled release tests. The improved stent formulation effectively met all evaluation parameters, which nearly matched the values predicted by the design model.

After a stent biodegradation period of 22 days, the improved formulation demonstrated a full plaque bursting

action at 21 days. Per the stent design, the cumulative medication release peaked at 22 days. This study confirms that stents are an essential treatment for atherosclerosis, highlighting their role in the process. In the context of treating atherosclerosis, the painstakingly created, assessed, and refined stents guarantee regulated and intended medication release for both clopidogrel and atorvastatin.

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