EJPMR, 2026, 13(6), 269-276 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

FORMULATION AND EVALUATION OF PIAVASTATIN CALCIUM LOADED WAFER

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DOI: https://doi.org/10.5281/zenodo.20443639

How to cite this Article: Urvesh Rangi*[1], Dr. Shailesh T. Prajapati[2]. (2026). Formulation and Evaluation of Piavastatin Calcium Loaded Wafer. European Journal of Pharmaceutical and Medical Research, 13(6), 269–276.

Article Received on 24/04/2026 **Article Revised on 14/05/2026** **Article Published on 01/06/2026**

ABSTRACT

Objective[1]: The primary goal of this study was to develop and assess a Wafer containing Pitavastatin Calcium by enhancing the drug's solubility through Solid Dispersion Method. The intent was to bypass hepatic first-pass metabolism, thereby improving bioavailability, ensuring faster onset of action, and increasing patient compliance. Materials and Methods: Wafer was produced using the solvent casting technique, chosen for its simplicity, cost-effectiveness, and time efficiency. Initially, a Solubility Enhancement of Pitavastatin Calcium was done using the Solid Dispersion method. A preliminary investigation was conducted to identify suitable excipients, including film forming agents and plasticizers. The trial formulations were evaluated for their physicochemical characteristics. To optimize the formulation, a 3^2 full factorial design was employed, focusing on two independent variables: the concentration of the film forming polymer (HPMCE5 denoted as X1) and the amount of plasticizer (PEG400 denoted as X2). The impact of these variables was assessed on two dependent responses- disintegration time Drug release(Y1) and percentage drug release (Y2).The optimization process was carried out using Design Expert V.13 software. Result and Discussion: The most promising outcome was observed in Batch F2, which contained Solid Dispersion in a 1:2 ratio, 5 mg of HPMC E5, and 1 ml of PEG 400. This batch showed a disintegration time of 33 seconds and a cumulative drug release of 99.21% within 10 minutes. An accelerated stability study conducted over one month confirmed the formulation's stability during that period. Conclusion: Based on the findings, it can be concluded that the Wafer of Pitavastatin calcium offers rapid disintegration and enhanced drug release. This formulation strategy effectively improves the drug's solubility and bioavailability while bypassing hepatic first-pass metabolism due to its sublingual mode of administration.

KEYWORDS: Pitavastatin Calcium, Wafer, Full Factorial Design, Solvent Casting, Solubility, Hyperlipidemia.

INTRODUCTION[1]

Hyperlipidemia is a condition characterized by abnormally elevated levels of lipids (fats) in the blood, such as cholesterol, triglycerides, and lipoproteins. It includes various genetic and acquired disorders leading to an imbalance, typically with high low-density lipoprotein (LDL)—often called "bad cholesterol"—and low high density lipoprotein (HDL), or "good cholesterol". Pitavastatin Calcium is an effective statin widely used for the treatment of hyperlipidemia due to its potent cholesterol-lowering activity and favorable safety profile. However, conventional oral administration of Pitavastatin Calcium may exhibit limitations such as delayed onset of action, reduced bioavailability due to hepatic first-pass metabolism, and the need for repeated dosing. To overcome these challenges, medicated Sublingual wafer formulations have gained attention as an innovative drug delivery system.

3^2 experimental designs, a statistical optimization technique, is ideal for pharmaceutical formulation development. It allows efficient screening of formulation parameters and their interactions with minimal experimental runs.[6]

MATERIALS AND METHODS

Pitavastatin Calcium is provided as gift sample by CTX Life Science Surat and excipients HPMC E5 and PEG 4000 was Available at SSSPC ZUNDAL College.

Preformulation studies

Determination of Absorbance Maxima of Pitavastatin Calcium.[7]

The λ max of Pitavastatin Calcium was carried out in phosphate buffer (pH 6.8) the λ max in solvent medium is shown below which found nearby at 240 nm, shown in fig. 5 Pitavastatin Calcium reported λmax value is 240 nm.

Drug excipients compatibility study by FTIR study.[8-9]

Infrared spectroscopy was conducted using FT-IR spectrophotometer and the spectrum was recorded in the wave number region of 4000 to 400 cm^{-1}.

Method of Preparation of Wafer[10]

Solvent Casting method was used

Preparation of Polymer Solution: The film suitable solvent, often water or alcohol, and thoroughly mixed to ensure complete dissolution.

Incorporation of Active Ingredients: The active pharmaceutical ingredient (API), plasticizers, and other excipients (such as flavorings and stabilizers) are add the polymer solution, with continuous stirring to ensure a uniform mixture.

Casting the Solution: The resulting homogeneous solution is poured onto a flat surface or casting plate, where it is evenly spread using an applicator to achieve the desired film thickness.

Drying the Wafer: The cast solution is dried at a controlled temperature to evaporate the solvent, solidifying the film. This is usually done in a drying oven or under ambient conditions, depending on the solvent used.

Cutting and Packaging: Once dried, the film is carefully peeled off the casting plate, cut into desired sizes, and then packaged to prevent exposure to moisture or other environmental factors.

Table 1: Formulation table for Trial batches.

Ingredients(mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Pitavastatin Calcium	4	**4**	4	4	4	4	4	4	4
PVPK 30	8	**8**	8	8	8	8	8	8	8
HPMC K4M	9.3	-	10	-	9	-	9	-	9.3
HPMC E5	-	**9**	-	10	-	9.3	-	10	-
PEG 400	1	**1**	1	1	1	1	1	1	1
Citric acid	4	**4**	4	4	4	4	4	4	4
Sucrose	4	**4**	4	4	4	4	4	4	4
Menthol	3	**3**	3	3	3	3	3	3	3
Water	q.s.	**q.s.**	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s

Table 2: Formulation table for Factorial batches.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pitavastatin Calcium	4	**4**	4	4	4	4	4	4	4
HPMC E5	5	**5**	5	10	10	10	15	15	15
PEG 400	0.5	**1**	1.5	0.5	1	1.5	0.5	1	1.5
Sucrose	4	**4**	4	4	4	4	4	4	4
Menthol oil	3	**3**	3	3	3	3	3	3	3
Water	10	10	10	10	10	10	10	10	10

Evaluation of Microsponges[11-13]

Organoleptic Evaluation

- Electronic tongue measurements to aid in taste masking and distinguish between differentÿ levels of sweetness Appearance, color, texture, and odor are assessed to ensure patient acceptability.

Thickness

- The wafer's thickness can be tested using a micrometer screw gauge at various key points. It is essential for assessing consistency in the wafer's density since it directly affects the accuracy of the wafer's dose.
- Individual wafers are weighed to check consistency within a batch, averaging multiple samples

Tensile strength

- Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Wafer thickness} \times \text{wafer width}} \times 100$$

Percent elongation

- When stress is applied, a strip sample stretches and this is referred to as a strain. Strain is the deformation of a strip divided by the original dimension of the sample. Generally, elongation of strip increases as the plasticizer content increases

$$\% \text{ Elongation} = \frac{\text{Increase in length of wafer}}{\text{Initial length of wafer}} \times 100$$

Tear resistance

- The tear resistance of plastic film or sheeting is intricately linked to its ability to withstand rupture. The test is conducted at a low loading rate of 51 mm/min to measure the tearing force. The rip resistance value is the maximal stress or force needed to tear the specimen, typically located around the beginning of tearing, and is measured in Newtons.

Young's modulus

- Young's modulus or elastic modulus is the measure of the stiffness of strip. It is represented as the ratio of applied stress overstrain in the region of elastic deformation as follows:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Strip thickness} \times \text{cross} - \text{head speed}} \times 100$$

- Hard and brittle wafer demonstrate a high tensile strength and Young's modulus with small elongation.

Folding endurance

- Folding endurance is determined by repeated wafer folding at the same location until the wafer breaks. The number of times the wafer is folded without breaking is calculated as the folding endurance value Surface

Disintegration time

- The disintegration time requirement of 30 seconds or less for orally disintegrating tablets as stated in the CDER instruction can be applied to fast dissolving oral wafers. Although there is no official protocol available for oral quickly dissolving wafers, they can serve as a qualitative reference for quality control testing or during the development process. For this investigation, Pharmacopoeia disintegrating test devices may be used. The usual duration for wafer disintegration ranges from 5 to 30 seconds. Research on wafer swelling is conducted using a simulated saliva solution.

Swelling property

- Wafer swelling study is conducted using simulated saliva solution. The wafer sample is weighed and put in a plastic container in a wire mesh of stainless steel comprising a 15mL medium. Increase in wafer weight is determined at a predetermined time interval until the observation of a constant weight. The swelling degree is calculated using formula is the weight of Wafers at time t, and WO is the weight of Wafers at time zero

$$\alpha = \frac{(Wt - Wo)}{Wo}$$

Taste evaluation

- A taste panel of six human volunteers evaluated the taste acceptability of a 10 mg medicine by placing a wafer sample containing the drug in their mouths until it disintegrated, then spitting it out and recording the flavor. The volunteers were asked to gargle with distilled water between the medication and sample administration. Following scale was Used for the indicating taste-masking values: + = very bitter, ++ = moderate to bitter, +++ = somewhat bitter, ++++ = tasteless/taste- masked.

Transparency

- A UV spectrophotometer can be used to measure the transparency of the wafers directly. Cut the wafer samples into rectangles and lay them on the spectrophotometer cell's inner surface. Calculate the transmission of wafers at a wavelength of 600 nm. Transparency = (logT600)/b = -
- €c Where T600 is the transmittance at 600 nm, b is the Wafer thickness (mm), c is the concentration.

Hydration capacity

- The hydration capacity (HC) of the wafers is performed by incubating them at 37±0.10C in 25mL of Phosphate buffer solution (PBS pH 6.8). The wafers (n¼4) were initially weighed and the swelling behavior was observed at predetermined time intervals. The samples have been separated, closely blotted out between tissue documents to remove liquid droplets adhered to the surface, and reweighed to constant weight. The proportion of water consumption was calculated as follows.

$$\text{Water uptake } \% = \frac{(Ws - W)}{W} \times 100$$

- Where Ws is the weight of the hydrated wafer and W is the initial weight of the wafer.

In-vitro Dissolution Test

- The traditional basket or paddle apparatus specified in the pharmacopoeia can be utilized for conducting dissolution testing. The dissolution medium will be selected based on the sink conditions and the highest API dose. The wafer's tendency to float on the dissolving liquid when the paddle system is utilized can make the dissolution test challenging.

Stability test

- A piece of wafer preparation was stored in an aluminum package at 250 C with 50-60% humidity (normal condition) or at 40 with 75% humidity (accelerated condition) for 4-24.

Assay/ Content uniformity

- Determine this using any standard assay method specified in the pharmacopoeia for the particular

active pharmaceutical ingredient. Content homogeneity is assessed by measuring the API content in a single strip. The content uniformity limit ranges from 85% to 115%.

RESULT AND DISCUSSION

Organoleptic Properties of Pitavastatin Calcium

Table 3: Organoleptic Properties of Pitavastatin Calcium.

Properties	Observation
Appearance	Off white crystalline powder
Taste	Tasteless
Odor	Odorless

Melting Point Determination

Melting point of API was found to be 219-230°C, which is in the range, is given in literature. So, the drug is considered as pure.

Table 4: Melting Point Determination.

Sr.no.	Observed
1	(219-230°C)

Solubility study of Pitavastatin Calcium

The solubility of drug was observed in different solvents on UV spectrophotometer by using calibration equation of drugs in particular solvents. Selected drug is freely soluble in methanol, slightly soluble in 6.8 phosphate buffer, very slightly soluble in distilled water.

Table 5: Solubility study of Pitavastatin Calcium.

Solvent	Result
Methanol	Freely soluble
6.8 phosphate buffer	Freely soluble
water	Very slightly soluble

Spectrophotometric identification of Pitavastatin Calcium

Determination of absorption maxima of drug (λ max)

- The λ max of Pitavastatin Calcium was carried out in phosphate buffer (pH 6.8) the λ max in solvent medium is shown below which found nearby at 240 nm, shown in fig. 5 Pitavastatin Calcium reported λmax value is 240 nm.

Table 6: Determination of absorption maxima of drug (λ max).

Solvent	λmax (nm)
Phosphate Buffer (pH 6.8)	240

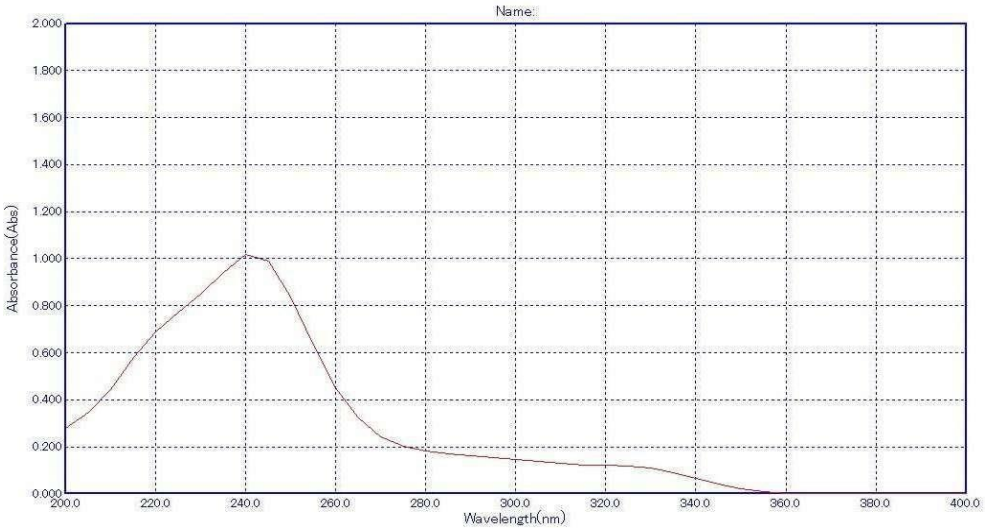

Fig. 1: Absorption maxima of drug (λmax).

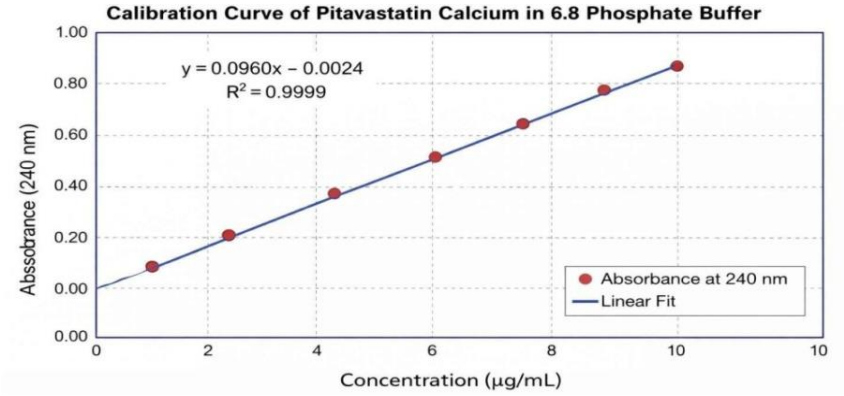

Fig 2: calibration curve.

FTIR Study

Infrared spectroscopy was conducted using FT-IR spectrophotometer and the spectrum was recorded in the wave number region of 4000 to 400 cm-1. The procedure consisted of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in Potassium bromide and compressed into discs by applying a pressure of 5 tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded which is shown in fig.3.

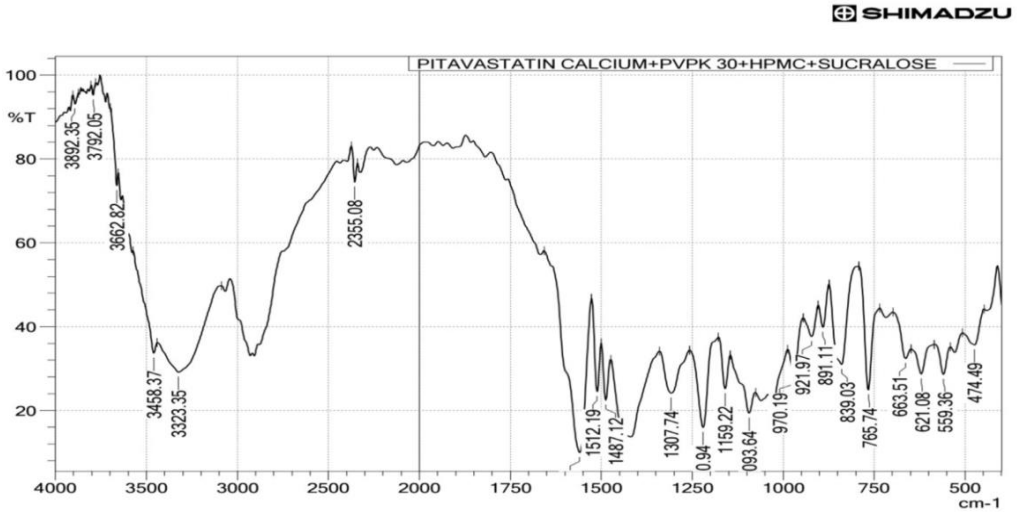

Fig. 3: FTIR of Pitavastatin Calcium + Excipients.

Evaluation of Microsponges

As we discuss the method and the equations of evaluation parameter in method and material section we find out the result as per table 7

Table 7: Evaluation of Wafer.

Factorial batches	Appearance	Smoothness	peel ability	Disintegration time (sec)	Thickness (mm)
F1	Translucent	Smooth	Good	43±2.32	0.35±0.05
F2	**Translucent**	**Smooth**	**Good**	**33±1.12**	**0.31±0.11**
F3	Translucent	Smooth	Good	42±2.52	0.41 ±0.2
F4	Translucent	Smooth	Average	54±1.23	0.35±0.2
F5	Translucent	Smooth	Average	55±2.24	0.30±0.03
F6	Translucent	Smooth	Average	56±1.63	0.37±0.12
F7	Translucent	Smooth	Good	65±3.12	0.40±0.05
F8	Translucent	Smooth	Average	67±2.32	0.40±0.02
F9	Translucent	Smooth	Average	66 ± 2.32	0.40 ± 0.05

Factorial batches	Folding endurance	Surface pH	Weight variation (mg)	Drug content (%)	% Moisture content
F1	149±3.41	7.3±0.21	74±1.13	98.26±0.21	1.864±0.029
F2	178±5.25	7.2±0.21	75±2.24	99.21±0.45	1.547±0.010
F3	142±4.13	6.8±0.19	73±3.15	99.14±0.36	1.613±0.042
F4	144±3.25	6.5±0.16	72±2.32	99.32±0.45	1.691±0.021
F5	155±2.12	6.6±0.14	73±2.23	99.21±0.36	1.681±0.059
F6	163±3.15	6.6±0.52	72±1.13	98.75±0.38	1.439±0.052
F7	154±2.36	7.3±0.9	75±2.36	99.78±0.98	1.549±0.064
F8	165±4.36	6.3±0.12	75±3.36	99.71±0.31	1.846±0.073
F9	160 ± 4.39	6.7 ±0.15	76 ±4.36	99.22 ±0.33	1.632 ±0.85

Graphical Evaluation

Contour plots were generated for each independent variable (Drug to polymer ratio, Concentration of PEG 4000 and HPMC E5) to visualize their individual effects on the selected responses, such as In Vitro Drug release and Disintegration time. These plots displayed constant contours (z-slices), enabling a two-dimensional representation of the three dimensional response surface. Additionally, 3D surface quadratic plots were created for each variable, providing a deeper insight into their interaction with the responses and highlighting the influence of different factor levels. The 3D plots are shown from fig5-7.

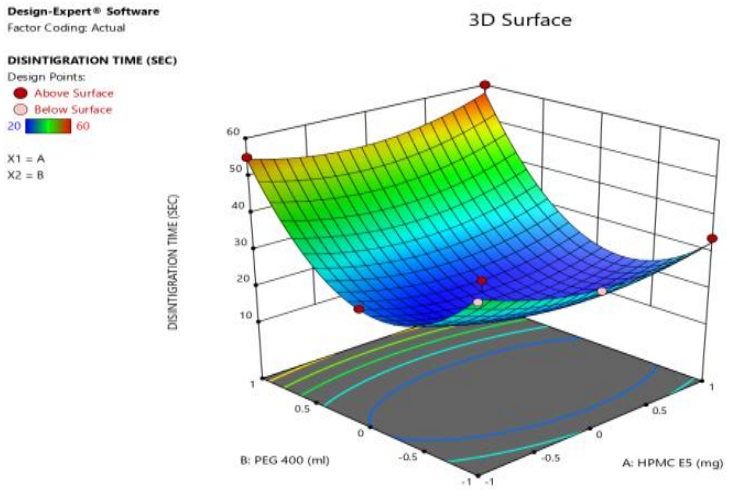

Fig. 4: 3D surface plot showing effect on response Y1 % Drug Release.

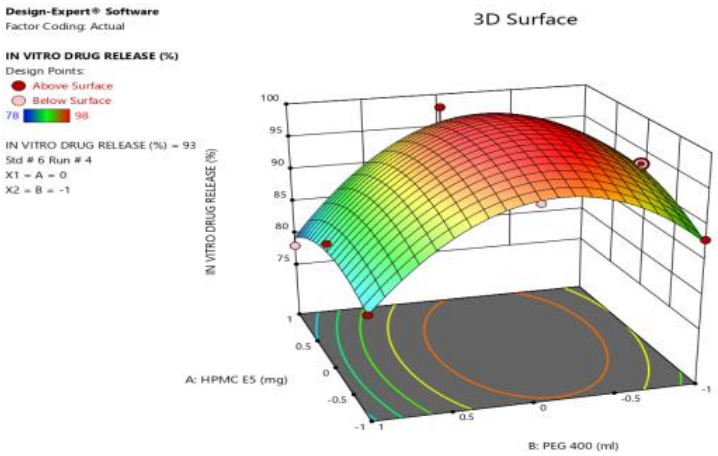

Fig 5: 3D surface plot showing effect on response Y2 Disintegration Time.

Check point batch analysis

To validate the accuracy of the design model, a check point batch was selected from the overlay plot for evaluation which is shown in fig.8. This batch was formulated and tested within the experimental domain to ensure model reliability. The observed experimental values of the response parameters were quantitatively compared to the predicted values, and the percentage bias was calculated to assess the deviation between them. The close agreement between experimental and predicted values confirmed the adequacy of the model, ensuring the reliability of the optimization process which is shown in table.8.

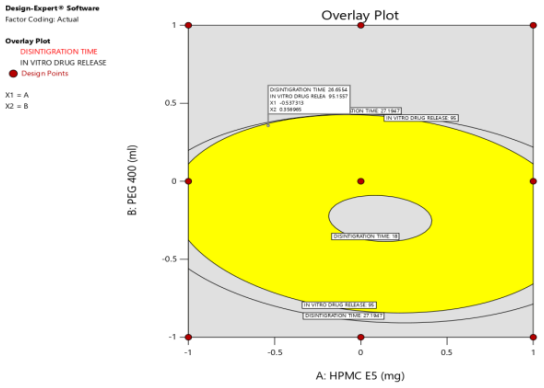

Fig 6: Overlay plot of checkpoint batch.

Table 8: Result of Check point batch.

Independent Variable		Dependent Variable	
X1	**X2**	**Y1**	**Y2**
HPMC E5	PEG 400	Disintegration Time(sec)	In vitro Drug release %
Coded Value:-0.537	Coded value:0.356	Predicted value:26.66	Predicted Value:95.16
Actual Value:7.32	Actual Value:1.18	Observed Value:26.60	Observed Value:95.12

Result of preformulation studies for Wafer batch F10:

By using the standard formula for performulation study of wafer we observed this result which is shown in table 9.

Table 9: Result of Preformulation study for wafer.

Evaluation Parameter	F10
Appearance	Translucent
Smoothness	Smooth
Peel ability	Good
Disintegration Time (sec)	38 ± 1.45
Thickness(mm)	0.33 ± 0.04
Folding Endurance	168±3.12
Surface pH	6.9±0.18
Weight Variation(mg)	74±1.95
Drug content %	99.12±0.42
%Moisture Content	1.58±0.041
In vitro drug release%	95.20±0.64

In- vitro Drug release of Check – point Batch

Table 10: In vitro Drug release of check point batch.

Time (min)	% In vitro Drug Release of F10
0	0
2	31.5±0.35
4	51.70±0.25
6	76.20±1.28
8	93.2±0.07
10	95.5±0.05

(n = 3±SD)

In vitro drug release

Ratio of in vitro drug release is shown in fig.10

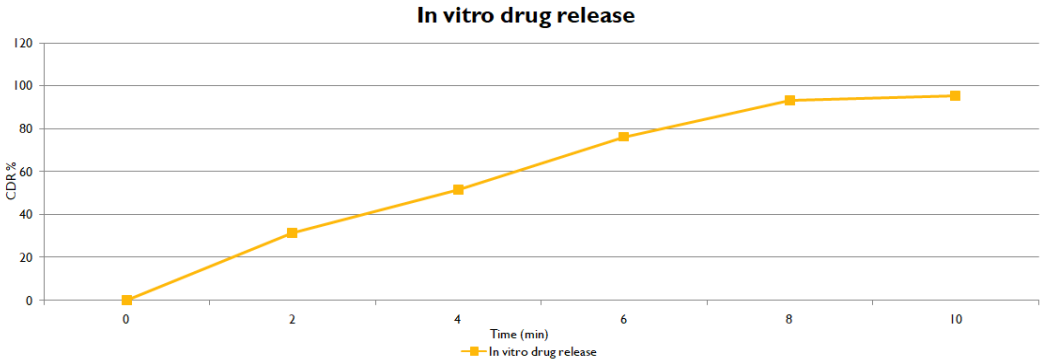

Fig. 7: Graphical representation of in vitro drug release.

Stability Study

The Wafer that were formed underwent a one-month accelerated stability investigation at 40°C±2°C and 75%RH±5%RH. After one month, Wafers were valuated according to several criteria.

Table 11: Result of stability study.

Condition	40 ± 2°C and 75 ± 5% RH	
Evaluation	**Initial**	**After a month**
Appearance	Translucent	Translucent
Weight Variation	74±1.95	74.6±2.10
Folding Endurance	168±3.12	165±2.84
Surface pH	6.9±0.18	6.87±0.22
Disintegration Time (sec)	38±1.45	39.21±1.62
%Cumulative Drug release at 10 min	95.20±0.64	91.72±0.05
%Drug Content	99.12±0.42	98.64±0.56

CONCLUSION

Based on the findings, it can be concluded that the Wafer of Pitavastatin calcium offers rapid disintegration and enhanced drug release. This formulation strategy effectively improves the drug's solubility and bioavailability while bypassing hepatic first- pass metabolism due to its sublingual mode of administration.

ACKNOWLEDGEMENT

I begin by showing my gratitude to My Prabhu for His grace, blessings, and guidance, which have made this work possible. I am profoundly grateful to my esteemed guide and Principal Dr.Suresh T. Prajapati, M. Pharm, PhD, Department of Pharmaceutics, SSSPC- Zundal.

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